ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

MINI-REVIEW

Electro-assisted delivery of quantum dots: Current advances and perspectives in cancer theranostics

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Abstract

High-voltage electric pulses induce transient permeabilization of the cell membrane (electroporation), thereby facilitating the intracellular delivery of molecules that would otherwise be unable to cross the lipid bilayer. This approach has been successfully applied in electrochemotherapy (ECT), significantly enhancing the therapeutic efficacy of anticancer agents. In recent years, quantum dots (QDs) have attracted considerable attention as promising nanomaterials for cancer theranostics owing to their exceptional optical properties, high photostability, and multifunctional capabilities. However, the efficient and safe intracellular delivery of QDs remains a major challenge. This review summarizes current knowledge regarding the electro-assisted delivery of QDs, with particular emphasis on the role of electroporation in enhancing cellular uptake. We discuss available *in vitro* and *in vivo* studies, examine the key parameters affecting delivery efficiency, and address important issues related to cytotoxicity and biocompatibility. Furthermore, we highlight the potential of integrating electroporation-based techniques with QD nanotechnology as an innovative strategy for cancer theranostics. Finally, current limitations, challenges, and future perspectives for clinical translation are discussed.

Keywords: Quantum dots; Electroporation; Electrochemotherapy; Nanoparticles; Cancer theranostics

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Citation: Tsoneva I, Semkova S, Nikolova B. Electro-assisted delivery of quantum dots: Current advances and perspectives in cancer theranostics. *Eurasian J Med Oncol*. 2026;10(5):026160176. doi: 10.36922/EJMO026160176

Received: April 14, 2026

Revised: August 12, 2026

Accepted: August 12, 2026

Published online: September 4, 2026

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1. Introduction

High-voltage electrical pulses induce transient membrane permeabilization (electroporation), enabling intracellular delivery of molecules. This electrical modulation has attracted the interest of scientists to treat medical conditions, such as amplifying drug availability in the tumors depending on the intensity, number, or shape of the applied pulses, as well as optimizing the structure of drug of interest.[1] The development of the new therapy (so-called electrochemotherapy) enables efficient loading of solid tumors with anticancer drugs, such as cisplatin and bleomycin, resulting in high intratumoral drug concentrations.[2,3] Suitable instrumentation, including electroporation devices and specialized electrodes, is required to ensure effective electro-assisted molecular delivery and electrochemotherapy.[4] Only few companies have developed pulse generators and electrodes approved for clinical application; for example: Inovio (Medpulser, Inovio Biomedical Corporation, CA, USA), and OncoSec Medical System (OMS ElectroChemotherapy technology, CA, USA)

or IGEA (Cliniporator, IGEA, Carpi, Italy), which is the most used electroporation device in European countries.[5] Chemipulse III and IV are advanced versions of the first high-voltage generator designed by Daskalov *et al.*[6] Shortly, the Chemipulse IV provides exceptional electrical safety for both patients and medical staff. One complete battery charge provides sufficient energy for the administration of more than 200 electrical pulses, supporting extended clinical or experimental use.[4] Chemipulse IV incorporates several safety and operational improvements compared with earlier electroporation systems. One notable feature is its automatic deactivation when the charger is connected to the electrical power supply, thereby enhancing user safety. Prior to pulse delivery, energy from the battery is used to charge a high-voltage capacitor, enabling reliable generation of pulse sequences.[4] The device supports adjustable pulse amplitudes ranging from 100 to 2200 V. For safety reasons, the selected voltage must be applied within 10 seconds; otherwise, the system automatically shuts down. Chemipulse electroporators can generate either 8 or 16 biphasic rectangular pulses, each consisting of two 50 µs phases separated by a 20 µs interval, while consecutive biphasic pulses are separated by an 880 µs pause. In contrast to Chemipulse III, where the QRS synchronization unit, pulse recorder, and pulse generator function as separate components, these elements are integrated into a single compact unit in Chemipulse IV.[4] The review by Tsoneva *et al.*[4] primarily addresses the application of electroporation and electrochemotherapy to improve the cellular uptake of anticancer agents through electrically induced membrane permeabilization. Particular attention is given to factors affecting membrane stability and cellular recovery following electroporation, including the influence of divalent cations such as calcium, magnesium, and zinc, as well as membrane-stabilizing compounds such as the triblock copolymer Poloxamer 188 (P188).[4] The authors also briefly discuss the electro-assisted accumulation of quantum dots in solid tumor models and examine the potential involvement of membrane microdomains (lipid rafts) in electroporation-mediated transport processes.[4] Despite significant advances in nanomedicine, efficient intracellular delivery of nanoparticles remains a major challenge. Electroporation-based approaches offer a promising solution by transiently increasing membrane permeability, thereby enhancing nanoparticle uptake in target cells.

