

# Functional Quantum Dots for Promising Cancer Diagnosis and Therapy

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## Abstract:

Functional nanoparticles are considered to have the potential as novel molecular probes for both carcinoma imaging and targeting delivery, which plays a critical role in cancer diagnosis and therapy. Functional quantum dots (QDs), conjugated with types of targeting ligands or anticancer drug/gene to simultaneously cancerous image, treat cancer through selective binding to the receptors over-expressed on cancerous cells and tissue surface, were introduced. A series of significant progress in the fields of the fabrication of functional QDs and their applications in cancer diagnosis and therapy were summarized in this review.

**Keywords:** Functional quantum dots; Fabrication; Applications; Cancer diagnosis; Cancer therapy

## Introduction

The diagnosis and treatment of cancer remains a key challenge for biomedical technology. The diagnosis and therapy of cancer at the cellular level will be greatly improved with the development of techniques that enable the delivery of molecular probes and therapeutic agents into cells and cellular compartments. Functional nanoparticles, one of the cutting-edge materials of the twenty-first century, are considered to have the potential as novel molecular probes for both imaging and targeting delivery, which plays a critical role in biomedicine. One major merit of using functional nanoparticles is that one can control and tailor properties in a very predictable manner to meet the needs of specific application. Recently, functional nanoparticles have received great interest in biomedical applications [1], especially their future application in the field of carcinoma diagnosis and therapy [2-5].

QDs are semiconductor inorganic nonmaterials ranging from 1-10 nm. QDs, containing elements found in groups II-IV (eg, CdSe, CdTe, CdS, and ZnSe) or III-V (eg, InP and InAs) of the periodic table, have shown great potential interest to medical scientists because of their unique advantages over traditional fluorescent dyes, such as broad excitation spectra, narrow and symmetric photoluminescence bands, large two-photon absorption cross-section, size-tunable absorption and photoluminescence spectra, exceptional photo stability, high quantum yield, and versatility in surface modification [3]. QDs have initially been used for carcinoma cell imaging. Additionally, QDs provide a versatile nanoscale scaffold for designing multifunctional nanoparticles with both imaging and drug delivery vehicles [4]. Herein, QDs, conjugated with types of targeting ligands or anticancer drug/gene to simultaneously cancerous image, cancer treatment through selective binding to the receptors over-expressed on cancerous cells and tissue surface, have the potential to considerably improve the efficiency of fluorescence imaging and target delivery [6-7]. This article provides a brief review on the recent developments of the fabrication of functional QDs and promising applications in cancerous image and cancer treatment.

## Fabrication of functional QDs

Although functional QDs as contrast agent or drug delivery vehicle

brings about many benefits to us, its fabrication is still a big challenge, because an ideal contrast agent or drug delivery vehicle must meet the need of increasing imaging or curative effect and simultaneously reducing the unintended severely side effects. In addition, to gather more information during specific cancer imaging or target delivery, QDs must be coupled with molecules which have the capabilities of recognizing the target. Surface chemistry modifications on the QDs are necessary for biomedical application. These surface modifications can also reduce the nonspecific binding, help prevent aggregation, and be critical to achieving specific target imaging and delivery. However, they often reduce the fluorescence quantum yield of the QDs.

Several recent studies have already discussed the synthesis and the biomedical imaging and targeting delivery applications of functional QDs [8-10]. There are many parameters that have to be taken into consideration and several fabrication methods that can be chosen in the design of the ideal functional QDs for cancer imaging (diagnosis) and targeting delivery (cancer therapy) (Figure 1). The main parameters are as following: i) the toxicity; ii) the fluorescence properties, including its quantum yield, its absorption cross-section, its lifetime, its resistance; iii) the ability to modify its surface chemistry without losing the QDs fluorescence; and iv) the specific target.

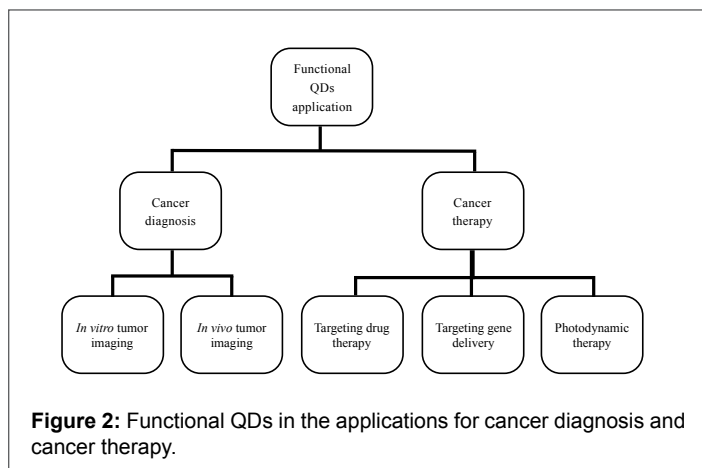
The toxicity of the functional QDs strongly depends on especially QDs' composition and surface chemistry [11]. The fluorescence properties of the functional QDs rely on the surface chemical modifications and properties of the QDs. The design to obtain low toxicity, ideal fluorescence, slow clearance and targeting as well as the strategies currently available to fabricate them will be firstly introduced.

