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QUANTUM DOTS FOR DRUG DELIVERY AND THERAPY

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Abstract:

Nanoparticles emerged as a promising tool in drug targeting, since, after appropriate modification, they are able to deliver their payload to specific sites, like tissues, cells, or even certain cellular organelles. Quantum dots (QD's) are one of the nanoparticles that are used in imaging, detection and targeting. They are nanometer-size luminescent semiconductor crystals, which range from 2 to 10 nanometers in diameter (about the width of 50 atoms), whose electronic characteristics are closely related to the size and shape of the individual crystal and have unique chemical and physical properties. Quantum dots have tunable optical properties which can be useful in a wide range of applications from multiplexed analysis such as DNA detection and cell sorting and tracking, to *in vivo* imaging and diagnostics. Quantum dots are ideal candidates as drug delivery systems because of their outstanding features like a small and uniform size, unique optical properties for most sensitive detection and modifiable surfaces. Newly engineered quantum dots with integrated targeting, imaging and therapeutic functionalities have become excellent material to study drug delivery in cells and small animals. Recent progress in the surface chemistry of quantum dots expanded their use in biological applications, reduced their cytotoxicity and rendered quantum dots a powerful tool for the investigation of distinct cellular processes, like uptake, receptor trafficking and intracellular delivery.

Key words: Quantum dots, nanoparticles, drug delivery, imaging, targeting.

Introduction:

Nanotechnology is the understanding of matter at the nanoscale, at dimensions between approximately 1 and 100 nanometers[1]. Because of their nano-size, nanoparticles have unique physical and chemical properties that give them

advantages as drug delivery carriers, or nano-carriers, and diagnosis probes. Owing to fundamental principles of quantum physics nanoscale materials have different properties than the properties of the same materials having larger dimensions[2].

When the dimension of a material is reduced from a large size, the properties remain the same at first, and then small changes occur, until finally when the size drops below 100 nm, dramatic changes in properties can occur. If only one length of a three-dimensional nanostructure is of nanodimension, the structure is referred to as a quantum well; if two sides are of nanometer length, the structure is referred to as a quantum wire. A quantum dot has all three dimensions in the nano range. Materials can be nanostructured for new properties and novel performance[3]. Moreover, at this size range, nanoparticles have a maximum surface:volume ratio, which makes it suitable for surface functionalization along with incorporation of good therapeutics load. Furthermore, due to their nano-size and tunable surface properties (enabling the synthesis of aqueous, injectable solutions and the development of passive or active targeted systems), nanoparticles potentially have better access to target sites as compared to conventional drug delivery carriers.

Over the past few decades quantum dots (QDs) have been an area of intense research due to their unique physical properties. Quantum dots, sometimes called artificial atoms, are tiny nanocrystals made of inorganic transition metal, that glow when stimulated by an external source such as ultraviolet (UV) light. How many atoms are included in the quantum dot determines their size and the size of the quantum dot determines the colour of light emitted. Gallium arsenide (GaAs) is a popular material out of which quantum dots can be made, because the effective mass of an electron and the shape of the crystal correlate at room temperature to form desirable properties.other than GaAs they are made up of cadmium selenide (CdSe), cadmium telluride (CdTe), indium phosphide (InP), and indium arsenide (InAs) as core elements inside a shell, usually zinc sulfide (ZnS)[4].

QDs are colloidal nanocrystalline semiconductors with unique photophysical and chemical properties along with exceptionally large surface-to-volume ratios. A quantum dot is a semiconductor whose excitons are confined in all three spatial dimensions. As a result, they have properties that are between those of bulk semiconductors and those of discrete molecules. The color of the emitted light depends on the size of the dots: the larger the dot, the redder the

light. As the dots shrink in size, the emitted light becomes shorter in wavelength, moving toward the blue. A rainbow of colors can be emitted from a single material simply by changing the dot size.

They were discovered at the beginning of the 1980s by Alexei Ekimov in a glass matrix and by Louis E. Brus in colloidal solutions. The term "Quantum Dot" was coined by Mark Reed. QDs range from 2-10 nm (10-50 atoms in diameter).

