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NANO TECHNICAL TRENDS FOR CANCER TREATMENT: QUANTUM DOTs A SMART DRUG DELIVERY SYSTEM

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ABSTRACT: Conventional chemotherapy drugs show lack of specificity, including reduced activity on cancer treatment with higher toxicity to normal cells and develop resistance after prolonged period of administration. Recently, to nullify all adverse effects of cancer chemotherapy nanometer sized carriers came into role for total cure. The advanced research community is focused on smart drug delivery system owing to their vivid biomedical and pharmaceutical applications. This article will provide an in-depth discussion on development of smart nanosized carriers for tumors targeting and highlight important role of QDs in highly challenging area of nanotechnology.

INTRODUCTION: Approximately 85% of tumors are solid tumors and can be surgically removed; the remaining cancerous cells are treated with radiotherapy, chemotherapy, immunotherapy, gene therapy, hyperthermia to achieve the objective of total cell kill resulting in total cure. However total cell kill is difficult especially when cancer has metastasized [1, 2]. Current treatment regimen requires high doses of anticancer drug to deliver systematically by I.V. or infusion. The larger the dose of drug that can be administered the greater the potential of cell death. The unmet medical need for treatment of cancer is the design of drug delivery system that can selectively deliver at cancer tissues with high local drug concentration thereby achieving therapeutic efficacy with minimized side effects.

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Medical application of nanotechnology is expected to be of major benefits to society within next 10 years, especially for the patients suffering from cancer, CVS, lung, blood and neurological disorders. The technology is not only important because of its social and welfare implications but also because of its economic potential [3, 95].

Drug targeting depends on great degree on how one defines "targeting". Drug targeting is the sense of manipulating the release and uptake of drug in specific body compartment for prolonged action as well as protecting drug/body compartment from unwanted side effects. Success in selective targeting to or away from organs or cells has been scarce to date, although extensive and ingenious efforts are being made [4].

The term "theranostatics" was coined to define ongoing efforts in clinics to develop more specific, individualized therapies for various diseases and to combine diagnostic as well as therapeutic capabilities into single agents [4].

In addition to low aqueous solubility, these compounds exhibit unfavorable pharmacokinetics, poor biodistribution and various toxicity issues, hence the conventional formulation and advanced drug delivery system have employed strategies to move these molecules from lab to market [4].

Advanced drug delivery systems have been developed as strategies to overcome many of the obstacles that are associated with conventional formulations. In addition, these advanced systems have been designed with an objective of developing "magic bullets" that provide site specific delivery of drug to the target or disease site. In this article we have described the advanced drug delivery system with their method of synthesis and application [5].

Micelle:

In aqueous media, the amphiphilic dib lock co-polymer is self assembled into nanosized micelle with hydrophobic core and is surrounded by hydrophilic corona. The hydrophobic core of micelle solubilizes/ entraps hydrophobic drug and hydrophilic block from hydrated corona that stabilize the micelle [6]. Several methods have been employed for micelle preparations depending on:

- Solubility of co-polymer in aqueous medium.
- Properties of drug to be encapsulated.

(i) The method for drug loading in micelle that are formed from copolymer and are soluble in water is termed as direct dissolution method (drug and co-polymer are directly dissolved in distilled water and buffer. The drug is then loaded into micelle by stirring, heating or sonicating the mixture. Various drugs like dox, nystatin, etoposides, and haloperidol have been successfully loaded into micelle [6].

(ii) Dry- down/ evaporation method:

This method is for the preparation of micelle from co-polymer that has fairly low aqueous solubility. In this method the thin film of polymer and micelle is formed by organic evaporation which is essential for both. Using this method a number of different drugs have been encapsulated like adriamycin, amphotericin B [7].

The stability of micelle is highly depenedent on the composition of micelle forming materials. In aqueous environment, the stability of micelle can be considered to include thermodynamic stability of micelle concentration (CMC) of co-polymer.

The CMC is the conc. below which co-polymer exists only as single chain and above which copolymer is assembled as micelle which are in equilibrium with small population of single chains [8].

CMC of copolymer α properties of core forming block.

❖ The kinetic stability of the micelle refers to the rate at which micelle disassembles into single chain as the copolymer concentration falls below CMC.

Kinetics stability α physical state of core

Examples of some micelle system:

SP1049C micelle system of Dox developed by Kabanovs grops and superatek Pharma Inc. (Monstreal QD, Canada composed of two Pluronic F127 and Pluronic L61 (1:8 w/w) for esophagus cancer and NK911 for pancreatic cancer [8].

