QUANTUM DOT APTAMERS-AN EMERGING TECHNOLOGY WITH WIDE SCOPE IN PHARMACY

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ABSTRACT

Quantum dot is a portion of matter whose excitons are confined in all three spatial dimensions. These thus have electronic properties intermediate between those of bulk semiconductors and those of discrete molecules. The surface modification of QDs with antibodies, aptamers, peptides, or small molecules that bind to antigens present on the target cells or tissues has resulted in the development of sensitive and specific targeted imaging and diagnostic modalities. Recently, QDs have been engineered to carry distinct classes of therapeutic agents for simultaneous imaging and therapeutic applications& medical applications. QD's are recently afflicted to contamination of aquatic and terrestrial ecosystems. In this review we gave general consideration to methods of production of quantum dots, non pharmaceutical and pharmaceutical applications and limitations.

Keywords: Quantam dots, Aptamers, Luminescence.

INTRODUCTION

Quantum dot is a portion of matter (e.g., semiconductor) whose excitons are confined in all three spatial dimensions. Consequently, such materials have electronic properties intermediate between those of bulk semiconductors and those of discrete molecules [1-3]. They were discovered at the beginning of the 1980s by Alexei Ekimov [4] in a glass matrix and by Louis E. Brus in colloidal solutions. The term "quantum dot" was coined by Mark Reed [5]. Quantum dots are semiconductors whose electronic characteristics are closely related to the size and shape of the individual crystal. Generally, the smaller the size of the crystal, the larger the band gap, the greater the difference in energy between the highest valence band and the lowest conduction band becomes, therefore more energy is needed to excite the dot, and concurrently, more energy is released when the crystal returns to its resting state. Semiconductor nanocrystals known as quantum dots (QDs) have been increasingly utilized as biological imaging and labeling probes because of their unique optical properties, including broad absorption with narrow photoluminescence spectra, high quantum yield, low photo bleaching, and resistance to chemical degradation.

Production

There are several ways to confine excitons in semiconductors, resulting in different methods to produce quantum dots. In general, quantum wires, wells and dots are grown by advanced epitaxial techniques in nanocrystals produced by chemical methods or by ion implantation, or in nanodevices made by state-of-the-art lithographic techniques

Colloidal synthesis

Colloidal semiconductor nanocrystals are synthesized from precursor compounds dissolved in solutions, much like traditional chemical processes. The synthesis of colloidal quantum dots is based on a three-component system composed of precursors, organic surfactants, and solvents. When heating a reaction medium to a sufficiently high temperature, the precursors chemically transform into monomers. Once the monomers reach a high enough super saturation level, the nanocrystal growth starts with a nucleation process. The temperature during the growth process is one of the critical factors in determining optimal conditions for the nanocrystal growth. It must be high enough to allow for rearrangement and annealing of atoms during the synthesis process while being low enough to promote crystal growth. Another critical factor that has to be stringently controlled during nanocrystal growth is the monomer concentration. The growth process of nanocrystals can occur in two different regimes, "focusing" and "defocusing". At high monomer concentrations, the critical size (the size where nanocrystals neither grow nor shrink) is relatively small, resulting in growth of nearly all particles. In this regime, smaller particles grow faster than large ones (since larger crystals need more atoms to grow than small crystals) resulting in "focusing" of the size distribution to yield nearly monodisperse particles. The size focusing is optimal when the monomer concentration is kept such that the average nanocrystal size present is always slightly larger than the critical size. When the monomer concentration is depleted during growth, the critical size becomes larger than the average size present, and the distribution "defocuses" as a result of Ostwald ripening. There are colloidal methods to produce many different semiconductors. Typical dots are made of binary alloys such as cadmium selenide, cadmium sulfide, indium arsenide, and indium phosphide. Although, dots may also be made from ternary alloys such as cadmium selenide sulfide. These quantum dots can contain as few as 100 to 100,000 atoms within the quantum dot volume, with a diameter of 10 to 50 atoms. This corresponds to about 2 to 10 nanometers, and at 10 nm in diameter, nearly 3 million quantum dots could be lined up end to end and fit within the width of a human thumb.

Fabrication

Self-assembled quantum dots are typically between 5 and 50 nm in size. Quantum dots defined by lithographically patterned gate electrodes, or by etching on two-dimensional electron gases in semiconductor hetero structures can have lateral dimensions exceeding 100 nm. Some quantum dots are small regions of one material buried in another with a larger band gap. These can be so-called core-shell structures, e.g. with CdSe (Cadmium-Selenium) in the core and ZnS (Zinc-Sulphide) in the shell or from special forms of silica called ormosil. Quantum dots sometimes occur spontaneously in quantum well structures due to monolayer fluctuations in the well's thickness. Self-assembled quantum dots nucleate spontaneously under certain conditions during molecular beam epitaxy (MBE) and metal organic vapor phase epitaxy (MOVPE), when a material is grown on a substrate to which it is not lattice matched. The resulting strain produces coherently strained islands on top of a two-dimensional wetting layer. This growth mode is known as Stranski–Krastanov growth. The islands can be subsequently buried to form the quantum dot. This fabrication method has potential for applications in quantum cryptography (i.e. single photon sources) and quantum computation. The main limitations of this method are the cost of fabrication and the lack of control over positioning of individual dots. Individual quantum dots can be created from two-dimensional electron or hole gases present in remotely doped quantum wells or semiconductor heterostructures called lateral quantum dots. The sample surface is coated with a thin layer of resist. A lateral pattern is then defined in the resist by electron beam lithography. This pattern can then be transferred to the electron or hole gas by etching, or by depositing metal electrodes (lift-off process) that allow the application of

external voltages between the electron gas and the electrodes. Such quantum dots are mainly of interest for experiments and applications involving electron or hole transport, i.e., an electrical current. The energy spectrum of a quantum dot can be engineered by controlling the geometrical size, shape, and the strength of the confinement potential. Also, in contrast to atoms, it is relatively easy to connect quantum dots by tunnel barriers to conducting leads, which allows the application of the techniques of tunneling spectroscopy for their investigation. The quantum dot absorption features correspond to transitions between discrete, three-dimensional particle in box states of the electron and the hole, both confined to the same nanometer-size box. These discrete transitions are reminiscent of atomic spectra and have resulted in quantum dots also being called artificial atoms [6].