Properties:

1. These nanoparticles have unique optical and electronic properties on account of quantum confinement effect.
2. Fluorescence semiconductor quantum dots have a tunable absorption spectrum, which is very broad, extending from the ultraviolet to a cut-off wavelength in the visible spectrum.
3. quantum dots have brighter emission and good photostability
4. Quantum dots can be molded into different shapes and coated with a variety of biomaterials.
5. Size of the dots controls its emitting colour. e.g. 2nm Quantum dots luminescence bright green,5 nm Quantum dots –luminescence red
6. As size of quantum dots decreases, the wavelength it emits turns shorter.
7. Quantum dots have a broad excitation range.
8. Quantum dots have precise emission wavelength, so the spectra doesn't overlap in multiple fluorescent emission[5].

Synthesis:

In large numbers, quantum dots may be synthesized by means of a colloidal synthesis. Colloidal synthesis is by far the cheapest and has the advantage of being able to occur at benchtop conditions. It is acknowledged to be the least toxic of all the different forms of synthesis. Highly ordered arrays of quantum dots may also be self assembled by electrochemical techniques [6].

Fabricating quantum dots with good control over size, material purity, and placement on a given surface is a difficult task. Two approaches are common: the "top-down approach" where a large piece of material is chiseled down to a small quantum dot using the process of lithography and etching. A slight variation of this approach is *electrostatic*

delineation of quantum dots where metal pads are placed on a thin layer of material. A negative potential is applied to the pads, which drives away the electrons from underneath, leaving a small puddle of electrons in the center; these form a quantum dot. However, these quantum dots are only in the nanometer scale in one dimension. The other two dimensions are limited by the resolution of the lithography.

The second approach is "bottom up" and is known as self-assembly. Here, spontaneous congregation of atoms into structures of well defined size (of a few nanometers) and shape form quantum dots.

Directed self assembly is a refinement of the process, where the spontaneous congregation is allowed to proceed on a patterned substrate that offers preferred sites for nucleation of quantum dots. This is also referred to as *template-based self assembly* since the patterned substrate acts as a template for spatially ordering the quantum dots[7].

QD synthesis can be tailored to specific requirements, with core, shell and coating characteristics all affecting photochemical properties. QDs may be manufactured with diameters from a few nanometers to a few micrometers, and size distribution can be controlled within 2% [8] using precise growth techniques, involving high annealing temperatures [9]. Choice of shell and coating are gaining particular importance, as the shell stabilises the nanocrystal and to some extent alters the photophysical properties, whilst the coating confers properties to the QD which allow its incorporation into a desired application.

In a general synthetic method, organometallic liquid precursors are injected into hot (290°-350°C) coordinating solvents, such as trioctylphosphine oxide (TOPO) and trioctylphosphine (TOP). Coordinating solvents stabilize the bulk semiconductors and prevent aggregation as the quantum dots grow. After the desired growth time is reached in relation to size and optical properties, aliquots are removed from the reaction mixture, cooled, and purified. Purification steps, such as precipitation in anhydrous methanol or butanol, are performed and can serve as size exclusion steps to ensure uniformity. The uniformity and average nanocrystal size can be affected by temperature differences of less than 1°C. If suitable conditions for injection temperature and growth time are maintained during synthesis, separate size-selection steps are not necessary to achieve a narrow size distribution.

Nanoparticles synthesized in this manner result in the semiconductor core surrounded by TOPO, in a nonpolar solvent such as chloroform. The semiconductor core material must be protected from degradation and oxidation to maintain

and optimize quantum dot performance. Bare core nanocrystals have drawbacks like structural imperfections and very unstable structure which is prone to photochemical degradation [10].

Both shell growth and surface modification enhance stability and performance and increase photoluminescence of the core. Shell growth provides protection by coating or capping the core with a thin layer of a second semiconductor material with a higher band gap. The semiconductor shells are also inorganic in nature, commonly employing compounds such as zinc sulfide or zinc selenide (ZnS, ZnSe). Surface protection can also be achieved through modification of the core, which is carried out in organic solvents, such as alkylamines, but including a semiconductor shell layer is most common protection method.

The inorganic core-shell semiconductor nanoparticles, once prepared, are soluble in nonpolar solvents only. To have utility in biological applications, nanoparticles must be soluble in aqueous solutions and require surface modifications to achieve biocompatibility. Two general approaches have been used to achieve aqueous solubility: surface ligand exchange and amphiphilic polymer coatings.

Two different surface ligand exchange approaches can be used for solubilization. The first method involves exchanging the coordinating ligands (e.g. TOPO) on the quantum dot shell surface. The exchange process is similar to surface exchange reactions of the core described previously, and optimally results in the addition of a heterobifunctional ligand. A bifunctional ligand employs a hydrophobic end to displace the TOPO from the quantum dot, while a hydrophilic end extends out into solution, aiding in solubility. Thiol groups are a common functionality employed to link to the shell surface, but this functional group can detach from the quantum dot surface in a reversible fashion.