(1) Polymer – Drug conjugates:

Polymer – Drug conjugates are the class of polymer therapeuties which consists of water- soluble polymer that is chemically conjugated to drug through biodegradable linkers. As small molecule drugs, especially hydrophobic compounds commonly have low aqueous solubility and broad tissue distribution profile, the conjugation of these compounds to hydrophilic biocompatible polymer would significantly increase in their aqueous solubility, modify their tissue biodistribution profile and enhance their plasma circulation half life. The first practical use of polymer therapeutics that resulted in FDA approved anticancer treatment was introduction of PEG-L-asparginase (Oncaspar®) in 1994 [9]. There are several key criteria that should be considered while designing a polymer – small molecule drug conjugates. Polymer that can be used for this purpose must be

nontoxic in terms of both intact polymer and their metabolites. The molecular weight of polymer must reach specific cut off if prolonged circulation half life is required. If polymer is non biodegradable then the molecular weight should be less than 40 KD in order to ensure its elimination from body by renal excretion. To date, there are four polymers that have been explored most extensively in preparation of P-D conjugates for anticancer therapy e.g. HPMA (N-(2-hydroxypropyl) methacrylamide), PEG, PGA (Poly glutamic acid) and dextran [10, 94].

The success of polymer drug conjugates and polymer based delivery system is evidenced by number of drugs that have reached stage of development of clinical trials and rely on these technologies for formulations [11].

(1) Lipid based colloidal system:

Liposomes are the spherical vesicles with aqueous core surrounded by one or more concentric bilayer of lipids. These lipids vesicles can be prepared widely in terms of size from 30 nm to several microns. But during i.v. delivery liposomes should be smaller than 200 nm in diameter, Ist explored over 40 yrs ago by Bangham as means to study membrane dynamics and gain an improved understanding of molecular flux in and out of cells.

The first liposomes were composed of phosphatidylcholine derived from egg, a material that is still commonly used to form liposomes [12].

The first FDA approved liposomes (1995) for anticancer activity was Doxil® consisted of Dox encapsulated HSPC (hydrogenated Soy Phosphatidylcholine, cholesterol (CH) and PEG-conjugated distear oyl phosphatidylethanolamine (PEG- DSPE). Liposomes are basically composed of 3 main types of materials phospholipids, sphingolipids and sterols. The physico- chemical properties of liposomes including zeta potential (overall charge of liposomes), size, size distribution and stability shows most significant influence on their performance as drug delivery system [13].

Various methods have been put forth for liposomes preparation and the most commonly employed methods are known as extrusion methods. Extrusion method involves use of high pressure to force the suspension through polycarbonate membrane [14].

There are a wide range of liposome- based formulations of anticancer drugs that are in various stages of clinical developments including few for hydrophobic drugs [15].

(2) Dendrimers:

Recent studies have demonstrated that PAMAM dendrimer of certain generations and surface charge can permeate epithelial barrier of gut suggesting their potential as oral drug delivery carriers. The toxicity and biocompatibility of these systems is dependent on size, surface charge and concentration which can be modulated by surface modification, particularly of positively charged primary amine groups [16].

Dendrimer synthesis involves the use of typical organic monomers to produce macromolecules with polydisparities of around 1.0005- 1.10 [16].

Two general synthetic methods have been used to produce dendrimers:

(i) Divergent method: it was procured by Tomalia which involves outward branching from initiator core around which the branches of dendrimer originates.

(ii) Convergent method: It was procured by Hawker and Frenchect. It involves inward growth from what will become dendrimer surface to the inner core by formation of individual Dendron. Excess monomers and extrusive purification techniques are required for divergent process, while the convergent method is limited to synthesis of lower generation dendrimers due to steric hindrances that occurs from attaching outer Dendron towards inner core. To address these challenges, two alternative synthetic strategies have recently been introduced. One such method termed lego chemistry involves the synthesis of phosphorous based dendrimers using functionalized core and branches. The monomers in which each generation is produced in single step reaction based on two types of alternating “layer blocks” and the only by product are nitrogen and water. Lego

chemistry produces phosphines, hydrazides and aldehydes as end groups which allows for further reaction to produce additional generations eg. PAMAM dendrimer which is first dendrimer family to be completely synthesized (divergent method), characterized and commercialized. The molecular size of PAMAM dendrimer increases by each generation with sizes range from 1 to 15 nm [17].

(3) Fullerenes:

Carbon nanotubes and Bucky ball clusters belong to the fullerenes, a family of structures composed entirely of carbon. Carbon nanotubes are carbon coaxial graphite sheets of less than 100 nm rolled up into cylinders. These can be classified in to two categories based on their structure: single-walled carbon nanotubes (SWNT) (one graphite sheet) or multi-walled carbon nanotubes (MWNT) (several concentric graphite sheets). They have been applied in biology as biosensors for detecting proteins and DNA, diagnostics, and carriers. CNTs were discovered in 1991. These display superior properties in electric current carrying capacity, thermal conductivity and thermal stability [18, 94].

Toxicity of CNTs:

(i) Atomic Oxygen makes reactive oxygen species of CNTs, which causes toxicity to cells.

(ii) Physical parameters such as size, mass and surface area of CNTs play determinant role and show specific effect on macrophage action and inflammatory action of cells.