Fig. 1: Fabricated quantum dot laser on silicon substrate[43].

Viral assembly

Engineered M13 bacteriophage viruses are used to create quantum dot biocomposite structures [7]. As a background to this work, it has previously been shown that genetically engineered viruses can recognize specific semiconductor surfaces through the method of selection by combinatorial phage display [8]. Additionally, it is known that liquid crystalline structures of wild-type viruses (Fd, M13, and TMV) are adjustable by controlling the solution concentrations, solution ionic strength, and the external magnetic field applied to the solutions. Consequently, the specific recognition properties of the virus can be used to organize inorganic nanocrystals, forming ordered arrays over the length scale defined by liquid crystal formation. Using this information, it is possible to create self-assembled, highly oriented, self-supporting films from a phage and ZnS precursor solution. This system allowed them to vary both the length of bacteriophage and the type of inorganic material through genetic modification and selection.

Electrochemical assembly

Highly ordered arrays of quantum dots may also be self-assembled by electrochemical techniques. A template is created by causing an ionic reaction at an electrolyte-metal interface which results in the spontaneous assembly of nanostructures, including quantum dots, onto the metal which is then used as a mask for mesa-etching these nanostructures on a chosen substrate.

Bulk-manufacture

Conventional, small-scale quantum dot manufacturing relies on a process called "high temperature dual injection" which is impractical for most commercial applications that require large quantities of quantum dots. A reproducible method for creating larger quantities of consistent, high-quality quantum dots involves producing nanoparticles from chemical precursors in the presence of a molecular cluster compound under conditions whereby the integrity of the molecular cluster is maintained and acts as a prefabricated seed template. Individual molecules of a cluster compound act as a seed or nucleation point upon which nanoparticle growth can be initiated. In this way, a high temperature nucleation step is not necessary to initiate nanoparticle growth because suitable nucleation sites are already provided in the system by the molecular clusters. A significant advantage of this method is that it is highly scalable.

Cadmium-free quantum dots

Cadmium-free quantum dots are also called "CFQD". In many regions of the world there is now a restriction or ban on the use of heavy metals in many household goods which means that most cadmium based quantum dots are unusable for consumer-goods applications. For commercial viability, a range of restricted, heavy metal-free quantum dots has been developed showing bright emissions in the visible and near infra-red region of the spectrum and have similar optical properties to those of CdSe quantum dots. Cadmium and other restricted heavy metals used in conventional quantum dots are of a major concern in commercial applications. For Quantum Dots to be commercially viable in many applications they must not contain cadmium or other restricted metal elements [9]. A new type of CFQD can be made from rare earth (RE) doped oxide colloidal phosphor nanoparticles [10]. Unlike semiconductor nanoparticles, excitation was due to UV absorption of host material, which is same for different RE doped materials using same host. Multiplexing applications can be thus realized. The emission depends on the type of RE, which enables very large stokes shift and is narrower than CdSe QDs. The synthesis is aqueous based, which eliminated issues of water solubility for biological applications. The oxide surface might be easier for chemical functionalizing more and chemically stable in various environments. Some reports exist concerning the use of such phosphor nanoparticles on biological targeting and imaging [11].

Optical Properties

Different sized quantum dots emit different color light due to quantum confinement [12]. Fluorescence spectra of CdTe quantum dots of various sizes. Different sized quantum dots emit different color light due to quantum confinement. An immediate optical feature of colloidal quantum dots is their coloration. While the material which makes up a quantum dot defines its intrinsic energy signature, the nanocrystal's quantum confined size is more significant at energies near the band gap. Thus quantum dots of the same material, but with different sizes, can emit light of different colors. The physical reason is the quantum confinement effect. Larger QD's gives redder fluorescence spectrum with lower energy. Conversely, smaller dots emit bluer (higher energy light. The coloration is directly related to the energy levels of the quantum dot. Quantitatively speaking, the band gap energy that determines the energy (and hence color) of the fluorescent light is inversely proportional to the size of the quantum dot. Larger quantum dots have more energy levels which are also more closely spaced. This allows the quantum dot to absorb photons containing less energy, i.e., those closer to the red end of the spectrum. Recent articles in nanotechnology and in other journals have begun to suggest that the shape of the quantum dot may be a factor in the coloration as well, but as yet not enough information is available. Furthermore, it was shown that the lifetime of fluorescence is determined by the size of the quantum dot[12]. Larger dots have more closely spaced energy levels in which the electron-hole pair can be

trapped. Therefore, electron-hole pairs in larger dots live longer causing larger dots to show a longer lifetime. As with any crystalline semiconductor, a quantum dot's electronic wave functions extend over the crystal lattice. Similar to a molecule, a quantum dot has both a quantized energy spectrum and a quantized density of electronic states near the edge of the band gap. Qdots can be synthesized with larger (thicker) shells (CdSe Qdots with CdS shells). The shell thickness has shown direct correlation to the lifetime and emission intensity.
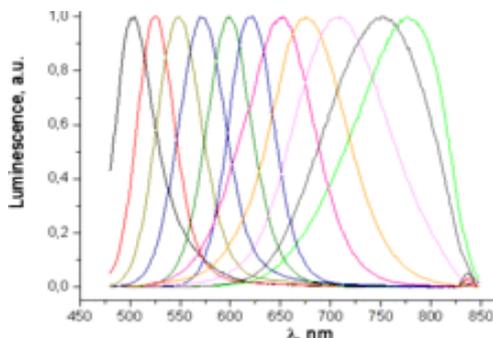