The second surface exchange method involves silane derivatives, used to displace the coordinating ligand on the quantum dot surface, and eventually resulting a layer of silica around the quantum dot. The reaction conditions, in particular reaction time, contribute to the thickness of the silica shell. Silica shell growth around a core/shell quantum dot involves mixing the quantum dots with a compound at basic pH over several days while continually heating, cooling, and washing the solution. Silica shell growth requires multiple purification steps. quantum dots coated with silica are more stable due to the high degree of crosslinking between the silane molecules. This extensive cross-linking

ensures solubility. An additional advantage of using silica shell coatings is that the procedures do not change if a different type of siloxane is used.

Alternately, core/shell semiconductor quantum dots can be coated with an amphiphilic polymer,

such as octylamine-modified polyacrylic acid, cyclodextrin[10]. This approach utilizes the nonpolar quantum dot shell for interaction with the hydrophobic portion of the polymer, allowing the hydrophilic portion of the polymer to increase solubility. Growing an amphiphilic polymer shell around quantum dots is similar to coating with silica, but instead of forming the shell by displacing the TOPO molecules left on the surface during synthesis, the amphiphilic polymer takes advantage of the hydrophobic nature of the coordinating ligands. The interactions associated with this type of solubilization are similar to those in micelle formation.

Surface coating has a profound impact on the cellular uptake of QDs. To make QDs biocompatible and stable polyethylene glycol (PEG) is used. PEG modification essentially blocks non-specific QD delivery into the cells. On the other hand, QDs coated with COOH were internalized quickly and with large amount by both cancerous and non-cancerous cells [11].

For biological applications, quantum dots must be linked to biomolecules without altering the biological activity of the conjugated form. A number of successful conjugation methods have been developed, including covalent and non-covalent attachment methodologies. Specific conjugation methodologies include direct adsorption on the quantum dot surface, the use of inert polymer coatings, or biotin-streptavidin linkages.

Covalent attachment is a simple, effective way of linking biomolecules to quantum dots and contributes minimally to the overall bioconjugate size. Another common conjugation scheme employs the biotin-streptavidin linkage, which requires coupling of the quantum dot to streptavidin. Quantum dot-streptavidin conjugates are useful because a wide range of proteins and other biomolecules can be biotinylated. These conjugates have applications in staining and labeling [12], live tracking, and drug screening [13]. Chitosan, a natural polymer with one amino group and two hydroxyl groups, has been used for intracellular delivery of specific molecules, and can be attached to the QD surface [10].

The development of proton-resistant surface coatings also opens new opportunities for directly observing and studying QDs in harsh physiological environments. In particular, acid-stable QDs could be used as model probes to predict the

oral absorption and biodistribution of therapeutic nanoparticles. Fluorescence emission of acid-stable QDs would be relatively stable in the gastrointestinal tract, specifically in the stomach, where the pH can be as low as 1 2. Therefore, the uptake and biodistribution of orally administered nanoparticlescould be tracked in real time Due to their colloidal and fluorescence stability in highly degradative gastric fluids, protonresistant QDs have promise as a new class of nanoparticles for oral delivery applications [14].

Uptake of QDs:

QD cellular uptake involves three major stages including endocytosis, sequestration in early endosomes, and translocation to later endosomes or lysosomes. The endocytosis was probably assisted by receptors specific to ligands with negative charges. These findings could be exploited to reduce non-specific targeting, thereby improving specific targeting of QDs in cancer diagnosis and treatment applications. The findings are also important in understanding the cytotoxicity of QDs and other nanomaterials in general and in emphasizing the importance of strict environmental control of nanoparticles [11].

Advantages of quantum dots

1. Quantum dots are much more resistant to degradation than other optical imaging probes, allowing them to track cell processes for longer periods of time and shed new light on molecular interactions.
2. As Quantum dots are nanocrystals they provide good contrast for imaging with an electron microscope as scattering increases.
3. Quantum dots have size-tunable emission (from UV to IR)
4. Fluorescence lasts for longer time as compared to conventional dyes.
5. Quantum dots have increased optical activity with innumerable avenues of applications in biotechnology and life sciences.
6. Anti-counterfering measure- their extremely small size gives them great versatility by allowing them to be injected into many environments, including liquid mixtures, fabrics, and polymer matrices [5].

