Expert Opinion

Quantum dots in cancer therapy

Guopei Luo, Jiang Long†, Bo Zhang, Chen Liu, Shunrong Ji, Jin Xu, Xianjun Yu† & Quanxing Ni

†*Fudan University Shanghai, Shanghai Cancer Center, Department of Pancreas&Hepatobiliary Surgery, Shanghai, China and *Fudan University Shanghai, Shanghai Medical college, Department of oncology, shanghai, china*

Introduction: Quantum dots (QDs) are nanometer-size luminescent semiconductor nanocrystals. Their unique optical properties, such as high brightness, long-term stability, simultaneous detection of multiple signals and tunable emission spectra, make them appealing as potential diagnostic and therapeutic systems in the field of oncology.

Areas covered: This paper summarizes the recent progress of promising applications of QDs in cancer therapy, from the following aspects: identifying molecular targets, sentinel lymph-node mapping, surgical oncology, drug delivery and tracking, fluorescence resonance energy transfer and photodynamic therapy, personalized and predictive medicine, and multifunctional design and development. Limitations and toxicity issues related to QDs in living organisms are also discussed.

Expert opinion: Bioconjugated QDs can be used to identify potential molecular biomarkers for cancer diagnosis, treatment and prognosis. They may allow the surgeon to map sentinel lymph nodes and perform a complete surgical resection. Their unique optical properties make them ideal donors of fluorescence resonance energy transfer and photodynamic therapy studies. Multifunctional QDs have become effective materials for synchronous cancer diagnosis, targeting and treatment. For QDs, toxicity remains the major barrier to clinical translation.

Keywords: cancer, molecular imaging, nanoparticles, nanotechnology, quantum dots, therapy

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1. Introduction

Molecular imaging is an area of considerable interest in understanding the complexity and dynamics of biological interaction in cancer [1,2]. Organic fluorophores have been used for these purposes. Unfortunately, they are subject to certain limitations, such as narrow excitation spectra, broad emission spectra and insufficient sensitivity [3].

QDs, such as CdSe–ZnS core-shell nanoparticles, are inorganic fluorophores that potentially circumvent the limitations of organic dyes (**Table 1**) [4-6]. In comparison with organic dyes, QDs are about 10 – 100 times brighter, mainly due to their large absorption cross sections, 100 – 1000 times more stable against photobleaching and show narrower and more symmetric emission spectra [1,7]. In addition, a single light source can be used to excite multicolor QDs, and the emission wavelength can be tuned from the ultraviolet, through the visible and near-infrared (NIR) spectra, and even into the mid-infrared [8]. QDs provide a large surface area to develop multifunctional nanoparticles for simultaneous drug delivery, targeting and imaging [9]. Finally, when conjugated with biomolecular affinity ligands, such as antibodies, peptides or small molecules, these nanoparticles can be used to target malignant tumors with high specificity [10-13].

The unique optical properties of QDs make them appealing as *in vivo* and *in vitro* fluorophores in a variety of cancer biological investigations, including

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Article highlights.

- By conjugating quantum dots (QDs) with antibodies, aptamers, oligonucleotides or peptides specific for the target, QDs can be used to identify potential molecular biomarkers.
- Novel QDs have been developed to provide real-time image-guided localization, which facilitates the detection and resection of the sentinel lymph nodes (SLNs) in various types of cancer with complex lymphatic draining systems.
- Recent advances in QD technologies may aid the surgeon to perform a complete surgical resection.
- QDs provide a versatile nanoscale scaffold to develop multifunctional nanoparticles for simultaneous drug delivery and tracking.
- The unique optical properties of QDs make them ideal donors in fluorescence resonance energy transfer and photodynamic therapy studies.
- Bioconjugated QDs have emerged as a new platform to detect a cancer's unique molecular profile, making personalized and predictive medicine a reality.
- Multifunctional QDs have become effective materials for synchronous cancer diagnosis, targeting and treatment.
- Although QDs offer potentially invaluable societal benefits of human disease, toxicity remains the major barrier to clinical translation.

This box summarizes key points contained in the article.

diagnosis and therapy [4,10]. In this article, we focus on recent progress and future challenges in cancer therapy using QDs.

2. QDs in cancer therapy

Recent developments in QD technology have already made a remarkable impact on cancer therapy. Here, seven applications of QDs in cancer therapy are discussed (**Figure 1**).

2.1 Identifying molecular targets

Molecular biomarkers play a critical role in the detection and diagnosis of cancer [14]. Biomarker assays may be useful for screening and diagnosis of cancer if a set of molecular markers can be quantified and statistically differentiated between cancerous cells and normal cells [15]. Markers of cancers are often present at very low concentrations, so methods capable of low detection limits are required. This could be achieved by conjugating QDs with antibodies, aptamers, oligonucleotides or peptides specific for the target, then administrating conjugated QDs *in vivo* for active tumor targeting (**Figure 2**) [16].