Fig. 2: Fluorescence spectra of CdTe quantum dots of various sizes[12]

Applications

Quantum dots are particularly significant for optical applications due to their high extinction co-efficient [13]. In electronic applications

they have been proven to operate like a single electron transistor and show the Coulomb blockade effect. Quantum dots have also been suggested as implementations of cubits for quantum information processing. The ability to tune the size of quantum dots is advantageous for many applications. For instance, larger quantum dots have a greater spectrum-shift towards red compared to smaller dots, and exhibit less pronounced quantum properties. Conversely, the smaller particles allow one to take advantage of more subtle quantum effects.

Researchers at Los Alamos National Laboratory have developed a wireless device that efficiently produces visible light, through energy transfer from thin layers of quantum wells to crystals above the layers. Being zero dimensional, quantum dots have a sharper density of states than higher-dimensional structures. As a result, they have superior transport and optical properties, and are being researched for use in diode lasers, amplifiers, and biological sensors. Quantum dots may be excited within a locally enhanced electromagnetic field produced by gold nanoparticles, which can then be observed from the surface Plasmon resonance in the photo luminescent excitation spectrum of (CdSe) ZnS nanocrystals. High-quality quantum dots are well suited for optical encoding and multiplexing applications due to their broad excitation profiles and narrow/symmetric emission spectra. The new generations of quantum dots have far-reaching potential for the study of intracellular processes at the single-molecule level, high-resolution cellular imaging, long-term in vivo observation of cell trafficking, tumor targeting, and diagnostics.
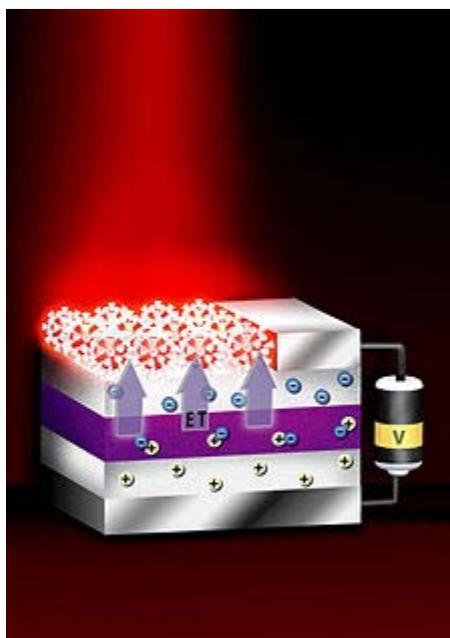

Fig. 3: Wireless device that efficiently produces visible light, through energy transfer from thin layers of quantum wells to crystals above the layers [44].

Computing

Quantum dot technology is one of the most promising candidates for use in solid-state quantum computation. By applying small voltages to the leads, the flow of electrons through the quantum dot can be controlled and thereby precise measurements of the spin and other properties therein can be made. With several entangled quantum dots, or cubits, plus a way of performing operations, quantum calculations and the computers that would perform them might be possible.

Biology

In modern biological analysis, various kinds of organic dyes are used. However, with each passing year, more flexibility is being

required of these dyes, and the traditional dyes are often unable to meet the expectation[14]. To this end, quantum dots have quickly filled in the role, being found to be superior to traditional organic dyes on several counts, one of the most immediately obvious being brightness (owing to the high extinction co-efficient combined with a comparable quantum yield to fluorescent dyes[15]) as well as their stability (allowing much less photo bleaching). It has been estimated that quantum dots are 20 times brighter and 100 times more stable than traditional fluorescent reporter for single-particle tracking, the irregular blinking of quantum dots is a minor drawback. The usage of quantum dots for highly sensitive cellular imaging has seen major advances over the past decade. The improved photo stability of quantum dots, for example, allows the acquisition of many consecutive focal-plane images that can be reconstructed into a