Applications: Quantum dots have properties that provide advantages beneficial for a number of different life science applications. The improved brightness and photostability exhibited by quantum dots are justification for their

increased use in imaging and labeling experiments. The ability to render quantum dots biocompatible and non-toxic extends their applicability to *in vivo* vasculature imaging and tracking. The robustness of their signal strength also affords utility in targeting and detection applications. Their simple, routine fabrication protocols and uniform spectral profiles are now allowing quantum dots to realize their full potential, as quantum dot applications are branching out into high throughput, multiplexed analyses and quantitative analysis of biomolecules *in vivo*.

The applications of QDs in experiments reveal that QDs are sensitive, stable, nontoxic, versatile fluorescent probes.To target the peptide-labeled QDs to specific tissues and cell types in vivo is believed important for diagnostics and therapeutics [15].

Biomedicine:

Among various nanomaterials, quantum dots (QDs) distinguish themselves in their far-reaching possibilities in many avenues of biomedicine. QDs are nanometersized fluorescent semiconductor crystals with unique photochemical and photophysical properties. Their much greater brightness, rock-solid photostability and unique capabilities for multiplexing, combined with their intrinsic symmetric and narrow emission bands, have made them far better substitutes for organic dyes in existing diagnostic assays [16]. These properties, combined with the development of ways to solubilize QDs in solution and to conjugate them with biological molecules, have led to an explosive growth in their biomedical applications [17]. Bioconjugated QD fluorescent probes offer a promising and powerful imaging tool for cancer detection, diagnosis and treatment [4]**.**

Imaging

Quantum dots, which range from about 2 to 10 nanometers across (roughly equivalent to a medium-sized protein), have distinct advantages over conventional fluorescent dyes. It has been estimated that quantum dots are 20 times brighter and 100 times more stable than traditional fluorescent reporters. By simply varying the crystal size, scientists can produce dots that emit light in a wide range of wavelengths, or colors, that are less prone to overlap than those of organic dyes. And whereas each organic dye must be excited with a specific wavelength of light, a single light source can excite quantum dots of many colors, so scientists can use the dots to label and detect multiple targets

simultaneously. In addition to this "multiplexing" capability, quantum dots are much brighter than organic dyes and retain their glow much longer [18].

Compared with the traditional organic fluorophores (e.g., organic dyes and fluorescent proteins), QDs have unique optical and electronic properties, such as larger absorption coefficients, size-tunable lightemission, superior signal brightness, resistance to photobleaching and simultaneous excitation of multiple fluorescence colors. In addition, the large-surface area of QDs is beneficial to covalently link to biorecognition molecules, such as peptides, antibodies, nucleic acids or small-molecule ligands for further application as fluorescent probes.

A recent advancement in QDs technology is the use of QDs for near infrared (NIR) imaging (700–1000 nm wavelength range) as an imaging probe [19,20]. The main advantage of NIR QDs over its counterpart, visible QDs, is that it increases the depth of tissue penetration, allowing for more accurate and sensitive detection of photons *in vivo*. Additionally, NIR QDs evade the problem of auto-fluorescence associated with optical imaging because of the naturally-occurring compounds present in animal tissue. The use of NIR QDs for *in vivo* imaging was demonstrated for lymphatic mapping in animal models [21], and for biological imaging, using InAs/ZnCdS as a core/shell. NIRQDs coated with PEG allowed imaging of tumor vasculature as deep as 200 um, contrary to the visible QDs-generated images with very poor vascular contrast [22].

QDs-As diagnostics in clinical applications

The most important potential applications of Quantum dots (QDs) are for cancer diagnosis. Luminescent and stable QD bioconjugates enable visualization of cancer cells in living animals. QDs can be combined with fluorescence microscopy to follow cells at high resolution in living animals. The use of QDs for *in vivo* cancer targeting and imaging in live mice was first reported by Gao *et al*. [6]. They showed the feasibility of *in vivo* imaging by subcutaneous injection of prostate cancer cells labeled with QDs. They also demonstrated the use of systemic injection of multifunctional QD probes that enable multicolor fluorescence imaging of cancer cells with high sensitivity [23]. Bagalkot and colleagues showed that QDs can be used for both imaging and therapy; QD-apatamer (Apt)-doxorubicin (Dox) conjugate was used for targeted cancer therapy and imaging of prostate cancer cells that express prostate-specific membrane antigen (PSMA) protein [8]. Significantly, these multifunctional QDs facilitated the targeted delivery

and monitoring of doxorubicin release into tumor cells through activation of QDs as well as simultaneous imaging of the tumor tissue [10].