## Toxicity and fluorescence of the functional QDs

Both low toxicity and ideal fluorescence are the primary factors which should be taken into account. Many efficient attempts were made to reduce the toxicity and preserve a good fluorescence of the QDs.

One attempt to reduce the toxicity was to choose non-toxic and biodegradable nano-materials as drug/gene carriers and to find the substitutions for heavy metal-based QDs. Up to now, non-toxic elements





90% 5-year survival rate [48] due to availability of curative treatment. Fluorescence labeling/imaging techniques are especially valuable tools in the arsenal of clinical diagnosis. Functional QDs have been wide used for improving fluorescence imaging [6,22,37,38] due to the photochemical stability and high fluorescence intensity of QDs.

**In vitro tumor imaging:** One of the most advancing applications of functional QDs is *in vitro* imaging of cancer cells. Many research groups applied functional QDs for *in vitro* fluorescence imaging of human cancer cells derived from ovarian carcinoma [6], melanoma [22], breast cancer [36], pancreatic cancer [37], glioblastoma [38], ovarian epidermoid carcinoma [49], lung adenocarcinoma [50], and hepatocellular carcinoma [24,51].

Zhang and his colleagues [36] found that QDs conjugated with anti-type 1 insulin-like growth factor receptor (IGF1R) is a promising candidate for targeting and imaging in breast cancer cells. The key in this targeting was the detection of up-regulated IGF1R in MCF-7 breast cancer cells by QD-anti-IGF1R conjugate.

Epidermal growth factor receptor (EGFR or HER1) or human epidermal growth factor 2 (HER2) is transmembrane glycoprotein that constitutes one of four members of the erbB family of tyrosine kinase receptors, is over-expressed in many cancers and can bind to epidermal growth factor (EGF) [52]. Based on that, the QD-EGF conjugate can be utilized for various cancer cells fluorescence imaging because EGFR is over-expressed in many cancers. Nakane and coworkers [53] reported most KPL-4 cells (breast cancer cells) were stained by the anti-HER2 antibody conjugated PbS QDs, whereas only very weak fluorescence signals were observed when stained with bovine serum albumin (BSA) conjugated PbS QDs after the incubation of anti-HER2 antibody conjugated PbS QDs and BSA-conjugated PbS QDs. This result clearly shows the specific targeting imaging ability of PbS QDs to HER2 surface receptors in KPL-4 cells.

Kawashima et al. [49] also explored intermolecular interactions involved in the lateral propagation of cell-signaling by EGFR single-molecules in human ovarian epidermoid carcinoma cells (A431) using nanocomposites loaded CdSe/ZnS QDs. Kawashima found that CHO and A431 cells were efficiently labeled by QD-EGF conjugates due to the specific binding of EGF to EGFR.

In research by Yong [37], they selectively detected human pancreatic cancer cells using QDs conjugated with anti-Claudin-4 antibody and anti-prostate stem cell antigen (anti-PSCA). These conjugates were recognized by the membrane proteins Claudin-4 and PSCA which are over-expressed in both primary and metastatic pancreatic cancer cells. This result clearly shows fluorescence images of human pancreatic cancer cells (MiaPaCa) treated with various nanocomposites loaded QDs. From these results, it

clearly showed that the nanocomposites loaded InP/ZnS QDs can serve as a potential biocompatible targeted nanoprobe to specifically diagnose human pancreatic cancer cells.