high-resolution three-dimensional image. Another application that takes advantage of the extraordinary photo stability of quantum dot probes is the real-time tracking of molecules and cells over extended periods of time[16]. Antibodies, streptavidin[17], peptides[18], nucleic acid aptamers[19], or small-molecule ligands can be used to target quantum dots to specific proteins on cells. Researchers were able to observe quantum dots in lymph nodes of mice for more than 4 months[20]. Semiconductor quantum dots have also been employed for in vitro imaging of pre-labeled cells. The ability to image single-cell migration in real time is expected to be important to several research areas such as embryogenesis, cancer metastasis, stem-cell therapeutics, and lymphocyte immunology. Scientists have proven that quantum dots are dramatically better than existing methods for delivering a gene-silencing tool, known as siRNA, into cells[21]. First attempts have been made to use quantum dots for tumor targeting under in vivo conditions. There exist two basic targeting schemes they are active and passive targeting. In the case of active targeting, quantum dots are functionalized with tumor-specific binding sites to selectively bind to tumor cells. Passive targeting utilizes the enhanced permeation and retention of tumor cells for the delivery of quantum dot probes. Fast-growing tumor cells typically have more permeable membranes than healthy cells, allowing the leakage of small nanoparticles into the cell body. Moreover, tumor cells lack an effective lymphatic drainage system, which leads to subsequent nanoparticle-accumulation. One of the remaining issues with quantum dot probes is their potential in vivo toxicity. For example, CdSe nanocrystals are highly toxic to cultured cells under UV illumination. The energy of UV irradiation is close to that of the covalent chemical bond energy of CdSe nanocrystals. As a result, semiconductor particles can be dissolved, in a process known as photolysis, to release toxic cadmium ions into the culture medium. In the absence of UV irradiation, however, quantum dots with a stable polymer coating have been found to be essentially nontoxic[20,22]. Then again, only little is known about the excretion process of quantum dots from living organisms[23]. These and other questions must be carefully examined before quantum dot applications in tumor or vascular imaging can be approved for human clinical use. Another potential cutting-edge application of quantum dots is being researched, with quantum dots acting as the inorganic fluorophore for intra-operative detection of tumors using fluorescence spectroscopy.

Photovoltaic devices

Quantum dots may be able to increase the efficiency and reduce the cost of today's typical silicon photovoltaic cells. According to an experimental proof from 2006 (controversial results[24]), quantum dots of lead selenide can produce as many as seven excitons from one high energy photon of sunlight (7.8 times the band gap energy)[25]. This compares favorably to today's photovoltaic cells which can only manage one exciton per high-energy photon, with high kinetic energy carriers losing their energy as heat. This would not result in a 7-fold increase in final output however, but could boost the maximum theoretical efficiency from 31% to 42%. Quantum dot photovoltaic's would theoretically be cheaper to manufacture, as they can be made "using simple chemical reactions". The generation of more than one exciton by a single photon is called multiple exciton generation (MEG) or carrier multiplication.

Light emitting devices

There are several inquiries into using quantum dots as light-emitting diodes to make displays and other light sources, such as "QD-LED" displays, and "QD-WLED" (White LED). In June, 2006, QD Vision announced technical success in making a proof-of-concept quantum dot display and shows a bright emission in the visible and near infra-red region of the spectrum. Quantum dots are valued for displays, because they emit light in very specific Gaussian distributions.

Pharmaceutical Applications

1. Used for live cells invivo imaging and detection[26] by observing the diffusion of individual glycine receptors in living neurons and the identification of lymph nodes in live animals by near-infrared emission during surgery.

2. For Synchronous Cancer Imaging, Therapy, and Sensing of Drug Delivery Based on Bi-Fluorescence Resonance Energy Transfer[27].
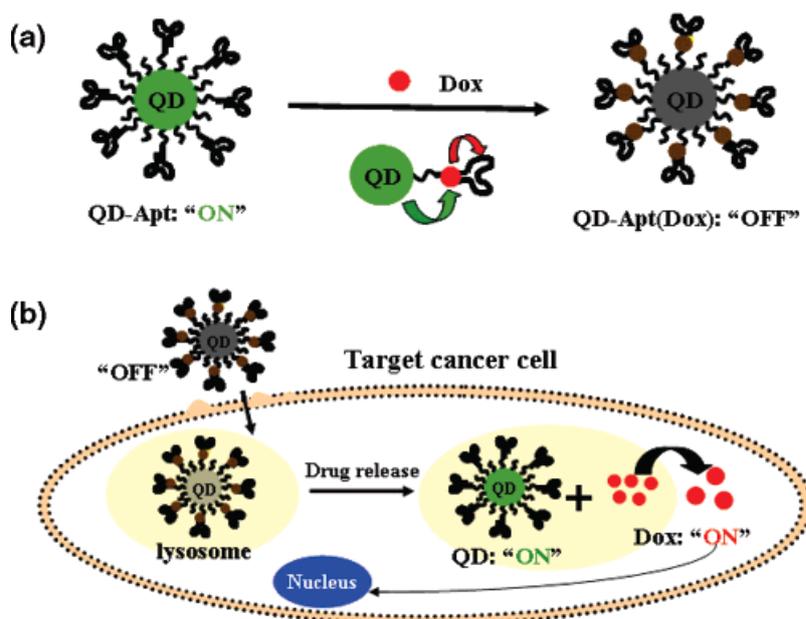

Fig. 4(a): Schematic illustration of QD-Apt (Dox) Bi-FRET system. (b). Schematic illustration of specific uptake of QD-Apt (Dox) conjugates into target cancer cell through PSMA mediates[27].

In the first step, the CdSe/ZnS core-shell QD are surface functionalized with the A10 PSMA aptamer. The intercalation of Dox within the A10 PSMA aptamer on the surface of QDs results in the formation of the QD-Apt(Dox) and quenching of both QD and Dox fluorescence through a Bi-FRET mechanism: the fluorescence of the QD is quenched by Dox while simultaneously the fluorescence of Dox is quenched by intercalation within the A10 PSMA aptamer resulting in the "OFF" state. Second step is the Schematic illustration of specific uptake of QD-Apt(Dox) conjugates into target cancer cell through PSMA mediate endocytosis. The release of Dox from the QD-

Apt(Dox) conjugates induces the recovery of fluorescence from both QD and Dox ("ON" state), thereby sensing the intracellular delivery of Dox and enabling the synchronous fluorescent localization and killing of cancer cells[27].