In addition to experimental investigations, computational and theoretical approaches have increasingly contributed to the understanding of quantum-dot properties and their interactions with biological systems. These methods can provide molecular- and electronic-level insights into energy-transfer processes and interaction mechanisms that are often difficult to assess experimentally. Therefore, computational studies complement experimental observations and may facilitate a deeper understanding of the biological effects and applications of quantum dots. Recent examples are reported by Alauwaji *et al.*[7] and Dakhlaoui *et al.*[8]

Although numerous reviews have discussed electroporation-based therapies or the biomedical applications of quantum dots separately, the potential synergy between electroporation and quantum-dot nanotechnology remains insufficiently explored. Efficient intracellular delivery remains one of the major barriers limiting the broader application of quantum dots in cancer theranostics. Electroporation offers a unique physical approach for overcoming membrane-associated delivery barriers while simultaneously enabling spatially controlled accumulation of nanoparticles within tumor tissues. This article summarizes the current evidence on electro-assisted quantum-dot delivery, critically evaluates the existing limitations, and discusses the major scientific and translational challenges that must be addressed before clinical implementation can be considered Figure 1.

Figure 1 provides a conceptual framework illustrating the overall strategy of electro-assisted quantum-dot delivery for cancer theranostics. It summarizes the sequential processes involved, beginning with systemic or local administration of quantum dots, followed by the application of electroporation to transiently permeabilize the plasma membrane and thereby enhance intracellular nanoparticle uptake. Once internalized, quantum dots can serve multiple functions, including fluorescence imaging, molecular diagnostics, targeted drug delivery, and theranostic applications.

In addition to highlighting these potential biomedical applications, the figure emphasizes the major barriers that currently limit clinical translation. These include concerns related to nanoparticle toxicity, biodistribution and long-term retention, optimization of electroporation parameters, tumor heterogeneity, and regulatory challenges associated with combined nanotechnology-device platforms. By integrating both the therapeutic opportunities and the remaining translational obstacles, Figure 1 provides the conceptual basis for the topics discussed throughout this review.

2. Electrochemotherapy and electroporation in cancer treatment

Belehradek *et al.* in their paper published in 1991 demonstrated that combination of low doses of bleomycin with electroporation enhanced drug penetration into targeted tumor cells, producing a strong cytotoxic effect. They were the first who describe the modality as