QDs have been coated with a polyacrylate cap and covalently linked to antibodies for immunofluorescent labelling of breast cancer marker Her2 carbohydrate encapsulated QDs with detectable luminescent properties are useful for imaging of cancer [24].

Owing to their unique properties such as photostability, size- and composition-tunable emission properties (from visible to infrared wavelengths), and their ability to deliver multiple diagnostic or targeting agents, QDs have emerged as a promising nanotechnology for cancer detection. Furthermore, utilization of NIR QDs can potentially not only maximize the depth of tissue penetration compared to conventional imaging, but also can enhance the accuracy and photon detection sensitivity in an *in vivo* systems [10].

Another application of QDs is for viral diagnosis. Rapid and sensitive diagnosis of Respiratory Syncytial Virus (RSV) is important for infection control and development of antiviral drugs. Antibody- conjugated nanoparticles rapidly and sensitively detect RSV and estimate relative levels of surface protein expression. A major development is the use of dual-colour QDs or fluorescence energy transfer nanobeads that can be simultaneously excited with a single light source. A QD system can detect the presence of particles of the RSV in a matter of hours. It is also more sensitive, allowing detection of the virus earlier in the course of an infection. When an RSV virus infects lung cells, it leaves part of its coat containing F and G proteins on the cell's surface. QDs have been linked to antibodies keyed to structures unique to the RSV coat. As a result, when QDs come in contact with either viral particles or infected cells they stick to their surface[24].

QDs could be used to study cell differentiation and development in embryogenesis. Quantum-dot staged micro beads, a new tool for identifications of target biomolecules have been applied in multiplexed biological analysis.

Mesenchymal stem cells (MSCs) are multipotent cells with the potential to differentiate into bone, cartilage, fat and muscle cells and are being investigated for their utility in cell-based transplantation therapy. Fluorescent QDs label MSC effectively in an *in vitro* co-culture model. QDs are easy to use, show a high yield and survival rate with minimal cytotoxic effects. Dose-dependent effects suggest limiting MSC QD exposure [25].

Drug screening:

A successful drug must be able to bind to several different molecular targets to achieve the desired effect, and steer clear of other targets to avoid side-effects. Testing could be made a simple matter by attaching quantum dots of different colors to the various targets. A good hit might be a drug that displaces blue, aqua and green nanocrystals where you want it to attach, but doesn't displace red, yellow and orange ones at proteins that indicate side-effects [26]. Mattheakis *et al*. (2004) described a quantum dots system for drug screening and studying mixed cell populations, consisting of encoding (different types of cells are tagged with different-colored quantum dots), imaging and decoding single cells. QDs-cells can be used to potentially multiplex virtually any microscope-based cell assay with an optical readout. Typically HTS measures a single target and binary in its output (i.e., it shows if the unknown compound produces an effect or not). Using different-colored quantum dots to tag different target, compounds against multiple targets can be screened in parallel which is called Multi-target High-throughput Screening (MTHTS). Even if the effect on some target is not desired one, it could be of interest for another target. Most importantly, based on MTHTS, a lead with different effects, different leads with different effects or multiple leads with same effect can be gained from multiple screening models simultaneously in one screening. QDs-based multiplexing assay being used to drug high-throughput screening can enhance screening throughput, which can achieve bi-high-throughput even multi- high-throughput screening [26, 27].

Drug delivery: University of Illinois researchers developed a nanoneedle that releases quantum dots directly into the nucleus of a living cell when a small electrical charge is applied. The quantum dots are tracked to gain information about conditions inside the nucleus. The group coated a single nanotube, only 50 nanometers wide, with a very thin layer of gold, creating a nanoscale electrode probe. They then loaded the needle with quantum dots. A small electrical charge releases the quantum dots from the needle. This provides a level of control not achievable by other molecular delivery methods, which involve gradual diffusion throughout the cell and into the nucleus [28].