HER2 (also known as ErbB-2) is a member of the erbB-like oncogene family and a protein giving higher aggressiveness in breast cancers [17]. Wu *et al.* [18] synthesized QDs linked to immunoglobulin G (IgG) and streptavidin to label HER2 on the surface of fixed and live cancer cells, to stain actin and microtubule fibers in the cytoplasm, and to detect nuclear antigens inside the nucleus. They found that all labeling signals are specific for the intended targets and are brighter and considerably more photostable than organic dyes [18]. Gao *et al.* [19] designed anti-HER2 affibody molecules with an *N*-terminus cysteine residue and precisely conjugated with maleimide-functionalized QDs to make nanoparticle–affibody conjugates. The *in vitro* and *in vivo* study showed that the conjugates are highly specific to target and image HER2-expressing cells and tumors [19]. Chen *et al.* [20] conducted quantitative determination of HER2 level by QD-based quantitative spectral analysis in specimens, which was in accordance with traditional method.

Epidermal growth factor receptor (EGFR) is overexpressed in a wide variety of solid human malignancies and is an important molecular for targeted therapy [21]. Nida *et al.* investigated the use of QDs conjugated to anti-EGFR antibodies to detect precancerous biomarkers *in vitro* and they found SiHa cervical cancer cells showed specific labeling of EGF receptors [22]. Jung *et al.* [23] investigated the potential of (99 m)Tc-hydrazinonicotinamide EGF-PEG-QDs *in vitro* and *in vivo* and they found that (99 m)Tc-hydrazinonicotinamide EGF-PEG-QDs can provide EGFR-targeted imaging of breast tumors.

Bioconjugated QDs also can be exploited to determine accurately the clinical benefit of molecular target therapy for any individual patient [24,25]. As an imaging method for overexpression of tumor markers, bioconjugated QDs can be expected to provide important information on the expression levels of tumor markers on the cancer cells before and after targeted therapy, which will directly affect the patients' future care [23]. In addition, the potential of multiplexed sensing using QDs with tunable emission spectra is promising for simultaneous detection of multiple biomarkers for cancer diagnosis and treatment [15].

2.2 Sentinel lymph-node mapping

Sentinel lymph nodes (SLNs) are the first lymph nodes or group of nodes reached by metastasizing cancer cells from a primary tumor, which contribute to stage and operative strategy in cancer surgery [26]. SLN mapping is one of the most revolutionary advances in surgical oncology in recent years [27]. Current SLN mapping techniques include using peritumoral injection of radioisotopes, such as Technetium-99 m-colloidal albumin, the isosulfan blue dye or the combination of the two [28]. Unfortunately, these techniques are limited by exposure to radiation, unpredictable drainage patterns, skip metastasis, high background signal and the inability to image lymphatic tracers relative to surgical anatomy in real time [29]. These limitations have encouraged the development of newer and more effective imaging methods.

Novel QDs have been developed to provide real-time image-guided localization, which facilitates the detection and resection of the SLNs (**Figure 3**) [29-35]. They can be employed for SLN mapping in various types of cancers with complex lymphatic draining systems, such as breast [36], gastrointestinal [29], esophageal [31], lung [32] and bladder [37]. In comparison with traditional techniques, QDs have the optimal separation from autofluorescence background and

Table 1. Representative papers of quantum dot (QD) applications in surgery.

Sentinel lymph-node mapping	
Kim *et al.*, 2004	First and significant paper showing QDs can be applied to SLN mapping
Ballou *et al.*, 2004	Study about the *in vivo* behavior of injected QDs into live mice
Parungo *et al.*, 2005	Identification of esophageal SLNs
Soltesz *et al.*, 2005	Identification of lung SLNs
Soltesz *et al.*, 2006	Identification of gastrointestinal tract SLNs
Frangioni *et al.*, 2007	Utilizing type II quantum dots in animal model systems of SLN mapping
Hama *et al.*, 2007	Simultaneous two-color spectral fluorescence lymphangiography with QDs to map two lymphatic flows from the breast and the upper extremity
Knapp *et al.*, 2007	Identification of bladder SLNs
Pons *et al.*, 2010	Cadmium-free $CuInS_2$/ZnS QDs for SLN imaging with reduced toxicity
Complete resection	
Cai *et al.*, 2006	QD705-RGD targeting to athymic nude mice bearing subcutaneous U87MG human glioblastoma tumors
Arndt-Jovin *et al.*, 2009	QDs coupled to EGF or anti-EGFR specifically label glial tumor cells in cell culture, glioma mouse models and human brain-tumor biopsies
Kantelhardt *et al.*, 2010	QDs coupled to EGFR specific visualization of glioma cells in living low-grade tumor tissue

EGFR: Epidermal growth factor receptor; SLNs: Sentinel lymph nodes; QDS: Quantum dots.

the increased penetration of both excitation and light emission through thick tissues [38]. These allow the surgeon to successful remove the incriminated SLNs and minimize the size of the necessary incision [30,39]. In addition, QDs injected into tumors drain to the SLNs very quickly [33,40], which suggests that, with the guidance of QDs, it should be possible to remove the primary tumor and the SLNs in a single surgery. In gastrointestinal SLN mapping, injection of 200 pmol of NIR fluorescent QDs into various intra-abdominal organs identified the SLNs in less than 60 s and the afferent lymphatics in 100% of the cases [29]. Furthermore, unlike blue dye that contains particles < 5 nm that can pass through multiple nodes, therefore, leading to false-positive results, QDs may be engineered to precise sizes that enable localization in the SLNs [29].

