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Translational Applications of Quantum Dots in Biomedicine: A Continuum from Fluorescence Detection to Image-Guided Intervention

Yang Yu

School of Materials Science and Engineering, Hohai University, Nanjing, China
1653567817@qq.com

Abstract. Quantum dots (QDs) are colloidal semiconductors with quantum confinement, allowing bright, narrowband, size-tunable emission under broad excitation. They operate robustly in protein-rich fluids and support precise bioconjugation. This review links fluorescence detection to imaging-guided intervention, using FRET, inner-filter, photo-induced electron transfer, and ratiometric schemes to convert molecular recognition into quantitative optical signals. Heavy-metal-reduced I–III–VI and III–V cores and carbon/graphene dots provide NIR-I/II readouts with high signal-to-background, enabling repeated irradiation. Integrating shared optical backbones across detection and treatment will increase information density per microliter, shorten decision cycles, and enable closed-loop theranostics in oncology and infection.

Keywords: Quantum dots, Fluorescence detection, Biomedical imaging, NIR-II imaging, Theranostics

1. Introduction

Colloidal quantum dots (QDs) have evolved into distinct biomedical fluorophores due to their ability to produce discrete states and emissions that redshift with size. This tunability aligns with practical requirements for bioscience, such as single-source excitation, narrow bands, and high photostability. Layered engineering, including epitaxial shells, compact ligands, and antifouling polymers, reduces nonspecific adsorption and preserves colloidal stability [1,2]. A materials landscape has coalesced around biocompatibility and emission control. II–VI core/shell structures long set benchmarks for quantum yield and linewidth, but cadmium and lead concerns accelerated cadmium/leadfree alternatives. I–III–VI semiconductors such as $CuInSe_2$ and $CuInS_2$ (often with ZnS shells) offer broadband absorption and bathochromic emission into NIRI (700–900 nm) and NIRII (1000–1700 nm), with surfaces that accept robust bioconjugation [3]. In parallel, III–V systems (e.g., InP, GaP, InAs) deliver bright, narrow emission when properly passivated, while carbon and graphene dots provide aqueous, lowtemperature syntheses from biomassderived or heterocyclic precursors with abundant functional handles and generally low acute toxicity suitable for biosensing and topical devices [4]. Biomedicine focuses on two main axes: detection and imaging. Transduction schemes match target class and matrix, with Cadmium/lead-free NIR-II probes demonstrating convergence of

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detection and imaging, suggesting a liquid biopsy-to-image guideline continuum. [5]. On the intervention axis, QDmediated photodynamic and photothermal therapies exploit spectral windows that minimize tissue autofluorescence and scattering. Hydrogels and wound dressings that integrate QDs act as transparent, benign depots that confine dose locally and permit repeated irradiation under controlled fluence. Translation balances performance with safety and manufacturing. Mechanistic toxicology now links specific surface chemistries on graphene dots to Ca^{2+} dysregulation and inflammasome activation in hepatic macrophages, providing levers for saferbydesign nanodots [6]. Continuous flow and microwave-assisted syntheses offer tighter batch control and lower impurity burdens than traditional flask routes, supporting assay standardization and regulatory review. As QDs move towards the clinic, integration with MRI/CT or ultrasound and validation against clinical chemistry norms will determine adoption. Two themes anchor the Main Body: matching mechanism to matrix and matching materials to mission, connecting fluorescence detection to imaging-guided intervention.