(iii) Membrane damage, protein denaturation DNA damage, immune reactivity are some of the leading examples of toxicity caused by surface coating of Zn, Cd etc, around CNTs.

(iv) Surface charge of polycations on membrane plays a significant role in toxicity e.g. multiwalled CNT like C_{60} shows toxicity due to surface modified by PVP.

(6) Polymeric nanofibers:

Polymeric nanofibers (1 nm to 1 µm) resemble the size scale of extracellular matrix (ECM) fibers and are derived from inorganic (*i.e.*, titanium, silicon or aluminum oxides) or organic (polyvinyl alcohol, gelatin, poly (*N*-isopropylacrylamide, polycaprolactone, or polyurethane) materials. They are synthesized by three available techniques: electro spinning, phase separation and self-assembly; however, the most commonly used technique is electrospinning. Nanofibers basically consist of large surface area, low density, high pore volume and tight pore size however; these properties can be easily changed by voltage, capillary collector distance, and polymer flow rate [19]. Nanofibers are used for several applications such as medical (tissue engineering), filtration, barriers, wipes, personal care, composite, insulation, garments, and energy storage.

These have also been used as drug delivery systems for e.g. Tseng and coworkers used biodegradable nanofibers to successfully deliver vancomycin, an antibiotic, to the brain tissue of rats and reduce the toxicity associated with parenteral antibiotic treatment [20].

(4) Metal based nanoparticles:

Metal-based nanoparticles are diagnostic as well as drug delivery systems available in different shapes, sizes (between 10 to 100 nm) [21]. Most common metallic nanoparticles include oxides of gold, nickel, silver, iron, zinc, gadolinium, and titanium dioxide particles. The large surface area of metallic nanoparticles enables the incorporation of high drug doses. Qian *et al*. demonstrated the utility of gold-based nanoparticles in human cancer cells and in xenograft tumor mouse models. They reported the use of biocompatible and nontoxic PEG-gold nanoparticles for *in vivo* tumor targeting which were spectroscopically detected by surface-enhanced Raman scattering (SERS). Although metallic nanoparticles are biocompatible and inert vehicles, a significant fraction of metal particles can be retained and accumulated in the body after drug administration, possibly causing toxicity. Therefore, the use of metallic nanoparticles for drug delivery is a matter of concern [22].

(5) Emulsifying agents:

Nanoscale systems like emulsification systems incorporate drug compounds and modify their bioavailability, stability, hence reduce their side effects. They are colloidal systems with distinct

morphologies and sizes range from 1 – 400 nm that consist of two or more immiscible liquids stabilized by surfactants [23]. They are mainly classified according to their differences in the composition, appearance, kinetic and thermodynamic stability into emulsions, micro emulsions and nano emulsions. The structure of the single-phase emulsification systems produced is affected by the fraction of oil and water [24]. The structure can be oil-in-water (o/w), water-in-oil (w/o) or bicontinuous. In each type, there is an interfacial surfactant monolayer, separating the water and oil domains.

The presence of o/w droplets is likely to be produced where the volume fraction of oil is low while the w/o droplets are formed at a lower fraction of water. In systems, where the amounts of water and oil are similar, a bicontinuous structure may result. The existence of micro domains of different polarity within the same single-phase solution enables both water-soluble and oil-soluble materials to be solubilized [25].

(6) Magnetic Drug targeting:

It has been noted that the disadvantage of most chemotherapies is the relatively non-specific and induced side effects in healthy tissue. One of the strategies to overcome this problem is to magnetize the drug-loaded carrier (*e.g.*, Fe_3O_4) so that it can be retained at or guided to the target site with the help of an external magnetic field of appropriate strength [26].

(7) Quantum Dots:

Quantum dots (QDs) are the semiconductors (group III–V and II–VI), pellucid nanoparticles having physical dimensions of 1 – 10 nm and are evident as fluorescence under a light source like laser. QDs have inherent photophysical properties that are enviable for the purposes of imaging and targeted drug delivery. QDs are nanometer-sized radiant semiconductor crystals and have inimitable chemical and physical properties due to their size and highly squashed structure. This enables its use in *in vivo* imaging including live-cell and whole-animal imaging, blood cancer assay, and cancer detection and treatment [27] **Table 1.**

TABLE 1: COMPARISON BETWEEN QDs AND ORGANIC FLUOROPHORES

	Quantum dots	Organic Fluorophores	References
Excitation	Very broad. UV light can excite a QD of any size.	Narrow excitation spectra	[23,24]
Emission band width	20–40 nm	50–100 nm	[58]
Fluorescence lifetime	10–40 ns	Few nanoseconds	[62,86]
Photostability (upon constant illumination with a 50 mW, 488 nm laser)	Stable for over 14 h	Fluorescein photobleaches completely in under 20 min	[3-7]
Molar extinction coefficient	~105–106 M−1 cm−1 (for CdSe QDs	10–100 times smaller than that of CdSe QDs	[24]

Current cancer therapy has high toxicity issues, which have been overcome using the direct targeting property of QDs. QDs could selectively deliver drug to the target site and by the imaging property, we could check whether the drug reached the desired target site or not [28].