2.3 Surgical oncology

Despite recent progress in adjuvant therapies, surgery is still the most effective and widely used procedure in treating human cancers [41]. The single most important predictor of patient survival is a complete surgical resection [41]. However, complete resection for malignant tumors often fails because of the high incidence of local recurrence [41,42]. Standard imaging techniques have been used to intraoperative microscale imaging in animal model systems [43]. Unfortunately, these techniques do not permit the intraoperative identification of individual or small clusters of residual tumor cells, precluding their selective removal while sparing the surrounding normal tissue [42].

Recent advances in QD technologies may aid the surgeon to perform a complete surgical resection [42,44]. When conjugated with targeting ligands such as monoclonal antibodies, peptides or small molecules, these nanoparticles can be used to target malignant tumor cells and tumor microenvironments with high specificity and affinity [10-12,19]. Their unique optical properties allow surgeons to delineate tumor margins, to identify residual tumor cells and micrometastases, and to determine whether the tumor has been completely removed [42,44-46]. For example, Arndt-Jovin *et al.* [42] investigated QDs coupled to EGF or EGFR, in combination with fluorescence microscopy, as tools for discriminating glioblastoma cells from normal tissue. They demonstrated a clear demarcation between brain and tumor tissues at the macroscopic as well as the cellular level provided by the fluorescence emission of the QDs [42]. Moreover, QDs coupled to EGF or anti-EGF receptor can specifically and sensitively label glial tumor cells in cell culture, glioma mouse models and human brain–tumor biopsies [42]. In another study, Kantelhardt *et al.* [47] demonstrated that QDs targeted to EGFR can clearly distinguish low-grade as well as high-grade glioma tissue from normal brain tissue both at the macroscopic and at the single cell level with very high contrast ratios in *ex vivo* experiments, which could allow intraoperative guidance for the removal of residual tumor cells from the resection cavity.

2.4 Drug delivery and tracking

QDs provide a versatile nanoscale scaffold to develop multifunctional nanoparticles for simultaneous drug delivery and imaging [48]. Utilization of single-QD carriers for *in vivo* applications is desirable, as intermediate size of such carriers (~ 10 – 20 nm in diameter) reduces the renal clearance as well as uptake by reticulo-endothelial system, thus increasing the blood circulation time and improving the delivery efficiency [5]. Moreover, QDs with water-soluble capping stabilizer such as mercaptoacetic acid, mercaptoethylamine and polyethylene glycol polymer are ready to conjugate with drug molecules via covalent bonds or electrostatic interaction [49].

QDs have been engineered to carry distinct classes of therapeutic agents, which represent an exciting advance in