It is a novel quantum dot (QD)–aptamer(Apt)–doxorubicin (Dox) conjugate [QD–Apt(Dox)] for cancer targeting imaging, therapy, and sensing system. Functionalizing the surface of fluorescent QD with the A10 RNA aptamer, recognizes the extracellular domain of the prostate specific membrane antigen (PSMA), thus developed a targeted QD imaging system (QD-Apt) that is capable of differential uptake and imaging of prostate cancer cells that express the PSMA protein. The intercalation of Dox in the double-stranded stem of the A10 aptamer results in a targeted–QD-Apt(Dox) conjugate with reversible self-quenching properties based on a Bi-FRET mechanism. A donor–acceptor model fluorescence resonance energy transfer (FRET) between QD and Dox and a donor–quencher model FRET between Dox and aptamer result when Dox intercalated within the A10 aptamer. This simple multifunctional nanoparticle system can deliver Dox to the targeted prostate cancer cells and sense the delivery of Dox by activating the fluorescence of QD, which concurrently images the cancer cells[27].

3. Quantum-Dot Aptamer Beacons for the Detection of Proteins. Quantum-dot aptamer beacons provide for the sensitive detection of protein targets, such as thrombin, as well as nucleic acid targets and offer the promise of simplified, multiplex detection[28].

4. Used for effective sensing of biomolecules by fluorescence resonance energy transfer (FRET) from quantum dots (QDs) to graphene oxide (GO).The QDs were first modified with a molecular beacon (MB) as a probe to recognize the target analyte. The strong interaction between MB and GO led to the fluorescent quenching of QDs. Recognition of the target causes the increase in distance between the QDs and GO and the interaction between target-bound MB and GO became weaker, which significantly hindered the FRET and thus, increased the fluorescence of QDs. The change in fluorescent intensity results in detection of the target.

5. Bioconjugated quantum dots for *in vivo* molecular and cellular imaging. QDs can be used to target tumor biomarkers as well as tumor vasculatures with high affinity and specificity[29].

Advantages

1. In invivo labeling QD's offer several advantages over conventional organic fluorophores for labeling. Quantum dots have broader excitation spectra and a narrow more sharply defined emission peak. Due to these properties, a single light source can be used to excite multicolor quantum dots simultaneously without overlap. (Fig.5)[31-32].
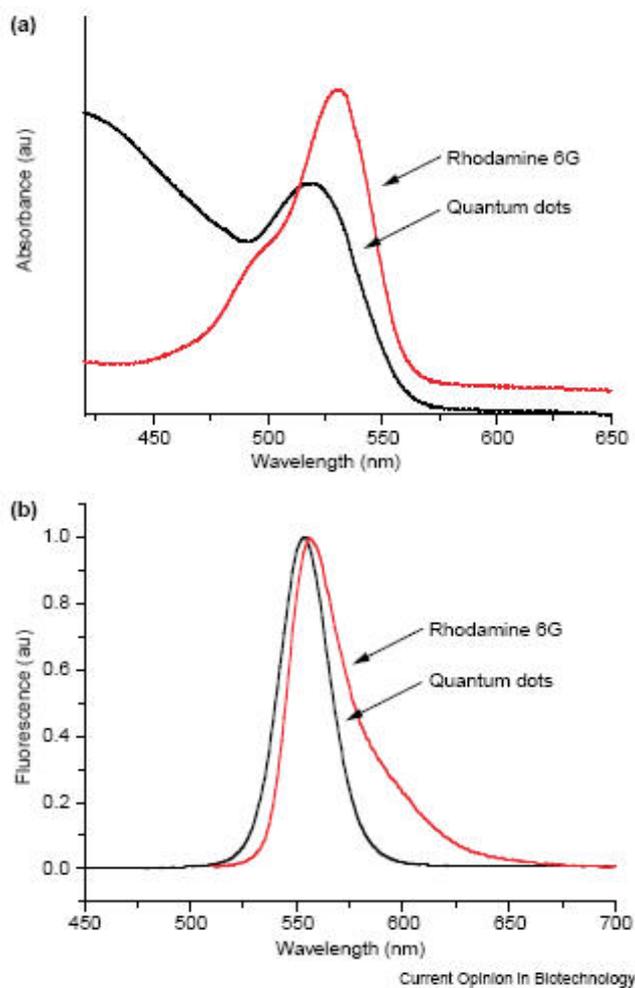

Fig. 5: The absorption (a) and emission (b) spectra of an organic dye (rodhamine 6G, red line) and quantum dots (black line)[32].

The organic dye has narrower adsorption and narrower fluorescence spectra while for quantum dots it is vice versa[32].

2. Quantum dots have high signal to noise ratio compared to organic dyes[30].The brightness of quantum dots compared to organic dyes is 10 to 20 times brighter[34].

3. Quantum dots are stable fluorophores due its inorganic composition which reduces the effect of photo bleaching compared to organic dyes (Fig6)[31,32]. QDs are 1000s of times more stable against photo bleaching than organic fluorophores. Researchers have taken advantage of this property not only to

accurately quantify emitted fluorescence but also to reduce (although not completely eliminate) tissue auto fluorescence [36].