1. ZnO QDs have also been evaluated as a platform for targeted and pH responsive intracellular delivery of an anticancer drug. The cancer targeting feature is endowed by conjugating folic acid on to the surface of ZnO–NH_2 QDs *via* an amidation reaction. Doxorubicin (DOX) is then successfully loaded onto the folic

acid functionalized ZnO QDs by capitalizing on its marked tendency towards the formation of metal complexes. Drug loaded ZnO-FA QDs remain stable at physiological pH but readily disintegrate in the mildly acidic intracellular environment of cancercells as validated by a drug release profile, confocal microscopy and a cell-cytotoxicity assay. Compared to the conventional drug nanovector, ZnO-FA QDs themselves manifest a significant therapeutic activity after reaching their targeted site, therefore, combined DOX and ZnO QDs can be more efficacious than either alone. Hence, this approach provides a valuable ZnO QDs-based nanovector that can simultaneously realize targeting, diagnosis, and therapy of cancercells [29].

2. Scientists in Switzerland studied that giving quantum dots an icing-like cap of certain sugars makes these nanoparticles accumulate in the liver but not other parts of the body. That selective targeting could be used to deliver anti-cancer drugs to one organ, without causing the body-wide side-effects that occur with existing cancer drugs, they suggest. They described development of a new type of quantum dot coated with certain sugar molecules that are attracted to receptors in specific tissues and organs. In a study with laboratory mice, the scientists coated quantum dots with either mannose or galactosamine, two sugars that accumulate selectively in the liver. The sugar-coated dots became three times more concentrated in the mice livers than the regular dots, demonstrating their higher specificity, the researchers say [30].
3. The potential of using a nanoparticle drug delivery approach provides a novel therapeutic strategy for treating lung diseases. The ability to target specific cells in the lung without exposing other pulmonary tissue or distant organs to detrimental actions of drugs is an exciting avenue to explore The ability to provide targeted therapeutic delivery in the lung would be a major advancement in pharmacological treatments for many pulmonary diseases. Critical issues for such successful delivery would require the ability to target specific cell types, minimize toxicity (e.g., inflammatory response), and deliver therapeutic levels of drugs. Our in vitro findings demonstrate that QD-Dox enhances intracellular uptake compared with free drug. We also demonstrate that Dox is released from the QD-Dox formulation and migrates to the nucleus (site of bioactivity), whereas the QDs remain in the cytosol. QDs as a carrier system present distinct advantages of having both diagnostic and therapeutic benefits [31].The ease of formulation and uniformity of QDs make a more efficient approach to lung cell targeting.

4. Adeli et al of Lorestan University and Tehran University of Medical Sciences, Iran, synthesized pseudopolyrotaxanes (Ps-PR) consisting of*α*-cyclodextrin rings, polyethylene glycol axes and end triazine groups. Dissociation of the *α*-cyclodextrin rings from the polyethylene glycol axes was avoided by the host–guest relationship between its end triazine groups and *β*-cyclodextrins conjugated onto the surface of quantum dots (*β*-CD-*graft*-QDs), leading to a new type of the dynamic polyrotaxanes in which QDs play the role of stoppers noncovalently. Stability of the synthesized supramolecules was depended on the efficiency of the host–guest relationships between the end triazine groups of Ps-PR and*β*-CD-*graft*-QDs through which release of *α*-cyclodextrin rings from the polyethylene glycol axes was controlled [32].
5. To prove the efficacy of the synthesized supramolecules as drug delivery systems (DDSs) cisplatin (Cis-Diamminedichloroplatinum (CDDP) a platinum-based chemotherapy drug) and folic acid as a tumor-recognition module were conjugated to their stoppers and they were subjected to the receptor-mediated endocytosis and release inside the cancer cells, murine colon adenocarcinoma tumor C26. Then, it was proved that these tumor-targeting DDSs are promising systems for future cancer therapy. Rate of the release of the drugs, conjugated to the functional groups of stoppers was also investigated [32].
6. After quantum dots are bioconjugated protein or peptide, single-molecule movement in single living cell can be track in real time. Another study provided new insight into erbB/HER receptor-mediated signal transduction. This study demonstrated that EGF-QDs (quantum dots bearing epidermal growth factor) were highly specific and potent in the binding and activated of the receptor (erbB1), being rapidly internalized into endosomes that exhibit active trafficking and extensive fusion. Similarly, when drug molecules are linked to the surface of quantum dots, the kinetics and transport of drug molecules can be recorded and tracked for a longer period of time, which help to understand the mechanism of diffusion, particle fusion and internalization into cells. The movement of different drug molecules tagged with quantum dots of different colors can also be studied simultaneously. In addition, the elaborate DDS that consist of drug molecules, quantum dots and target molecules (e.g., antibody or peptide) can be designed. After the DDS are transported into cancer cell guided by target molecules, under UV irradiation momently the photoluminescence of quantum dots trigger the DDS, and drug molecules are released into cancer

cells and kill them. Furthermore, under UV irradiation continuously, quantum dots behave photocatalysis of semiconductor nanocrystals. On the surface of quantum dots photochemical reactions take place resulting in a production of the cytotoxic singlet oxygen (O_2^-), which causing biomembrane of cancer cell oxidation and degradation [33].