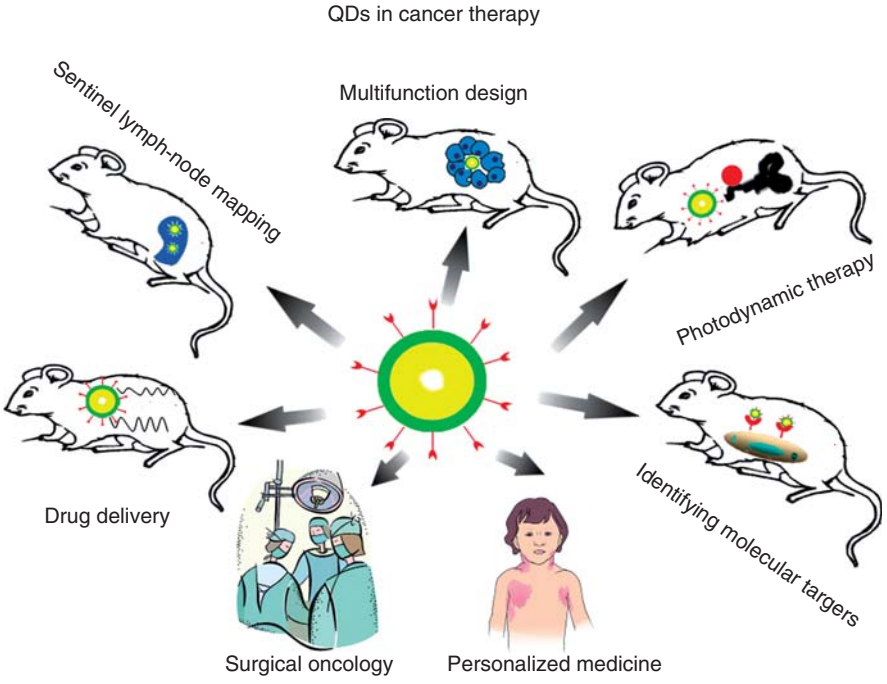

Figure 1. Quantum dots (QDs) in cancer therapy. QDs can be exploited to a variety of investigations associated with cancer therapy, including identifying molecular targets, sentinel lymph-node mapping, drug delivery and tracking, surgical oncology, fluorescence resonance energy transfer and photodynamic therapy, personalized and predictive medicine, and multifunctional design and development.

the field of nanomedicine [40,50,51]. Bagalkot *et al.* [50] reported a novel QD-aptamer(Apt)-doxorubicin (Dox) conjugate [QD-Apt(Dox)] as a targeted cancer imaging, therapy and sensing system *in vitro*. This simple multifunctional nanoparticle system can deliver doxorubicin to the targeted prostate cancer cells and sense the delivery of doxorubicin by activating the fluorescence of QD, which concurrently images the cancer cells [50]. Zhao *et al.* [51] synthesized QDs coated with beta-cyclodextrin (beta-CD) coupled to amino acids with different surface charges through direct ligand-exchange reactions and used them to deliver siRNA *in vitro*. They found that the QDs were localized in vesicles in the cytoplasm of the cells and the unique optical properties of QDs allow visible imaging of siRNA delivery in live cells [51].

QDs attached covalently to therapeutic agents can serve as a tracker to evaluate the delivery effectiveness and the pharmacodynamics of the agents noninvasively in real time [40,52-57]. For example, several studies have employed QDs to track the RNA interference (RNAi) process [40,58]. RNAi is an effective technique for regulating or silencing specific genes, which can be applied to treat various diseases. Incorporation of suitable molecular imaging techniques into future RNAi-based clinical trials will provide more pieces of the puzzle, thus facilitating the transformation of RNAi into a powerful therapeutic modality in the clinic [59]. Tan *et al.* conjugated QDs with HER-2 siRNA to track the delivery of therapeutic siRNA and to monitor the effectiveness of siRNA-mediated downregulation of the receptor in breast cancer cell lines [58]. Targeted delivery and gene-silencing effects of HER2 siRNA was established by the self-tracking siRNA delivery nanoparticles [58].

2.5 Fluorescence resonance energy transfer and photodynamic therapy

Fluorescence resonance energy transfer (FRET) is a process in which energy is transferred from an excited donor to an acceptor via a resonant, near-field dipole–dipole interaction [60]. It is one of the most general techniques for imaging biologically interacting molecules in a cell [61]. Problems of using conventional dyes for FRET include fast photobleaching and significant emission overlap between donor and acceptor [62]. The long-term photostability and highly tunable emission properties of QDs make them ideal donor species in FRET studies [62]. Bawendi *et al.* were among the first groups to report on the energy transfer process in semiconductor QDs [63]. Since then, various protein and DNA assays utilizing QD-based FRET have been explored by several groups [50,64-67]. Ghadiali *et al.* [68] demonstrated that self-assembled peptide–QD conjugates can serve as surrogate substrates in a simple homogeneous assay for protein kinase activity through FRET. Kang *et al.* [61] applied FRET to image the colocalization of QD-RGD and Cy3-AS1411 in a single HeLa cell. They showed that the fluorescence overlay by FRET was quantitatively and geographically quite different from that of