The general physicochemical properties of QDs, which gives answer why they are better than other imaging systems, are summarized and discussed below [30-34]:

a)QDs are more resistant to degradation than other optical imaging probes and hence allow tracking of the cellular process for longer period of time.

b)They have a longer-lasting fluorescent and photostability than traditional dyes, due to their inorganic composition and fluorescence intensity.

c) QDs have high S/N ratio compared to organic dyes.

d) QDs have broader excitation spectra and a narrow, sharply defined emission peak.

e) QDs are 10 – 20 times brighter than other organic dyes. QDs are stable fluorophores due to their inorganic composition, which reduces the effect of photobleaching when compared to organic dye.

f) QDs have large stokes shift and sharp emission spectra.

g) QDs could be easily molded into any shape and coated with a variety of biomaterials.

h) QDs are nanocrystals and provide better contrast with electron microscope as the scattering increases.

i) QDs have novel optical and electronic properties due to quantum confinement of electrons and photons in the nanostructure. The phenomenon of QD confinement arises with the particle diameter being of the same magnitude as the wavelength of electron wave function. Quantum confinement results in a widening of band gap (gap between valence and conduction band), which increases when the size of the nanostructure is decreased. QDs of the same material with different sizes emit different colors [29, 93].

j) QDs are semiconductor nanocrystals that possess unique optical properties including broad-range excitation, size-tunable narrow emission spectra and high photo stability, giving them considerable value in various applications. The size and composition of QDs can be varied to obtain the desired emission properties and make them amenable to simultaneous detection of multiple targets. These properties arise from interaction between electrons, holes and the local environment. QDs absorb photons when excitation energy exceeds band gap, and after absorbing that energy, electrons jump from the ground state to the excited state. The energy associated with optical absorption is directly related with the electronic structure of the material [35, 36].

k) In recent years, QDs have attracted tremendous attention as the most valuable and promising candidates in the areas of drug delivery, targeting and imaging [37].

l) Low toxicity, low cost, and good biocompatibility make them excellent candidates for *in vivo* bioimaging, gene/drug delivery, and cancer detection. This has created a powerful impact in various fields of disease diagnosis, intracellular tagging as photo sensitizers for treatment of cancer, biotechnology and bioassays [38]. Current advancement in the surface chemistry of QDs has expanded their use in biological applications, reduced their cytotoxicity and rendered QDs a powerful device for elaborating distinct cellular processes like uptake, receptor trafficking and intracellular delivery. Some of them (ZnO) have also promised significant breakthrough in the search for antibacterial agents and the detection of antigens and allergens, due to their isoelectric point [39].

Operation of QDs:

QDs have been originated from quantum confinement effect which is observed with optical properties of a semiconductor smaller than 10-20 nm. As the excitation depends on size of QDs i.e. when size of QDs is smaller than Bohr exciton radius, the energy level of photons is quantized and direct relationship between QDs size as well as energy quanta exists [40,41].

Synthesis of Quantum Dots

In the 1980s, traditional lithography-based techniques (a combination of electron beam lithography and etching) were used to make quantum dots. However, these quantum dots were only in the nanometer scale in one dimension. The other two dimensions were limited by the resolution of the lithography. In the early 1990s, quantum dots were mainly prepared in aqueous solutions with added stabilizing agents. This procedure yielded low-quality quantum dots with poor fluorescence efficiencies and large size variations [42]. From 1993 onwards, the high-temperature organometallic procedure was used for growing quantum dots. This procedure yields nearly perfect crystal structures and narrow size

variations, but the fluorescence was still relatively low [43].

Now, QDs with high luminance properties can be synthesized by following chemical method. Equivalent amount of 0.1 M of Zinc acetate and 0.2 mM of manganese acetate aqueous solution was mixed with 0.2 M DEA aqueous solution. All three solutions were mixed with vigorous stirring at 600 rpm. Further, 14mM oleic acid was added to it with vigorous stirring at 2800 rpm at 20^{o} C for 30 mins at basic pH 6.2. The temperature and stirring speed should be taken into consideration during nucleation step. After 30 mins of this nucleation step, the solution is refluxed and stirred for 2hrs (100^{o}C and 1221 rpm). The unreacted molecules were filtered and redispersed in ethanol and isopropanol followed by centrifugation at 1600 rpm for 30 mins. Mn^{+2} ions were removed from QDs surface by heating the solution in DEA at 150^{o}C for 30 mins. Obtained nanocrystals were precipitated with ethanol and again centrifuged for 10 mins at 1600 rpm which are then dispersed in water (**Fig. 3**) [44, 45].