**In vivo tumor imaging:** The basic principles underlying *in vitro* targeting of cancer cells can be applied *in vivo*. However, *in vivo* applications of functional NIR QDs are more complicated and challenging. One main challenge for *in vivo* targeting and imaging using the functional QDs is their biodistribution and pharmacokinetics. Additionally, the type and structure of organic/bioorganic shells of QDs determine their biocompatibility and are crucial for their application in imaging *in vivo*, due to the effects of the shell on the following properties: colloidal stability, solubility in physiological fluids, influence of the basic physiological parameters, and cytotoxicity [11]. Chen *et al.* have monitored the dynamic distribution of CdHgTe/SiO<sub>2</sub> nanocomposites *in vivo* by near infrared fluorescence imaging system. They also show that CdHgTe/SiO<sub>2</sub> nanocomposites acted as a novel fluorescence probe have a maximum fluorescence emission of 785 nm and high photo-stability and the hydrodynamic diameter of CdHgTe/SiO<sub>2</sub> nanocomposites could be adjusted to 122.3 nm [54]. Another main challenge for *in vivo* targeting and imaging is the fluorescence emitting property of the functional QDs. Visible emitting QDs provide poor signal-to background ratio in deep tissue and when imaging targets in small animals [23]. While NIR QDs offer several advantages for the non-invasive visualization of living tissues because of its deeper photon penetration, low absorption and scattering. So, functional NIR QDs are considered to have the potential as novel probe for tumor diagnostics, for example, carcinoma cell labeling or tracking [55-57], tumor markers targeted imaging [58,59], tumor vessel imaging [60,61].

Carcinoma cell labeling or tracking in living organisms was monitored efficiently and sensitively, which may provide tools to locate tumors and metastases or map tumor margins during surgery. This could be achieved by functional QDs, then administrating conjugated QDs for *in vivo* targeted imaging of various human cancer cells such as oral squamous carcinoma cell [52], brain cancer [55], hepatocarcinoma cell [56], and colon carcinoma cell [57]. Fang *et al.* reported that *in vivo* fluorescence imaging of a breast tumor in a mouse were taken through anti-HER2 antibody conjugated PbS QDs injected into the tail vein. Immediately after the injection of QDs, 2nd-NIR fluorescence signals for the QDs were observed over the whole body with time: after about 1 h QDs were detected in the liver and after 48 h the breast tumor was clearly detected [51]. Yu *et al.* subcutaneously implanted HCCLM6 cancer cells in mice, and intravenously injected the QDs conjugated with an antibody to alpha-fetoprotein (anti-AFP). The QD-anti-AFP conjugate was effectively accumulated in human hepatocarcinoma cells, which have demonstrated that the QD-anti-AFP conjugate was an ideal candidate for *in vivo* targeted imaging of HCCLM6 human hepatocarcinoma cells [56].

Tumor markers play a critical role in the detection and diagnosis of cancer [58]. Biomarker assays may be useful for screening and diagnosis of cancer if a set of tumor markers can be quantified and statistically differentiated between cancerous cells and normal cells [58].

Angiogenesis, the formation of new blood vessels from preexisting vasculature, is essential for tumor growth and progression. Integrin  $\alpha\beta_3$ , which binds to RGD-containing components of the interstitial matrix, plays a key role in tumor angiogenesis and metastasis [60]. Functional QDs represent excellent tool for tumor vessel imaging [61] or multimodal molecular imaging of angiogenesis [62].

### Cancer therapy applications

**Targeting drug therapy applications:** Recently, targeted therapy has been widely explored. Drug/gene targeting by nanoparticles or nanocapsules offers the following enormous advantages, as examples:

reduces dosage, ensures the pharmaceutical effects, and minimizes side-effects, and enhances drug stability. QDs are newer luminescent nanoparticles with rich surface chemistry and unique optical properties that make them useful as visualization probes or carriers for traceable targeted delivery and therapy applications [63]. Thus, it has been developed functional QDs that can perform imaging and drug delivery tasks without the need for external dyes [64]. We will briefly describe developments of functional QDs as probes and carriers in targeting drug delivery applications.

By directly noncovalent coupling or covalent coupling drug molecules to the QD surface, drug-conjugated QDs can be delivered to specific sites and subsequently release drug molecules from the QD surface in response to local biological conditions such as pH or the presence of enzymes. Several research groups have demonstrated the integration of drug molecules with conjugated QDs and targeting moieties for targeting drug delivery *in vitro* and *in vivo*. Chakravarthy *et al.* [65] found that doxorubicin (Dox) can be effectively released from the functional CdSe/CdS/ZnS QDs conjugated with Dox and accumulated in the cell nucleus. They also demonstrated that the functional QDs can provide targeted macrophage-selective therapy for the treatment of pulmonary disease. And, several researches recently suggested that QDs conjugated therapeutic antibody [66] or drug [67] can be used as a suitable nanoparticles for breast cancer treatment. Xu *et al.* [66] demonstrated for the first time that the functional QDs conjugated with anti-GRP78 scFv could be efficiently internalized by cancer cells, thus up-regulate phosphatase-AKT-ser473 and possess biological anti-tumor activity by inhibition of breast cancer growth in a xenograft model. Fibrinogen (fib) coated CdTe/ZnTe and paclitaxel (PTX) [PTX-fib-QDs] can target MCF-7 cells and effectively deliver PTX towards breast cancer cells via the  $\alpha 5\beta 1$ -integrins [67]. Furthermore, Jeyadevia's study revealed that using TGA-CdTe QDs as nanocarrier of quercetin could enhance the anti-arthritis effect of quercetin even at a lower concentration of the drug in rheumatic complications [68].