Drug target identification and validation:

1. Recently Xu *et al.* (2003) described a new method for high-throughput and multiplexed SNPs (Single Nucleotide Polymorphisms) genotyping for using the Qbead system that employs quantum dots to encode microspheres used as a platform for multiplexed assays. By combining mixtures of quantum dots with distinct emission wavelengths and intensities, unique spectral barcodes are created that enable the high levels of multiplexing required for complex genetic analyses. In theory, N intensity levels with m colors will produce N^m-1 unique codes. For example, a combination of three colors and ten intensity levels theoretically would produce 999 unique codes. In practice, however, fewer unique codes may be produced due to spectral overlapping, fluorescence intensity variations and signal-to-noise requirements. Nonetheless, a realistic scheme using 5-6 colors with six intensity levels would be expected to yield at least 10000 to 40000 recognizable codes. So the Qds-encoded bead technology is the potential encoding capacity that enables the high level of multiplexing necessary for genetic analysis. This technology will improve efficiency of drug target identification and validation. Gene analysis using QDs-encoded bead system is an ideal technology that has the powerful potential to accelerate the discovery of new targets and to improve the efficiency of the drug discovery process [34].
2. The use of gelatin *in situ* for the production of CdTe QD–gelatin nanocomposites was studied (Gun'ko et al 2007). The gelatin–QD composites readily pass through the cell membrane and illuminate the cytoskeleton of the THP-1 macrophage cells. In comparison to the original thioglycolic acid stabilized QDs, the gelatin–QDs display much lower rates of toxicity (assessed through decreased cell permeability and an aversion to increased lysosomal pH), which are comparable to those of control samples. The free cadmium demonstrates the highest responses for both of these tests and quickly induces cellular apoptosis [35].

Quantum dots as tags for other drug carriers

The second type of QD application in traceable drug delivery is more straightforward – labeling a conventional drug carrier with QDs, which serve as photostable fluorescent reporters. The majority of current drug carriers are made of polymers, such as poly(lactic-co-glycolic acid) and polyethyleneimine (PEI), and fewer are based on inorganic materials. A common limitation shared by these delivery vehicles is the lack of an intrinsic signal for long-term and real-time imaging of drug transport. This problem has been partially addressed by conjugation with organic fluorophores. However, the photobleaching problem associated with essentially all organic dyes (including fluorescent proteins) prevents long-term tracking or imaging. In this context, QDs become a natural choice because of their unique spectral properties. Indeed, they have been used to label both organic and inorganic drug carriers and potentially even bacteria and viruses , with a burst of activity in the area of ODN and siRNA delivery.

Innovative approaches have opened up exciting opportunities in targeted DNA and RNA delivery. For example, after being treated with QD – oligonucleotides, cells with differential expression levels of the protein of interest, which correlates with QD fluorescence, can be isolated using fluorescence-activated cell sorting; and, if multicolor QDs are used, it will allow the screening of siRNA sequences and the monitoring of downstream cell behaviors in a multiplexed manner [6].

Proton-Resistant Quantum Dots

The fluorescence of traditional polymer-encapsulated QDs is often quenched by proton-induced etching in acidic environments. This is a major problem for applications of QDs in the gastrointestinal tract because the gastric (stomach) environment is strongly acidic (pH 1 2). The use of proton-resistant surface coatings to stabilize QD fl uorescence under acidic conditions was reported. Using both hyperbranched polyethylenimine (PEI) and its polyethylene glycol derivative (PEG-grafted PEI), the fl uorescence of core shell CdSe /CdS/ ZnS QDs is effectively protected from quenching in simulated gastric fluids. In comparison, amphiphilic lipid or polymer coatings provide no protection under similarly acidic conditions. The proton-resistant QDs are found to cause moderate membrane damage to cultured epithelial cells, but PEGylation (PEG grafting) can be used to reduce cellular toxicity and to improve nanoparticles stability [14].