4. Multicolor property of quantum dots allows the use of many probes to track several targets *in vivo* simultaneously[34]. Not only will this decrease the number of sections of tissue that need to be cut for biomarker analysis, but individual cells can be assessed for co expression of molecules. The ability to localize gene products in the same cell provides the basis for diagnosing some leukemia's. QD probes are particularly attractive because their broad absorption profiles allow simultaneous excitation of multiple colors, and their emission wavelengths can be continuously tuned by varying particle size and chemical composition. The emission peak width of QDs in solution is typically about 20 to 25 nm, although it can be as narrow as 14 nm (full width at half-maximum or FWHM) at room temperature[41]. Such a narrow emission light results in minimum spectral overlap between adjacent colors and allows fitting three to four colors into the visible spectrum.
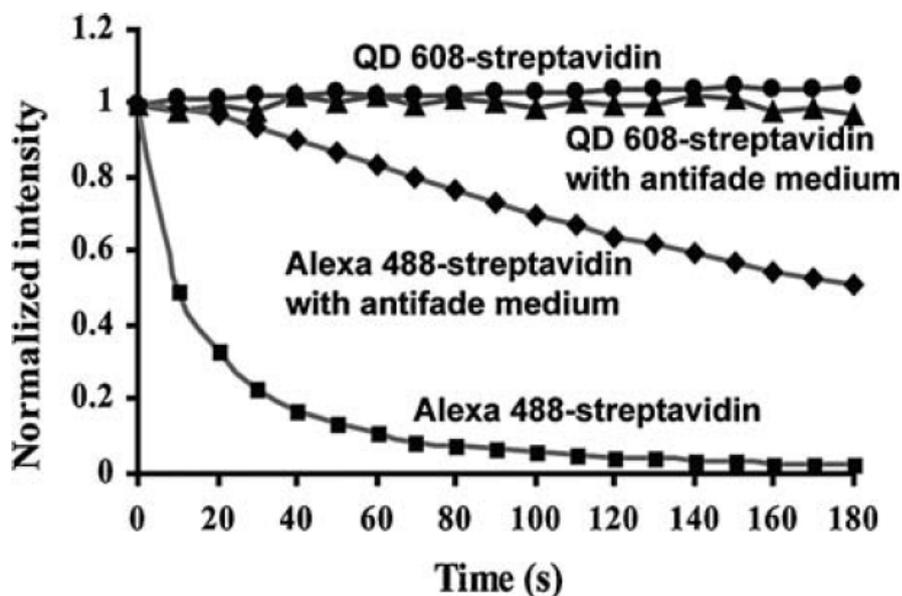

Fig. 6: Comparision of fluorescence intensity of organic dyes and quantum dots[31]

The fluorescence intensity of quantum dots do not diminish with time while organic fluorophores lose their intensities in 20s [31].Photo bleaching is reduced for quantum dots while organic dyes shows considerable photo bleaching [34].

5. The large Stokes shifts (difference between peak absorption and peak emission wave lengths) of QDs provide a means for separating the QD fluorescence from background auto fluorescence[39]. This factor becomes especially important for imaging tissue due to the high background auto fluorescence typically seen in formalin-fixed, paraffin-embedded tissue specimens.

6. The fluorescence time for quantum dots is about 10 to 40ns which is longer than the fluorescence of few nano seconds of organic dyes [31-33]. The time constant of quantum dots is longer than the time constant of organic fluorophores [34].
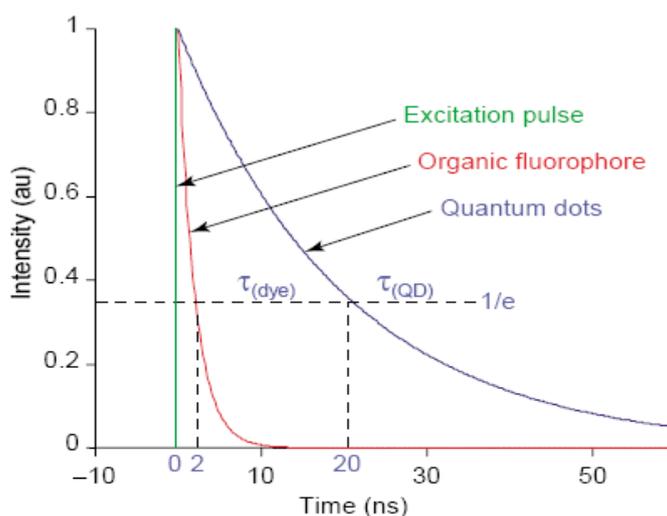

Fig. 7: The excitation decay of organic fluorophores and quantum dots[34].

Disadvantages of Quantum Dot Aptamers

1. Quantum dots have surface defects which can affect the recombination of electrons and holes by acting as temporary traps. This results in blinking and detoriates yield of the dots [33].

2. Quantum dots when placed in live cells exhibit aggregation and may kill the cells[39].

3. Biconjugation of quantum dots leads to an increase in size so making delivery into will be difficult[38].

4. Coating agents such as mercaptoacetic acid and CdTe or CdSe ions in the core can be cytotoxic [40-42].

5. Their metabolism and degradation is unknown. They may accumulate in kidney, spleen, and liver. Their clearance from the body is unknown[42].