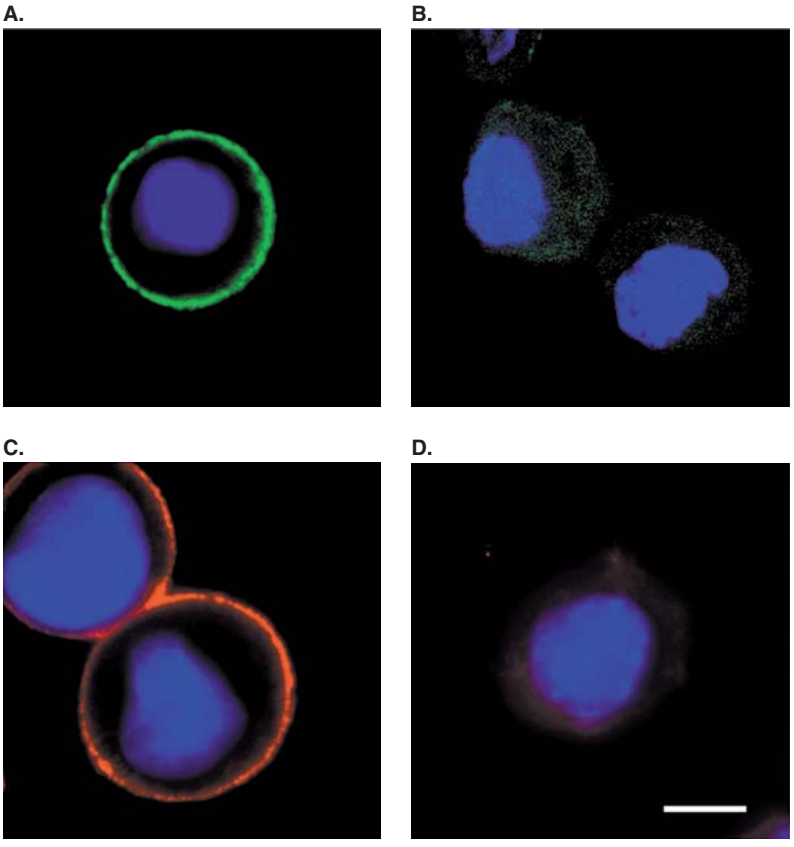

Figure 2. HER2 was clearly labeled with (A) quantum dot (QD) 535–IgG and (C) QD 630–IgG in fixed breast cancer SK-BR-3 cells. There were no detectable or very weak nonspecific signals on the cell surface when incubated with normal mouse IgG and QD-IgG (B, D).
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individual confocal images, indicating that QD-based FRET analysis can provide information on geographical colocalization of proteins in naive cells [61].

Since its discovery in the early 1900s, photodynamic therapy (PDT) has developed from an emerging cancer treatment to an FDA-approved therapy for different malignancies [69-71]. QDs can serve as energy donors to conventional photosensitizers through FRET or interact directly with molecular oxygen via energy transfer mechanisms, to generate reactive $^1O_2$ species that can be exploited for PDT [72]. In view of their flexible spectral characteristics, QDs can be engineered in size and composition to match those of any PDT photosensitizer and be used as energy donors [72]. In the work of Samia *et al.*, CdSe QDs were linked to a silicon phthalocyanine photosensitizer through an alkyl group and used as a primary energy donor [72]. Excitation of CdSe QDs activated emission of silicon phthalocyanine photosensitizer at 680 nm, which enabled the use of an excitation wavelength that is not absorbed by the sensitizer [72]. Through the FRET mechanism from QDs to the silicon phthalocyanine photosensitizer, oxygen reactive species were generated for photodynamic cancer therapy [72]. This was the first demonstration of utilizing QD-based FRET to facilitate excitation of a PDT photosensitizer, which is known to generate reactive $^1O_2$ species available for photodynamic cancer therapy [72]. Morosini *et al.* [73] synthesized hydrophilic near-infrared emitting CdTe(S)-type QDs conjugated with folic acid *in vitro*, which showed a targeted and enhanced photocytotoxicity response to folic acid-positive KB cells. Although several challenges remain before they can be adopted for clinical use, these active or second-generation PDT nanoparticles probably offer the best hope for extending the reach of PDT to regions deep in the body [74].

2.6 Personalized medicine

Personalized medicine is a broad and rapidly advancing field of health care that is informed by each person's unique clinical, genetic, genomic and environmental information [75]. It is an emerging field of medicine promising to provide efficient tools against cancer and other challenging diseases [5]. Theoretically, a cancer's unique molecular profile can be used to predict its invasive and metastatic potential, its ability to evade immune surveillance and its potential response to treatment, making personalized and predictive medicine a reality [76,77].