Cytotoxicity

Cytotoxicity of QDs has been observed in a large number of in vitro studies , affecting cell growth and viability. The extent of cytotoxicity has been found to be dependent upon a number of factors including size, capping materials, colour, dose of QDs, surface chemistry, coating bioactivity and processing parameters. A number of mechanisms have been postulated to be responsible for QD cytotoxicity. These include desorption of free Cd (QD core degradation), free radical formation, and interaction of QDs with intracellular components. Examination of QD toxicity in a hepatocyte culture model showed that exposure of core CdSe to an oxidative environment causes decomposition and desorption of Cd ions. Such exposure during synthesis and processing played an important role in subsequent toxicity. Addition of a silica (SiO2) and ZnS shell can reduce oxidation, but is unable to eliminate it, particularly under concomitant exposure to UV light. The addition of ligand shells has also been observed to reduce Cd desorption, but again is unable to eliminate it under oxidative conditions, and ligand addition brings its own attendant problems. The generation of free radicals, particularly reactive oxygen species has also been seen to contribute to toxicity. In addition to the effects of the QD core, ligands added to render the probe biologically active may have toxic effects on cells. Mercaptopropionic acid (MPA) and mercaptoacetic acid, which are commonly used for solubilisation, have both been shown to be mildly cytotoxic. MUA, cysteamine and TOPO have all been shown to have the ability to damage DNA in the absence of the QD core. PEGylated QDs have been shown to have reduced cytotoxicity, but modification of these to produce PEG-amine for biological activity renders them cytotoxic once again.

Unfortunately, interpretation of information on cytotoxicity is difficult as a result of differences in cellular handling of QDs and the possible contribution of unexpected factors to toxicity. The reduced cytotoxicity seen with QD-PEG compared with unmodified QDs has been found to be related to reduced uptake of these modified QDs, and not necessarily to an inherently reduced toxicity. The way in which QDs are handled by cells after uptake is also variable, and different intracellular fates are likely to contribute to different toxicity. With the limited data accumulated so far it is very difficult to estimate the true extent of QD cytotoxicity, which factors contribute, and the effects they may have.Groups III–V QDs may provide a more stable alternative to groups II–VI QDs due to the presence of acovalent, rather than an ionic, bond, and have been reported to have lower cytotoxicity. However these QDs are difficult to

prepare on a competitive time scale, and tend to have much lower quantum efficiencies, meaning uptake has been slow. Data relating to cytotoxicity is understandably much more limited for these QDs, making it difficult to draw firm conclusions, and comment either way[10].

Quantum Dot Products [6]:

EviDots® Core & core-shell quantum dots EviDots are available as core quantum dots in their fundamental state, or enhanced with our proprietary coating technologies as core-shell semiconductor nanocrystal quantum dots. EviDots are available in wavelengths ranging from 490nm - 2100nm.

EviComposites™ Quantum dot composites. EviComposites use the properties of Evident's proprietary EviDot quantum dots as well as common insulating polymer matrix materials.

EviTags™ Water soluble quantum dots. EviTags are conjugation-ready with a bio-active surface. Carboxyl or amine functionalized dots are available in wavelengths ranging from 490nm - 680nm.

EviFluors® Water soluble quantum dots conjugated to antibodies and proteins. EviFluors are ready-to-use high quality, activated quantum dots coupled to secondary antibodies and proteins. Goat anti-Mouse, Goat anti-Rabbit, Goat anti-Rat, Streptavidin, and Biotin conjugated quantum dots are available in wavelengths ranging from 520nm - 680nm.

Conclusion

QDs play an important role in fundamental biology and *in vitro* disease diagnostics and prognostics as potent imaging probes. Their unique structural and surface properties, such as their tunable and uniform size, flexible drug linking and doping mechanisms, large surface to- volume ratio and wide spectrum of surface reactive groups have enabled a new avenue of research to be opened: targeted and traceable drug delivery. However, high-quality QDs (visible and near infrared dots with a narrow emission profile and high quantum yield) are mainly made with heavy metals whose long-term toxicity are largely unknown at the current time. Despite this limitation, QDs have been applied to cells and small animals as drug carriers, serving as an outstanding discovery tool for drug screening and validation, and as prototype materials for drug carrier engineering. If high-quality QDs can be prepared from relatively non-toxic compounds (e.g., silicon and carbon), or if the toxic components can be inertly protected from exposure and subsequently cleared

from the body, then the clinical relevance of QDs could be anticipated. It seems that future technology will be based entirely on nanotechnology like quantum dots in all sphere of life.

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