6. The increasing production and use of quantum dot (QD) nanoparticles have the possibility of contaminating the aquatic and terrestrial ecosystems with wastes that may contain QDs[43].
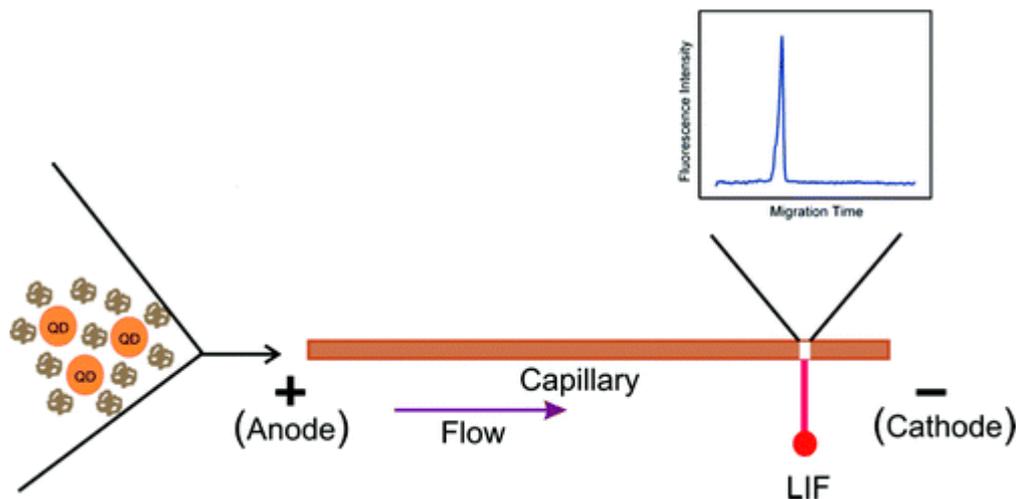

Fig. 8: The increasing production and use of quantum dot (QD) nanoparticles have the possibility of contaminating the aquatic and terrestrial ecosystems with wastes that may contain QDs [43].

A study that investigated the fluorescence and electrophoretic mobility of carboxylic or amine polyethylene glycol (PEG)-functionalized CdSe/ZnS QDs in the presence of two aquatic humic substances (HS), Suwannee River humic and fulvic acids, using capillary electrophoresis with laser-induced fluorescence detection showed initial enhancement in fluorescence of QDs at the onset of the interaction with HS, followed by fluorescence quenching at longer exposure with HS (>30 min)& also observed that the electrophoretic mobility of QDs increases with increasing concentration of HS, suggesting an increase in the ratio in charge to hydrodynamic size of the nanoparticles. To determine if the QDs degraded upon interaction with HS, the HS-QD mixtures were dialyzed to separate free Cd2+ from intact QDs, followed by analysis of the solutions using inductively coupled plasma-mass spectrometry [43].

CONCLUSION

Semiconductor quantum dots (QDs) are tiny light-emitting particles on the nanometer scale, and have wide applications for simultaneous imaging, sensing, and targeted drug delivery. In comparison with organic dyes and fluorescent proteins, they have unique optical and electronic properties, with size-tunable light emission, superior signal brightness, resistance to photo bleaching, and broad absorption spectra for simultaneous excitation of multiple fluorescence colors. When linked with targeting ligands such as antibodies, peptides or small molecules, QDs can be used to target tumor biomarkers as well as tumor vasculatures with high affinity and specificity. Coating of QD's can be cytotoxic. Biconjugation of dots increases the size causing difficulty in delivery to cells. These QD's can also cause pollution of water systems. Despite of disadvantages there is a great scope for quantum dots in research for medical and pharmaceutical applications.

REFERENCES

1. http://www.columbia.edu/cu/chemistry/fac-bios/brus/group/pdf-files/seminanowebsite-2007.
2. http://hdl.handle.net/1721.1/11129.
3. Murray CB, Kagan CR, Bawendi MG. Synthesis and Characterization of Monodisperse Nanocrystals and Close-Packed Nanocrystal Assemblies. Annual Review of Materials Research.2000;30(1):545-610.
4. Ekimov AI, Onushchenko AA. Quantum size effect in three-dimensional microscopic semiconductor crystals. JETP Lett.1981;34:345-349.
5. Reed MA, Randall JN, Aggarwal RJ, Matyi RJ, Moore TM, Wetsel AE. Observation of discrete electronic states in a zero-dimensional semiconductor nanostructure. Phys Rev Lett .1988;60(6):535-537.
6. Silbey, Robert J.; Alberty, Robert A. Bawendi, Moungi G. Physical Chemistry; 4th ed. John Wiley &Sons: 2004.
7. Lee SW, Mao C, Flynn CE, Belcher AM. Ordering of quantum dots using genetically engineered viruses. Science.2002;296(5569):892.
8. Whaley SR, English DS, Hu EL, Barbara PF, Belcher AM. Selection of peptides with semiconductor binding specificity for directed nanocrystal assembly. Nature.2000;405 (6787):665.
9. http://www.nanocotechnologies.com/content/AdvancedMaterials/CadmiumFreeQuantumDotsQFQDHeavyMetalFree.aspx.
10. http://www.nanomaterialstore.com/nano-phosphor.php.
11. Beaurepair B, Boilot J et al. Functionalized Fluorescent Oxide Nanoparticles: Artificial Toxins for Sodium Channel Targeting and Imaging at the Single-Molecule Level Nano Lett. 2004;4:11.
12. VanDriel AF. Frequency dependent spontaneous emission rate from CdSe and CdTe nanocrystals: Influence of dark states. PhysicalReviewLetters.2005; 95(23):236804.
13. Leatherdale CA,Woo WK, Mikulec FV, and Bawendi MG. On the Absorption Cross Section of CdSe Nanocrystal Quantum Dots. J. Phys. Chem. B.2002;106(31): 7619-7622.
14. Walling, Novak MA, Shepard. Quantum Dots for Live Cell and In Vivo Imaging. Int. J.Mol.Sci. 2009;10(2):441-491.
15. Michalet X, Pinaud FF, Bentolila LA, Tsay JM, Doose S, Li JJ, Sundaresan G, Wu AM, Gambhir SS,Weiss S . Quantum Dots for Live Cells, in Vivo Imaging and Diagnostics .Science 2005;307(5709):538-544.