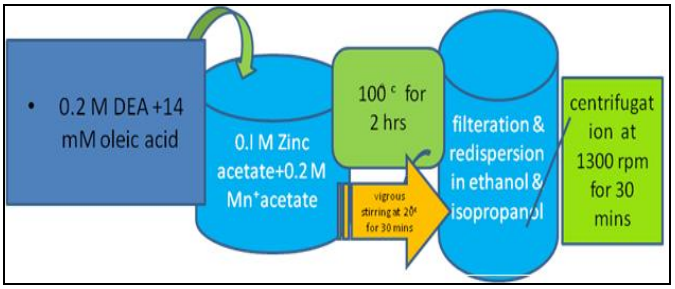

FIG.3: SYNTHESIS OF QUANTUM DOTs

Biocompatibility:

To make QDs biocompatible following strategies like silanization and surface exchange with bifunctionalized molecules. These are the molecules with hydrophobic and hydrophilic side. The biocompatibility can also be enhanced by encapsulation of QDs with phospholipid micelles, polymer beads/shells containing hydrophilic and hydrophobic parts. Hence, QDs are made biocompatible by coating with various polymers like silica and mercaptohydrocarbonic acid [46, 97].

Fictionalization of QDs: QDs are adapted to desired application by conjugation with recognition moiety. For functionalizing the QDs, they have been conjugated with desired biomolecules by various methods like electrostatic attraction, covalent linkage, adsorption and mercapto (-SH) exchange [46]. The choice of interaction depends on the features of biomolecules of interest like the thiol containing molecules which can be conjugated with QDs via mercapto exchange. The factors affecting the absorption are pH, ionic strength, temperature and surface charge of molecules [47].

The method which provides more stable conjugation between QDs and biomolecules is by covalent bonding [47].

Characterization of quantum DOTS:

The optical characterization of quantum dots is usually done by UV-VIS and photoluminescence spectroscopy, which offers fast, non destructive and contactless option. The quantum dots size is calculated using conventional techniques like scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM) or more preferably scanning tunneling microscopy (STM), dynamic light scattering (DLS) studies and zeta size analyzer [48]. Besides these techniques, field flow fractionation was also successfully employed an excellent complement to characterization of water soluble quantum dots by the conventional tools (**Fig. 4**) [49].

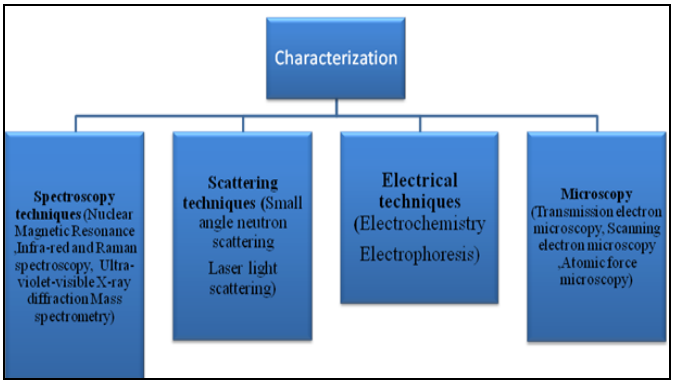

FIG. 4: METHODS OF QUANTUM DOTs CHARACTERIZATION

Mode of action of QDS:

QDs colloidal solution is basically administered by S.C. or I.V. injection which they identify and bound to target. Once bound to target, each quantum dot particle emits light and depending on their size, they can fluorescence in a variety of colours which can be identified or detected by different techniques [50].

Applications:

The relevant advantageous properties include controllable emission wavelengths, sharp emission profiles, robust signal strength and the use of a single excitation source. The optical properties can be influenced by varying different aspects of the quantum dots, all of which can be controlled including core size, core composition, shell composition and surface coating. While all the aforementioned qualities influence quantum dot emissions, the core size and composition have the most influence over the range of the emission spectra. Varying, either the size of the quantum dot core or its composition, can result in a customizable emission profile with a specific maximum anywhere across the electromagnetic spectrum, starting in the ultraviolet (UV) region and including the near-infrared (near-IR) region [51, 91]. Altering the shell composition and/or surface coating, affects the stability of the core and results in increased photoluminescence but does not significantly affect the emission range. Emission spectra for semiconductor nanoparticles is distinctive containing narrow and symmetric peaks independent of the excitation energy as long as the excitation energy is greater than that of the band gap energy.