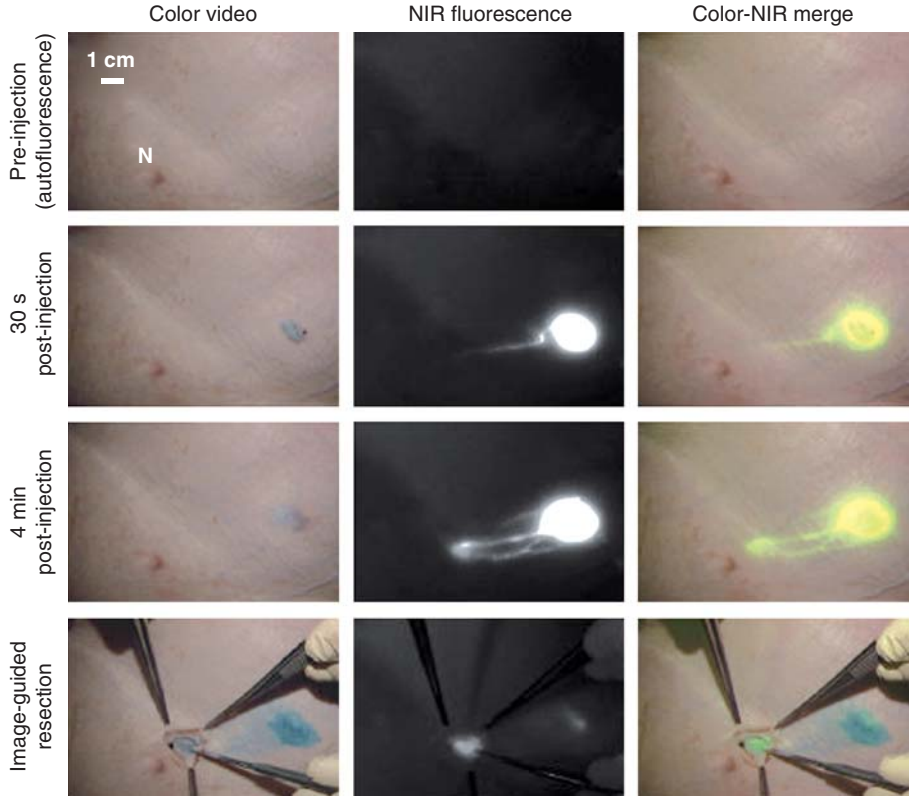

Figure 3. Near-infrared quantum dot (QD) imaging *in vivo*. Images of the surgical field in a pig injected intradermally with 400 pmol of near-infrared QDs in the right groin. Four time points are shown from top to bottom: before injection (autofluorescence), 30 s after injection, 4 min after injection and during image-guided resection. Note the lymphatic vessel draining to the sentinel node from the injection site.
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NIR: Near-infrared.

Bioconjugated QDs have emerged as a new platform to quantify cancer's unique molecular profile in intact cancer cells and tissue specimens [1,2,5,78]. A great advantage of QDs is that multicolor QD probes can be used to image and track multiple molecular targets simultaneously, which represents a significant challenge for traditional imaging modalities (**Figure 4**) [5,79]. Liu *et al.* reported the use of multiplexed QDs and wavelength-resolved spectral imaging for molecular mapping of tumor heterogeneity on human prostate cancer tissue specimens [80]. They demonstrate extensive tumor heterogeneity at the molecular, cellular and architectural levels, allowing direct visualization of human prostate glands undergoing structural transitions from a double layer of basal and luminal cells to a single layer of malignant cells [80]. Overexpression of the HER2 protein occurs in 25 – 30% of human breast cancers, which is closely related to the malignant biological behaviors of the tumor and personalized treatment of breast cancer [81]. Several studies have used QDs to directly observe the HER2 expression level [20,82,83]. Liu *et al.* [83] use a QD-based double-color imaging technique to simultaneously show the HER2 level on breast cancer cells and the type IV collagen in the tumor matrix. With the increase of HER2 expression level, there has been a progressive decrease in type IV collagen around the cancer nest [83]. In another study, *Chen et al.* [20] conducted quantitative determination of hormone receptors and HER2 by QD-based quantitative spectral analysis in specimens, which had excellent consistence with traditional method. Personalized medicine of cancer, facilitated by QDs, is expected to enable early detection of cancer, more effective and less toxic treatment increasing the chances of cure [84].

2.7 Multifunctional design and development

Treatment of cancer generally involves the sequential use of diagnostic tools and therapeutic modalities. Multifunctional platforms combining therapeutic and diagnostic imaging functions in a single vehicle have the potential to change this paradigm [85]. Structurally, the large surface area combined with versatile surface chemistry makes QDs convenient scaffolds to accommodate anticancer drugs, leading to the development of nanostructures with integrated imaging, targeting and therapeutic functionalities [9]. Multifunctional QD-integrated imaging, targeting and therapeutic functionalities have become effective materials for