2. Fluorescence detection in biomedicine

2.1. Sensing mechanisms and assay architectures

Fluorescence detection using quantum dots uses optical transduction schemes to map molecular recognition events to quantifiable spectral changes. Four design logics dominate: fluorescence resonance energy transfer (FRET), inner-filter effect (IFE), photo-induced electron transfer (PET), and ratiometric strategies. FRET-centered QDs use a spectrally overlapping acceptor, which can be excitation-matched and configured into multiplexed panels with minimal crosstalk. IFE designs use spectral attenuation by an absorber, resulting in turn-off responses for chromophoric analytes and redox metabolites. PET serves as a complementary route for small-molecule sensing, where electron transfer between a surface-bound redox center and the QD core toggles emission. Common implementations include enzyme-responsive linkers that create or destroy PET-active groups and metal-ion chelation that modulates the driving force for charge transfer. These systems rely on dual emission signals derived from three main configurations: (i) a QD paired with a co-doped or co-embedded reference fluorophore; (ii) two QDs of distinct sizes (and thus distinct emission wavelengths); or (iii) a QD-dye conjugate. Through self-normalization of the two emission signals, these architectures enhance the robustness of quantitative detection.. Assay platforms have diversified in parallel. Microplate readers and confocal microscopy remain standards for discovery and validation, but paper-based microfluidics and capillary flow devices now support low-cost, instrument-lean formats suitable for near-patient testing. On-chip preconcentration (e.g. electrokinetic, immunocapture) and magnetic separation (utilizing QD–magnetic bead tandems) mitigate matrix complexity in plasma, whole blood, and sputum. A growing subset of platforms integrates single-excitation, multi-emission readouts to minimize hardware complexity while preserving analytical depth [7].

2.2. Biomarkers and redox metabolites

Biomedical decision-making is increasingly depends on panels of biomarkers that encompass proteins, nucleic acids, metabolites, and enzymatic activities. QDs enable panelization due to high photostability and narrow spectral bands. In oncology,for instance, multiplexed FRET assays target panels such as EGFR/HER2 receptors, cfDNA mutations, and microRNA signatures implicated in glioblastoma and other solid tumors. Analytical validation emphasizes limits of detection (LoD) in

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the low pM–fM range, linear dynamic ranges spanning 2–3 orders of magnitude, and cross-reactivity testing against homologous sequences and serum proteins [8].

Redox metabolites are particularly well-suited for detection via the inner-filter effect (IFE) and ratiometric readout strategies. Carbon or graphene QDs can be paired with chromogenic quenchers whose overlap with QD emission yields a turn-on signal upon GSH-mediated reduction; inversely, enzyme cascades (glutathione peroxidase) generate oxidized species that restore attenuation. Ratiometric formulations, where a stable reference band (from an internal fluor or a second QD) is measured alongside the responsive band, reduce matrix-induced artifacts and improve quantitative robustness in plasma and cell lysates. Similar architectures quantify reactive oxygen/nitrogen species (e.g. H_2O_2, •OH, ONOO−) that report inflammatory status and therapy response in oncology and sepsis [9].

The principles of QD-based detection are further extended to mapping enzyme activity. For example, protease-cleavable peptides on QD surfaces can stage FRET loss-of-signal assays for caspases or matrix metalloproteinases; kinase substrates bearing PET-active moieties invert emission upon phosphorylation; and CRISPR-associated nucleases enable isothermal nucleic-acid detection coupled to QD reporters, bridging molecular biology with optical analytics. Assay cross-validation with orthogonal methods e.g., quantitative PCR [qPCR], enzyme-linked immunosorbent assay [ELISA], liquid chromatography-mass spectrometry [LC-MS])remains essential for clinical translatability and for establishing commutability across instruments and specimen types [10].

2.3. Pathogens and rare cells

QDs have significantly improved infectious disease diagnostics by reducing time to answer and supporting multiplex pathogen panels. FRET/IFE schemes differentiate virus serotypes and track viral replication in cultured cells. Aptamer-functionalized QDs selectively bind bacterial surface markers and exotoxins. Magnetic enrichment and QD readout reduce sample preparation burdens, while paper-based vertical flow assays enable rapid triage in low-resource settings. A frontier application in oncology is enumerating and phenotyping circulating tumor cells (CTCs). Using cadmium-/lead-free, NIR-II emissive CISe@ZnS nanoprobes, workflows can detect CTCs directly in anticoagulated whole blood without elaborate processing [11].

2.4. Platform engineering and clinical gatekeeping

Clinic performance relies on materials and surface chemistry, with three main principles: bright, stable cores, antifouling, bio-orthogonal surfaces, and manufacturability. III-V and I-III-VI platforms offer cadmium-/lead-free alternatives, while carbon/graphene QDs provide aqueous routes and functional handles for conjugation. Targeting ligands include antibodies, nanobodies, aptamers, and cell-penetrating peptides. Zwitterionic coatings and click-compatible handles standardize bioconjugation. On-device sample preparation can improve precision for matrix-heavy specimens. Analytical validation must meet clinical chemistry norms and establish commutability across instruments. Harmonized protocols and external quality assessment are essential for regulatory approval and adoption [12].