This characteristic means quantum dots of varying sizes and compositions can be excited with a single source [52]. However, the relative intensities of different quantum dot emission profiles will vary with excitation wavelength independently of one another, based on their quantum efficiency at that wavelength. Finally, because quantum dot emission peaks are substantially narrower than those of organic dyes, more quantum dot emissions are resolvable within the visible spectrum than possible with standard fluorophores (**Fig. 2**) [53, 90]. Other applications of quantum dots have been listed below [54-62] **Table 2.**

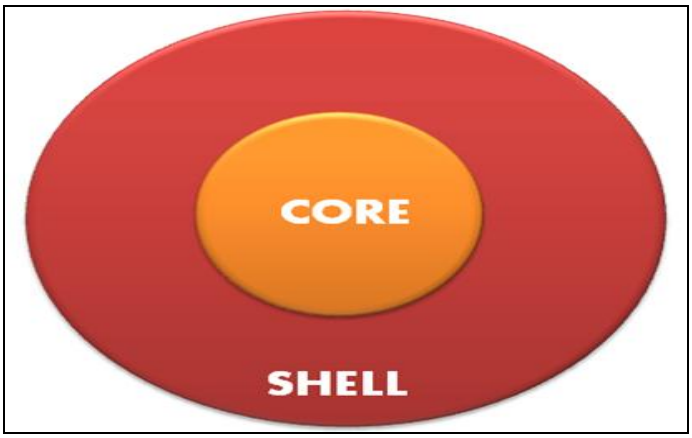

FIG.1: STRUCTURE OF QUANTUM DOTs

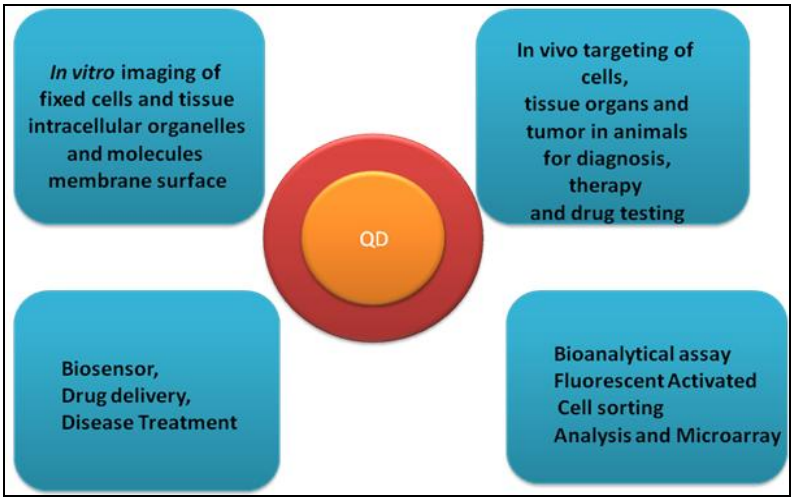

FIG.2: APPLICATION OF QUANTUM DOTs

TABLE 2: SELECTED QD-BASED MEDICAL APPLICATIONS [54-62]

Application area	Description	References
Diagnostics	• Detection of Her2 (hairy-related 2) on SK-BR-3 breast cancer cells by employing humanized anti-Her2 antibody, a biotinylated goat antihuman gG, and streptavidin-coated QDs. • Immunofluorescence labeling of mortalin using QDs showed different staining patterns between normal and cancer cells. • Detection of ovarian cancer marker CA 125 in various specimens using streptavidin-conjugated QDs. • Fluoroimmunoassay for the detection of prostate-specific antigen using streptavidin-coated QDs • QD-based FISH labeling was used to detect specific repeats in the Y chromosome in fixed human sperm cells • Antibody-conjugated QDs were used to detect prostate cancer cell marker PSA, the QD conjugates detected the tumor site in mice transplanted with human prostate cancer cells	[54,55,57]
Imaging	• Imaging skin and adipose tissues in mice by injection of water-soluble QDs • Mapping sentinel lymph nodes at 1 cm tissue depth using oligomeric phosphine-coated QDs that emit in the near-infrared region • Tracking diffusion dynamics of glycine receptors using QDs	[59,60]
Drug delivery and therapeutics	Surface-modified CdS QDs were used as chemically removable caps to retain drug molecules and neurotransmitters inside a mesoporous silica nanosphere-based system. • QDs showed potential in use as photosensitizers or to excite other photosensitizers in photodynamic therapy • Screening of siRNA sequences and monitoring RNAi delivery using QD–siRNA conjugates	[61,62]

QDs as carriers with integrated functionalities

In quantum dot core, small molecule hydrophobic drugs can be embedded between the inorganic core and the amphiphilic polymer coating layer. Polymer coating of quantum dots is a powerful tool toward diagnostics.

Cellular targeting and Imaging:

QDs have utility for no. of types of live cell imaging and detection application. It helps in detection of various cell proteins or other components of heterogeneous tumor / tissue samples.

Protein Biomarkers detection:

The ability to screen cancer in its earliest stages acts as biomarkers of carcinogens. QDs have been successfully used as substitutes for organic fluorophores and colorimetric reagents in variety of immunoassay for detection of specific proteins.

High – throughput multiplexing:

Instead of using single QDs for identifying single biomarkers it has been proposed that different colours of QDs can be combined into larger structure such as microbeads to yield an optical barcodes.

Bimodal molecular imaging:

Quantum dots will act as a molecular imaging probe for both fluorescence microscopy and magnetic resonance imaging.