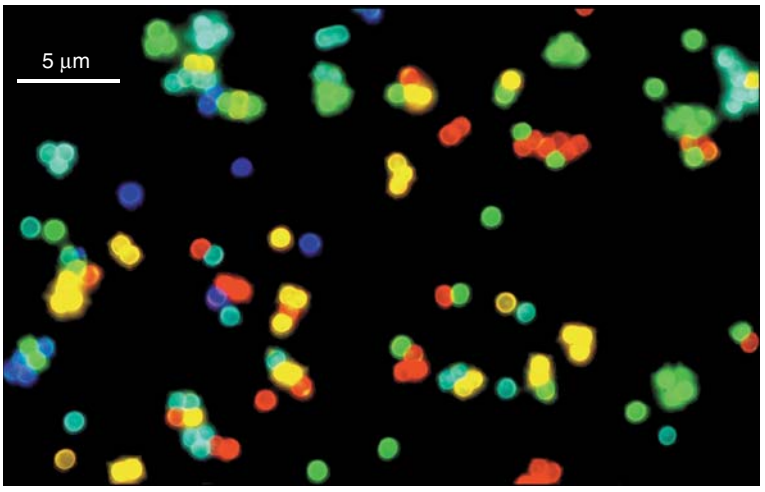

Figure 4. Fluorescence micrograph of a mixture of CdSe/ZnS quantum dot (QD)-tagged beads emitting single-color signals at 484, 508, 547, 575 and 611 nm. The beads were spread and immobilized on a polylysine-coated glass slide, which caused a slight clustering effect.
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synchronous cancer diagnosis, targeting and treatment. In one example, Bagalkot *et al.* [50] reported a ternary system composed of a QD, an aptamer and the small molecular anticancer drug doxorubicin (Dox) for *in vitro* targeted imaging, therapy and sensing of drug release. By functionalizing the surface of fluorescent QD with the A10 RNA aptamer, which recognizes the extracellular domain of the prostate-specific membrane antigen (PSMA), they developed a targeted QD imaging system (QD-Apt) that is capable of differential uptake and imaging of prostate cancer cells that express the PSMA protein [50]. This simple multifunctional nanoparticle system can deliver Dox to the targeted prostate cancer cells and sense the delivery of Dox by activating the fluorescence of QD, which concurrently images the cancer cells [50].

In addition, QDs may be combined with other nanomaterials to assemble small but complex multifunctional machines (**Figure 5**) [86-89]. For example, Al-Jamal *et al.* encapsulated poly(ethylene glycol)-coated QD in the internal aqueous phase of different lipid bilayer vesicles to make functionalized-quantum-dot-liposome (f-QD-L) hybrid nanoparticles [90]. f-QD-L are injected intratumorally into solid tumor models leading to extensive fluorescent staining of tumor cells compared with injections of the f-QD alone. f-QD-L hybrid nanoparticles constitute a versatile tool for very efficient labeling of cells *ex vivo* and *in vivo*, particularly when long-term imaging and tracking of cells is sought [90]. Moreover, f-QD-L offer many opportunities for the development of combinatory therapeutic and imaging modalities by incorporating both drug molecules and QDs within different compartments of a single vesicle [90].

3. Challenges

Although QDs offer potentially invaluable societal benefits of human disease, toxicity remains the major barrier to clinical translation [91,92]. Questions regarding biochemical mechanisms of cytotoxicity are beginning to be answered. QD size, charge, concentration, outer coating bioactivity (capping material and functional groups) and stability have each been implicated as factors in QD toxicity [93-96]. Mechanism study also suggested involving production of reactive oxygen species such as free hydroxyl radicals and singlet oxygen [97]. In a more adequate model based on 3D cell culture, Lee *et al.* [98] found significantly reduced nanoparticle-induced toxicity compared with 2D cell cultures, emphasizing the impact of tissue morphology on toxicity. MicroRNAs have also been reported as participants in the cytotoxicity of QDs [99]. Studies of bovine serum albumin–QDs conjugates have shown bovine serum albumin to provide protection against QD-induced cytotoxicity [100]. Albumin reduced or eliminated toxicity through possession of peptides responsible for the extracellular antioxidant defense system. Prevention of core atoms, Cd atoms, from being accessible to the surrounding environment has been passivated by shelling the core in extra layers of material.

The most common QD composition, (CdSe)ZnS, contains a core of cadmium and selenium, both of which are known to be toxic [101]. Almost all studies so far have reported negligible cytotoxicity of these QDs [10,102-108]. A ZnS shell, combined with a robust organic coating, can protect the core well enough to prevent oxidation and release of elemental cadmium and selenium, within the time course of an assay [102]. However, *Chan et al.* demonstrated that CdSe-core QDs can induce apoptotic biochemical changes, including c-Jun amino-terminal protein kinase (JNK) activation, loss of mitochondrial membrane potential, mitochondrial release of cytochrome c and activation of caspase-9 and caspase-3 in the IMR-32 human neuroblastoma cell line [109]. More studies about QDs toxicity need to be done before they can be applied in clinical settings.