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3. Biomedical imaging & therapeutic applications

3.1. Imaging-grade probes and hybrid architectures

A corel objective for translational nanophotonics is to produce probes that maintain high brightness, spectrally stable, and target-selective in vivo while meeting safety constraints. Quantum dots satisfy the optical brief through large absorption cross-sections and narrow, tunable emission, but clinical viability also depends on surface chemistry and composite design. Hybrid constructs that pair QDs with conductive or polymeric scaffolds—such as carbon nanotubes, elastomeric matrices, or zwitterionic hydrogels—can enhance charge/energy transfer, reduce nonspecific adsorption, and reinforce mechanical stability under biological shear. Notably, this design served as an early "imaging-grade" hybrid template, laying the groundwork for the development of subsequent cadmium/lead-free QD platforms—an important advancement for improving biocompatibility and clinical safety [13].

I-III-VI cores grown with ZnS or alloyed shells have achieved high quantum yields and bathochromic emission for near-infrared imaging in small animals. Gradient shells suppress interfacial traps and Auger pathways, while compact zwitterionic ligands or dense polymer brushes minimize protein corona formation and reticulo-endothelial uptake. III-V systems deliver narrow emission with favorable toxicology profiles. Design choices directly correlate with performance metrics like signal-to-background ratio, photobleaching half-life, and target-to-background ratios in orthotopic tumor models. Beyond simple colloids, biopolymer-stabilized nanohybrid probes bring handling and dosing advantages. Biopolymers such as collagen, gelatin, alginate, and chitosan matrices can encapsulate QDs while maintaining transparency in NIR bands and providing reactive handles for conjugation. Encapsulation also enables solvent-free formulations, longer room-temperature stability, and slow release where a time-integrated, local optical density is desired (e.g., with targeting ligands or therapeutic payloads). In practice, the same encapsulation platforms can be re-purposed for therapeutic delivery of small molecules or immunomodulators, providing a single carrier architecture that supports both imaging and therapy with shared targeting logic [14].

3.2. Cancer diagnostics and image-guided interventions

Fluorescence-based diagnostics (QD probes) are valuable in oncology by mapping receptor overexpression, hypoxia markers, and protease activity. They can be used to visualize tumor heterogeneity and support decisions about margin extension or nodal dissection. Intraoperatively, NIR-emissive QDs delineate ill-defined borders and normalize for excitation inhomogeneity across curved surgical fields. Translational case studies show that QD formulations tuned for deep red to NIR emission can highlight residual disease after bulk resection, reducing local recurrence in follow-up. This convergent workflow exemplifies how QD detection paradigms in the clinic extend to image-guided interventions [15].

3.3. QD-enabled phototherapies and antimicrobial wound care

QD-based photodynamic therapy (PDT) and photothermal therapy (PTT) complement imaging by providing optically gated cytotoxicity—enabling precise spatiotemporal control over therapeutic action. A key strategy to optimize these therapies involves embedding QDs into hydrogel dressings or implant-adjacent films: this design not only localizes the therapeutic dose to target sites (reducing off-tissue toxicity) but also maintains a hydrated microenvironment (critical for tissue repair) and

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simplifies light delivery via the transparent carrier matrix (ensuring efficient activation of QDs). In photoregulated wound care, carbon QDs or cadmium-free chalcogenide QDs immobilized within poly(vinyl alcohol)–chitosan (PVA/CS) films generate reactive oxygen species under moderate irradiation, accelerating closure while suppressing bacterial colonization without systemic antibiotics [16]. The same matrices can host quorum-sensing inhibitors or metal-ion cofactors to potentiate microbial killing, while barrier properties limit biofilm penetration and protease degradation.