All these studies have laid an important foundation in the functional QDs as probes and carriers for target drug delivery research and applications.

**Targeting gene delivery applications:** Gene therapy has emerged as a powerful strategy for cancer treatment over the past several decades because of the genetic link associated with tumor development and progression. The delivery of nucleic acid therapeutics to down-regulate or replace mutated genes, and to silence unexpected gene expression, is becoming an attractive approach to suppressing tumor cell growth and invasion. There have been intensive efforts to develop safe and efficient gene delivery carriers to provide high transfection efficiency at the desired target.

Besides the delivery of small molecule drugs, QDs have also been proved to have prospect for delivery of more intricate genes, such as small interfering RNA (siRNA). The short and double-stranded therapeutic siRNA works by silencing the expression of unwanted, disease-causing genes. Nevertheless, free forms of them owe high negative charge and are easy to degrade in body environment. Thus, in order to achieve optimal function in physiological conditions, they must be delivered via combination with cationic nanocarriers. Because of appropriately surface functionalized with cationic moieties, nanocomposites including QDs are good choices of siRNA carriers as they not only render these genetic drugs with physiological stability and target specificity, but also the entire nanocomposites can be optically traced. Therefore, nanocomposites loaded with QDs were specifically designed to overcome barriers in siRNA delivery such as siRNA protection, cellular penetration, endosomal release, carrier unpacking, intracellular transport and gene silencing. Li *et al.* confirmed that functional QDs could efficiently deliver siRNA into HeLa cells and

silence a target gene, and the nanocomposites loaded with QDs could also be used as fluorescence probes, allowing real-time tracking and localization of QDs during delivery and transfection *in vivo* [69]. More importantly, multifunctional QDs have been demonstrated to deliver an active siRNA to knockdown EGFRvIII receptors in human glioma cells, and subsequently monitor the resulting down-regulated signaling pathway with high efficiency [70], suggesting that functional QDs could be designed to deliver gene to a specified target cell type.

**Photodynamic therapy of cancer:** Photodynamic therapy (PDT) is still considered to be a new and promising invasive antitumor strategy that can exert a selective cytotoxic activity toward malignant cells. The antitumor strategy involves administration of a photosensitizing (PS) agent followed by irradiation at a wavelength corresponding to an absorbance band of the photosensitizing agent. Clinical studies revealed that PDT can be curative, particularly in early stage tumors because sensitizer may lead to direct tumor cell death, damage to the microvasculature, and induction of a local inflammatory reaction [71]. QDs can be designed to have fluorescence peaks at different wavelengths by adjusting their size. The unique property of the QDs allows QDs to be fabricated for specific functions such as Fluorescence Resonance Energy Transfer (FRET), in which a specific emission wavelength can transfer energy to drug molecules or photosensitizers. Consequently, FRET phenomenon can be potentially used for the development of novel therapeutic approaches for cancer treatment. Additionally, photo stability of QDs is the most promising property for PDT. Recent reports showed that QDs can be used in photodynamic and radiation therapy of cancer [72,73].

Although targeted delivery of QDs in cancer cells and tumor milieu by using QDs conjugated with anticancer antibodies or other bio molecules have become possible recently, compared with conventional PS drugs such as porphyrins and phthalocyanines, the efficiency of QDs to produce ROI under direct photoactivation is low. Herein, preparation of conjugates between QDs and conventional PS drugs, investigation of energy transfer efficiencies from QDs to PS drugs and ROI production by the conjugates are being widely investigated.

## Conclusions

Real-time imaging and targeting delivery have been hot topics in cancerous diagnosis and therapy fields. Current investigation of the functional QDs *in vitro* and *in vivo* has offered less invasive imaging and targeting drug delivery. However, up to date the clinical applications of the functional QDs have been limited due to side-effects. Various novel nanoparticles such as CNTs have been explored with recent developments in the preparation and characterization techniques of nanoparticles. The emergence of functional QDs, targeting moieties, and other nanoparticles enabled to improve imaging and targeting delivery applications because of their better biocompatibility, lower toxicity and longer circulation time *in vivo*, which were better applied for high-resolution noninvasive cancer diagnosis and therapy.

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