Detecting Cell Death:

By combining a quantum dot with a novel carrier of the magnetic resonance imaging (MRI) agent (gadolinium) can spot apoptosis or programmed cell death.

***In-vivo* imaging and targeting:**

Targeting:

QDs can target specific receptors *in vivo*. QDs can be conjugated with folate specific receptors which are over expressed on cancerous cells and hence are important to cancer diagnosis.

Imaging QDs photostability property, images are to be recorded for longer period of time compared with other fluorescent dyes. EviTags (non-targeted near infrared emitting quantum dot) as non-invasive optical molecular imaging probes, will have a great impact on the early detection, diagnosis and treatment monitoring of cancer.

Tumor Cell Markers

There are two methods by which quantum dots locate and mark tumor cells. These two schemes are active targeting and passive targeting. In active targeting, quantum dots can be conjugated with tumor-specific active binding sites so as to attach themselves to tumor cells.

Gene technology:

A number of studies have revealed that quantum dot-conjugated oligonucleotide sequences (attached

via surface carboxylic acid groups) may be targeted to bind with DNA or mRNA.

Pathogen and toxin detection:
Several different pathogens have been targeted so far, including *Cryptosporidium parvum* and *Giardia lamblia, Escherichia coli* and *Salmonella Typhi* and *Listeria monocytogenes*.

Detection of viral infections:
Quantum dots bind to molecular structures that are unique to the virus coat and the cells that it infects. Quantum dots come in contact with either viral particles or infected cells, they stick to their surface and illuminate bright fluorescence.

Neuroscience:
Quantum dots can be used to visualize, measure and track individual molecular events using fluorescence microscopy and they provide the ability to visualize and track dynamic molecular processes over extended periods (e.g., from seconds to many minutes).

Drug discovery:
The features of quantum dots such as their multiplexing potential, photo stability and inorganic nature make them of value for drug discovery.

Biosensor and bio labels:
A number of analytical tools have been developed with application of this smart and potential technology.

Surgical guidance: Quantum dots also have a potential surgical utility by providing optical guidance that can result in reduction of cancer metastases.

***In vitro* nanodiagnostic:**
(a) Immunohistochemistry: QDs utility in immunohistochemical application was demonstrated by Nees et al who developed immunohistochemical protocol for detection of intercellular antigen in mouse and rat brain tissue. The result showed that use of QDs for immunohistochemical labeling had superior sensitivity to conventional dyes and better sections was obtained with QDs compared to enzymatic signal amplification methods e.g. detection of ovarian cancer marker CA125 by Wang et al. in which the streptavidin- conjugated QDs were used to detect CA125 by conjugating streptavidin coated QDs to CA125 monoclonal antibodies, the result showed superior specificity and brighter fluorescence signal compared with organic dyes.

(b) Immunoassay:
Immunoassay by QDs is simpler compared with different organic fluorophores. Goldman et al. performed a multiplex immunoassay for cholera toxin resin using relevant antibodies conjugated with QDs of different sizes (colors). By excitation of QDs at single wavelength toxin conc. of 30 and 100ng/ml were examined and simultaneously signals were detected.

(c) Nucleic acid detection:
QDs can be used as labels for detection of multiple mRNA target using FISH (Fluorescence in situ hybridization). Organic fluorescent labels for DNA detection has two major problems:

- Cleavage of DNA molecule due to photobleaching.
- Allows two colour determination of orientation of single DNA molecule.

(d) Detection of genetic polymorphism:
QDs can be used for simultaneous detection of multiple single nucleotides polymorphism (SNPs) in which QDs were conjugated with four nitrogenous bases. Four QDs linked monobases result in specific complementary sites of target DNA and distinct electron is generated.

(e) Single molecule detection:
QDs are used as single molecule detection by conjugating antibodies with QDs and they will bind to different sites of target biomolecules. A signal is detected if both QDs labeled antibodies bind with target at same time. Similar assays can be developed for detection of disease biomarkers and bioterrorism agents in biological fluids and drinking water.

Pit falls and toxicity concerns:
There are some of technical challenges which we overcome while using QDs in biological

applications and some of which have been circumvented and other still remain in challenges, some of them are [63, 64, 71-76]:

- Quantum dots, when positioned in live cells, may kill the cells due to aggregation.
- Biconjugation of quantum dots, leads to delivery into the target difficult.
- Building material of the quantum dots can be cytotoxic e.g. cadium QDs.
- Their metabolism and excretion is unknown, so the accumulation in body tissues can leads to toxicity.
- Reproducibility during manufacturing and quenching in solution.
- QDs may also be subject to reduce luminescence activity due to relatively large surface area.
- Problems come across regarding ability of QDs to reach target with in cellular compartments.
- With functionalizing QDs, the size can reach up to 100nm and hence the increased size is hurdle.
- QDs use would not be possible for whole blood analysis however they can be used with serum and other body fluids.