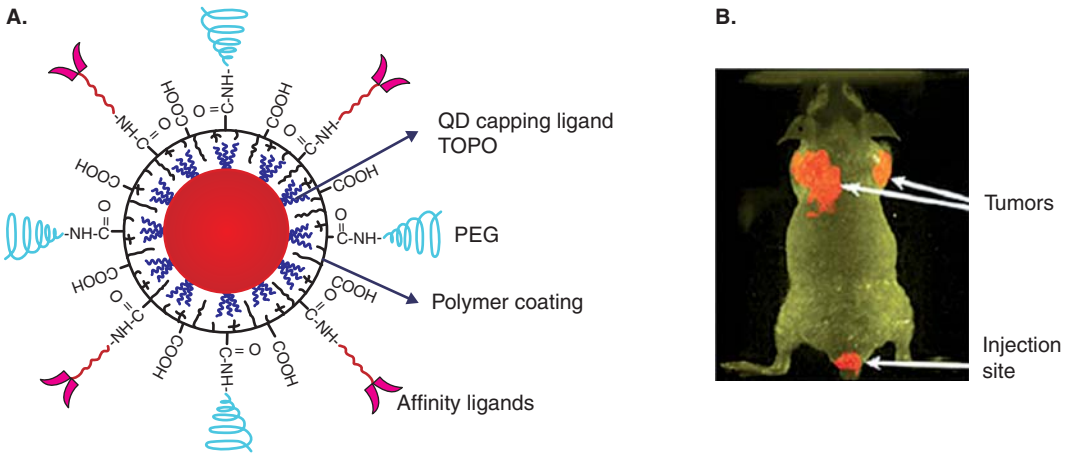

Figure 5. A. Structure of a multifunctional quantum dot (QD) probe, showing the capping ligand TOPO, an encapsulating copolymer layer, tumor-targeting ligands (such as peptides, antibodies or small-molecule inhibitors) and PEG. **B.** *In vivo* fluorescence images of tumor-bearing mice using QD probes with PEG-PSMA Ab conjugations.
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Besides cytotoxicity, it is also important that QDs do not interfere with other cellular or physiological processes, either through nonspecific binding, by preventing specific binding through steric hindrance, or by changing biomolecule functionality or diffusivity [110]. Nonspecific binding is a problem that can be addressed through surface coatings, as hydrophilic polymers such as PEG are known to reduce nonspecific interactions with particles [111]. The fact that QDs are on the same size scale as large proteins could alter the ability of coupled biomolecules to bind to their targets, either by steric hindrance or by altering biomolecular functionality [112]. The large size of QDs would also decrease the rate of diffusion of attached biomolecules. If these problems are significant, smaller sized QD probes will need to be designed or small-molecule organic dyes may be used instead of QDs [112].

4. Expert opinion

As a new class of molecular imaging agents, QDs have already fulfilled some of their potential in cancer therapy. We divide the application of QDs in the field of oncology into peri- and intraoperation stages, as currently surgery is the most effective method of cancer therapy.

In the peri-operation stage, bioconjugated QDs can be used to identify and quantify a set of molecular cancer markers. These markers can be applied to find molecular targets to aid targeted therapy, evaluate disease behavior, clinical outcome, treatment response and disease recurrence. In addition, because of their ultra-sensitivity, bioconjugated QDs can be used to detect metastasis, especially micro-metastasis. QDs may also be employed to track circulating tumor cells or even circulating stem cells, which are important prognosis factor and sources of recurrence [113].

Besides identifying molecular cancer markers in the peri-operation stage, QDs could be engineered to carry distinct classes of therapeutic agents, representing an exciting advance in the field of nanomedicine. Additionally, QD tags can serve as a tracker to monitor the delivery effectiveness and the pharmacokinetics of the agents noninvasively in real time. Interestingly, QDs may be inherently therapeutic, as they have been shown to be photosensitizers for the generation of reactive oxygen species, which could induce apoptosis in cancer cells. Finally, simple QDs may be combined with other nanomaterials to assemble small but complex multifunctional machines, including imaging (single or dual modality), therapy (single drug or combination of two or more drugs) and targeting (one or more ligands).

In the intraoperation stage, QDs can be employed to mapping the primary tumor and any potential metastasis around the tumor in real time through fluorescence imaging. They have the optimal separation from autofluorescence background and the increased penetration of both excitation and light emission through thick tissues. In addition, QDs can also be applied to find any tumor residual after removing the primary tumor. Furthermore, by correlating the deep imaging capabilities of magnetic resonance imaging with QDs, a surgeon could visually identify tiny tumors during an operation and remove the diseased cells and tissues completely [114]. It is worth to mention that QDs applied in SLN mapping are the most promising area to integrate into clinical practice.

The rapid development of QD technology, especially surface modification and bioconjugation, has already fulfilled some of the hopes of developing newer, more effective cancer-treating methods. However, most studies are still at a proof-of-concept stage and are not immediately relevant to clinical settings. Fundamental studies are needed to enhance stability and sensitivity, maximize specificity and minimize toxicity, which must be tackled before introducing into clinical practice. In a word, QDs have far from exhausted

their biological potential in cancer therapy. They will complement organic fluorophore deficiencies in particular applications such as *in vivo* imaging. Undoubtedly, researchers will catch on to these exciting developments and find as yet unforeseen applications for this new modality, thus open new doors to cancer therapy.

Declaration of interest

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Affiliation

Guopei Luo[1], Jiang Long[†1], Bo Zhang[2], Chen Liu[2], Shunrong Ji[2], Jin Xu[2], Xianjun Yu[†2], Quanxing Ni[2]
[†]Author for correspondence
[1]Fudan University Shanghai, Shanghai Cancer Center, Department of Pancreas&Hepatobiliary Surgery, No. 270, Dong'An Road, Xuhui District, Shanghai, 200032, China
Tel: +021 64175590 1306; Fax: +021 64031446; E-mail: surgeonlong@gmail.com
[2]Fudan University, Shanghai Medical College, Department of Oncology, Shanghai, 200032, China
E-mail: yuxianjun88@hotmail.com