In oncology, advances in supramolecular chemistry have led to the development of hydrogels that respond to circularly polarized near-infrared light, elevating photothermal conversion and ROS yield without resorting to high radiant exposures that risk collateral damage. By engineering the hydrogels to exhibit handedness-dependent absorption and heat diffusion, these materials produce deeper, more uniform ablation zones within solid tumors and exhibit durable tumor growth inhibition in murine models. Critically, these hydrogels serve dual roles: they act as optical transducers (activating QDs upon light exposure) and benign depots (retaining QDs at the lesion site), enabling repeated illumination cycles without the need for catheter replacement[17]. Related strategies exploit NIR-II absorption to minimize scattering and improve dose conformity in anatomically constrained sites (e.g., pancreas, head and neck), expanding the therapeutic window relative to visible-light regimens [18].

At the probe level, oxygen-tolerant photosensitizers and photothermal agents can be co-loaded with QDs to stabilize performance in hypoxic niches. Ratiometric thermal reporters embedded in the same construct provide closed-loop feedback on intratumoral temperature, guiding pulse train selection and irradiation duration. When coordinated with systemic therapies (chemotherapy, immunotherapy), QD-enabled phototherapy can re-condition the tumor microenvironment—debulking the mass, releasing tumor antigens, and improving perfusion—to enhance drug delivery and immune infiltration.

3.4. Safety, personalization, and the road to theranostics

Clinical adoption of quantum dot-detection (QD) platforms depends on a safety profile that allows for repeated dosing and long-term follow-up. Chronic responses, such as macrophage polarization and complement activation, must be quantified with the same rigor as small-molecule drug development. Standardized panels combining hematology, serum chemistry, cytokines, and organ histopathology across multiple species will be needed for regulatory submissions [19]. Personalization is another pillar, as QD platforms support multiplexed detection, allowing for patient-specific biomarker constellations to drive probe selection and light-delivery prescriptions. Continuous-flow synthesis and automated in-line purification offer tighter batch control, while modular conjugation chemistries simplify last-mile assembly within hospital pharmacies [20].

Finally, toward theranostics, QD architectures are beginning to integrate sensing, imaging, and therapy into single “closed-loop” constructs. For example, a nanosystem can sense an enzyme or metabolite, report the readout ratiometrically, and modulate PDT/PTT payload release or irradiation parameters accordingly. Such feedback-enabled nanosystems are well-suited to adaptive oncology and infection control, where response heterogeneity is the rule rather than the exception. Equally important, these constructs produce rich metadata—spectral, thermal, and biochemical—that can be fused with MRI/CT or ultrasound for multi-modal decision-support, reducing uncertainty and enabling finer-grained, patient-specific control over risk and benefit.

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4. Conclusion

Quantum dots (QDs) have become a crucial molecular toolkit for modern biomedicine, delivering spectroscopic control, spatiotemporal control, and surface chemical control across various applications. These properties enable investigators to re-engineer clinical questions into quantitative optical problems. On the diagnostic side, heavy-metal-free emissive cores and carbon family nanodots (CQDs/GQDs) now match or surpass cadmium norms in many bioassays while mitigating legacy hazard profiles. QD logic is increasingly moving from benchtop to sample-proximal systems, and assay physics is being co-designed with clinical operating constraints without sacrificing analytical performance. Therapeutic uses QDs as informational richness, with phototherapies based on NIR-I/II windows adding centimeter-scale penetration, heat/ROS confinement, and co-delivery of small-molecule antibiotics or siRNA. QD carriers have matured as immunological and genetic couriers, stabilizing nucleic acids, tuning macrophage polarization, and enabling trackable CRISPR or RNAi logistics in vivo. Translation still pivots on safety, stability, and manufacturability, with safe-by-design rules and colloidal and photostability under realistic physiological insults needing engineering. Continuous-flow reactors, green/carbohydrate precursors for CQDs, and automation are shrinking batch variability and cost, bringing clinical lots within reach. Three recommendations are actionable: (1) Converge diagnostics and therapy around shared materials, (2) Embrace clinical systems engineering, and (3) Prioritize human-relevant models for indications where QD advantages are decisive. If these threads hold, QDs will continue to convert photons into decisions, compressing the distance from molecular signatures to personalized interventions and making fluorescence a way to steer biology.

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