QDs Toxicity and Clinical Potential:

The potential toxic effects of semiconductor QDs have recently become topic of considerable importance and discussion. Quantum dots can be considered as an alternative for organic dyes in the imaging of biological systems due to their excellent fluorescent properties, good chemical stability, broad excitation ranges and high photo bleaching thresholds [65].

The main shortcoming of quantum dots is their toxicity and therefore, their application is problematic. e.g. cadmium telluride quantum dots (CdTe - which is toxic) used as fluorescent probes for biological imaging, they can also be utilized to monitor targeted drug delivery [66]. Scientists have been using gelatin during the production of CdTe quantum dots thereby reducing the toxicity of the particles. By resolved toxicity issues of QDs with couple of decades, QDs base drug delivery system can be seen in market [67, 96].

QDS Products:

The U.S. Food and Drug Administration (FDA) recently (2011) approved the first clinical trial of quantum-dot technology in humans. The decision represents that for the first time the FDA has approved the use of inorganic material—in the same manner as a drug [68] **Table 3**. The technology that will be tested, was developed by researchers at Cornell University (Ithaca, NY) and is thus called Cornell dots or C dots. The trial will involve five melanoma patients at Memorial Sloan-Kettering Cancer Center (MSKCC) and will seek to verify that the dots are safe and effective [69, 88].

TABLE 3: SELECTED QD PATENTS [66 ,68, 72]

Patent	Assignee Issue	Date/Patent No.
Fluorescent labels for immunoassays	Eastman Kodak Company	1987 /4637988
Method of detecting an analyte in a sample using semiconductor nanocrystals as a detectable label	Quantum Dot Corporation	2001/ 6274323
Functionalized nanocrystals and their use in detection systems	BioCrystal Ltd.	2000/ 6114038
Functionalized nanocrystals as visual tissue-specific imaging agents, and methods for fluorescence imaging	Bio-Pixels Ltd.	2001/ 6333110
Materials and methods for near infrared lymph node mapping	Massachusetts Institute of Technology, Beth Israel Deaconess Medical Center	2007/ 7181266
Preparation and application of anti-cancer medicament carrier with dual functions of targeting and fluorescence		2009/CN101732720B
Graphene quantum dot nuclear targeting medicine carrying system as well as preparation method and application thereof		2013/CN103432590B

EviDots®:
Core & core-shell quantum dots EviDots are available in wavelengths ranging from 490 nm – 2100 nm. PbS EviDots® are available in emission wavelengths from 85 nm to 1500 nm [70, 78, 89].

EviComposites™:
EviComposites are available which use the properties of Evident's proprietary EviDot quantum dots as well as common insulating polymer matrix materials [70, 78].

EviTags™:
EviTags are Water soluble quantum dots and the carboxyl or amine functionalized dots are available in wavelengths ranging from 490 nm – 680 nm [70, 78, 87].

EviFluors®:
These are water soluble QDs 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 QDs are available in wavelengths ranging from 520 nm – 680 nm [70, 78].

Regulatory considerations:
The toxicities associated with the QDs are yet unclear. Several research studies demonstrated the toxicity of pristine QDs, which could fortunately be minimized via surface engineering that renders them more biocompatible and non-immunogenic [77]. Additionally, there is a significant need for research and development in the field of analytical and detection methods. Strict norms and regulations are needed in the development of new drug products for being safe, effective and economic in generally regarded as safe (GRAS) prominence [79, 92].

Future Prospective:
In future, nanotechnology will show its controlled effect on deathly diseases like cancer. Quantum dots, a smart drug delivery system will be used to identify various categories of cancer with almost negligible side effects identify the molecular mechanism of diseases and the mechanism of action of new drugs [80]. Research into more luminescent hydrophilic QDs is ongoing since there is an urgent need for increasing QD efficiency and achieving better fluorescence with its higher biosafty synthesis. Moreover, NASA scientists are working on quantum dots as drug carrier for Mars expedition in near future. Single quantum dots of compound semiconductors were successfully used as a replacement of organic dyes in various bio-tagging applications. This idea has taken one step further by combining differently sized and hence having different fluorescent colors quantum dots, and combining them in polymeric micro beads [81-86].

CONCLUSION: Nanotechnology tools are now recommended as challenging therapy of cancer. Several drug delivery systems were introduced namely liposomes, microparticles, dendrimers, carbon nanotubes, quantum dots, supramolecular biovectors, polymeric conjugates and nanoparticles to facilitate effective chemotherapy with the anticancer agents. Recently, QDs have attracted tremendous attention as the most valuable and promising approach in the areas of drug delivery, targeting, and imaging. Low toxicity, low cost, and good biocompatibility make them excellent candidates for *in vivo* bioimaging, gene/drug delivery, and cancer detection. This has created a powerful impact in various fields of disease diagnosis, intracellular tagging as photo sensitizers for treatment of cancer, biotechnology and bioassays. Research is still going on in eliminating its toxicity so that it can be safely used as biomedical application.

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