16. Dahan M, Lévi S, Luccardini C, Rostaing P, Riveau B, Triller A .Diffusion dynamics of glycine receptors revealed by single-quantum dot tracking Science.2003;302(5644): 442-445.
17. Howarth M, Liu W, Puthenveetil S, Zheng Y, Marshall LF, Schmidt MM, Wittrup KD, Bawendi MG, Ting AY. Nat Methods, Monovalent, reduced-size quantum dots for imaging receptors on living cells. Nature methods.2008;5(5):397-399.
18. Akerman ME, Chan WC, Laakkonen P, Bhatia SN, Ruoslahti E. Nanocrystal targeting in vivo. Proceedings of the National Academy of Sciences of the United States of America. 2002; 99(20):12617-21.
19. Dwarakanath S, Bruno JG, Shastry A, Phillips T, John AA, Kumar A, Stephenson LD.Quantum dot-antibody and aptamer conjugates shift fluorescence upon binding bacteria. Biochemical and biophysical research communications. 2004;325(3):739-743.
20. Ballou. B, Lagerholm. Bc, Ernst. La, Bruchez. Mp, Waggoner. As. Noninvasive imaging of quantum dots in mice. Bioconjugate chemistry.2004;15(1):79-86.
21. http://newswise.com/articles/view/542018/..Pelley JL, Daar AS, Saner MA. State of academic knowledge on toxicity and biological fate of quantum dots. Toxicological sciences: an official journal of the Society of Toxicology.2009;112(2):276-96.
22. Choi HS, Liu W, Misra P, Tanaka E, Zimmer JP, Itty Ipe B, Bawendi MG, Frangioni JV. Renal clearance of quantum dots. Nature biotechnology.2007;25(10):1165-70.
23. Service, Rf. Shortfalls in electron production dim hopes for MEG solar cells. Materials Research Society fall meeting, Science;322(5909):1784.
24. David Talbot.TR10: Nanocharging solar. Technical review2007.
25. Michalet X, Pinaud FF, Bentolila LA, Tsay JM, Doose S, Li JJ, Sundaresan G,Wu AM, Gambhir SS, and Wess S. Quantum Dots for Live Cells, in Vivo Imaging, and Diagnostics. Science. 2005;307(5709):538-544
26. Vaishali Bagalkot, Liangfang Zhang, Etgar Levy-Nissenbaum, Sangyong Jon, Philip W. Kantoff, Robert Langer, and Omid C. Farokhzad. Quantum Dot-Aptamer Conjugates for Synchronous Cancer Imaging, Therapy, and Sensing of Drug Delivery Based on Bi-Fluorescence Resonance Energy Transfer, NANO LETTERS.2007;7(10):3065-3070.
27. Matthew Levy, Sean F. Cater, and Sandrew D. Ellington. Quantum-Dot Aptamer Beacons for the Detection of Proteins, ChemBioChem.2005;6:2163-2166.
28. Andrew M. Smith, Hongwei Duan, Aaron M. Mohs, and Shuming Nie. Bioconjugated Quantum Dots for In Vivo Molecular and Cellular Imaging, Adv Drug Deliv Rev.2008; 60(11):1226-1240.
29. Kawasaki et al. Nanotechnology, nanomedicine, and the development of new, effective therapies for cancer. Nanomedicine: Nanotechnology, Biology, and Medicine.2005; 1:101-109.
30. Alivisatos, et al. Quantum dots as cellular probes. Annu Rev Biomed Eng 2005;7:55-76.
31. Chan et al. Luminescent quantum dots for multiplexed biological detection and imaging. Current opinion in biotechnology.2002;13:40-46.
32. Michalet et al. Quantum dots for live cells, in vivo imaging, and diagnostics. Science. 2005;307(5709):538-544.
33. Gao et al. In vivo molecular and cellular imaging with quantum dots. Current opinion in biotechnology.2005;16:63-72.
34. Shin et al. Nanoscale controlled self-assembled monolayers and quantum dots. Current opinion in chemical biology. 2006;10(5):423-429.
35. Yezhelyev MV, Gao X, Xing Y, Al-Hajj A, Nie SM, O'Regan RM. Emerging use of nanoparticles in diagnosis and treatment of breast cancer. Lancet Oncol. 2006;7:657–667.
36. Rogach et al. Infrared-emitting colloidal Nanocrystal: synthesis, assembly, spectroscopy, and applications. Small. 2007;3(4): 536-557.
37. Weng et al. Luminescent quantum dots: a very attractive and promising tool in biomedicine. Current medicinal chemistry.2006;13:897-909.
38. Fu, et al. Semiconductor nanoparticles for biological imaging. Current opinion in neural biology. 2005;15:568-575.
39. Hardman R. A toxicologic review of quantum dots: toxicity depends on physicochemical and environmental factors. Environmental Health Perspectives.2006;114(2):165-172.
40. Zhong XH, Feng YY, Knoll W, Han MY. Alloyed ZnxCd1-xS nanocrystals with highly narrow luminescence spectral width. J Am Chem. Soc.2003;125:13559-13563.
41. Alivisatoss AP. Semiconductor clusters, nanocrystals, and quantum dots. Science.1996;271:933-937.
42. Mary Dawn Celiz,Luis A.Colon, David F.Watson, and Diana S.Aga. Study of effects of humic and fulvic acids on quantum dot nanoparticles using capillary electrophoresis with laser- induced fluorescence detection.Environ.Sci.Technol.,2011;45(7):2917-2924.
43. https://www.london-nano.com/news-and-events/media-gallery/image/quantum-dot-lasers-fabricated-on-a-silicon-substrate
44. http://www.lanl.gov/orgs/pa/newsbulletin/2004/06/10/text02.shtml