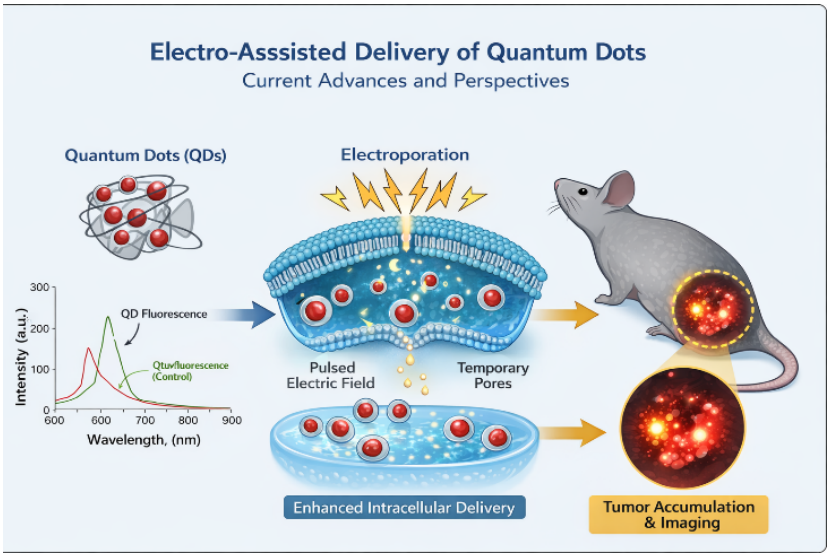


Figure 1. Conceptual overview of electro-assisted quantum-dot delivery for cancer theranostics, illustrating nanoparticle administration, electroporation-enhanced tumor uptake, intracellular delivery, imaging and therapeutic applications, and major translational challenges including toxicity, biodistribution, and clinical implementation.

electrochemotherapy.[1] The last five years saw a rise in the investigations and review papers describing the state of the art in this interesting field using animals or human patients.[9-19] Rompianesi *et al.*[15] demonstrated the potential of electrochemotherapy to enhance local tumor control, alleviate symptoms, and potentially extend survival time in patients with pancreatic cancer;[15] however, further studies are necessary to validate these outcomes and refine its clinical use. Schipilliti *et al.*[16] introduced an endoscopic electrochemotherapy procedure combined with systemic chemotherapy as a treatment option for obstructive rectal cancer, offering a potential alternative for patients in whom surgery was not initially planned. In their review, Hadzialjevic *et al.*[18] showed the role of the combined approach electrochemotherapy and immunotherapy. Recently, a novel approach to electrochemotherapy, termed Bleomycin ElectroScleroTherapy (BEST), has emerged as a treatment for vascular malformations (VMs), combining low-concentration bleomycin with electroporation. This new modification of electrochemoterapy could be one promising treatment for slow-flow vascular malformations (SFVMs). The latest results have been summarized in a review by Lisec *et al.*[19]

At different electric pulses and frequencies of their application, delayed long-lasting electrosensitization of both healthy and cancer cells could be induced. When repeated pulses are applied after some time to the electrosensitized cells, the overall impacts on cancer cell mortality, transmembrane potential, cell membrane growth due to the inclusion of microvilli material, *etc.*, can be augmented, *i.e.*, electrochemotherapy on electrosensitized cancer cells could be successful at a reduced dose of the drug amount and reduced intensity of the electrotreatment. Based on these findings, it can be concluded that cell electrosensitization is a chain of events, and additional studies are required to assess the general applicability of this phenomenon and to clarify the underlying mechanisms.[20,21]

Electrochemotherapy is available as a therapy not only in Europe. However, clinical trials were already underway in China, Australia, and the United States, and more recently in Latin America.[12]

3. Quantum dots in biomedical applications

As a semiconductor nanoparticles, quantum dots (QDs) are used in numerous application areas, such as electronics, television, portable electronics, and biomedical research. Although the QDs have been known for over 40 years, the pioneering work of Professors Alexei Ekimov, Moungi G. Bawendi, and Louis E. Brus was recognized with the 2023 Nobel Prize in Chemistry. QDs have very good quantum yield and good photobleaching resistance. QDs display longer blood circulation time. According to their characteristics, the particles can be appropriated for biological and biomedical applications: drug delivery, live cell, and tissue imaging, biosensing, monitoring of the intracellular processes, and medical diagnostics. Among the features that make QDs attractive for fluorescence-based applications are their exceptional brightness, spectrally narrow emission bands that permit multiplex imaging, high photochemical stability, and versatile

surface functionalization capabilities for bioconjugation. Recently, considerable efforts have been directed toward the development of efficient intracellular QD delivery systems.[4] Among the most widely investigated methods are electroporation, microinjection, cell-penetrating peptides, surface-engineered coatings, and liposome-based delivery platforms.[22,23] In their review, Souza *et al.*[23] present several methods, such as electroporation, microinjection, cell penetrating peptides, molecular coating, and application of lyposomes, along with their advantages in research. According to the most recent findings, we summarize the specific properties of electro-treatment and the nature of cancer cells that facilitates the internalization of QDs or reduces the level of toxicity. Lately, several review papers are focused on the toxicity, advances, biomedical and clinical applications of QDs. The unique QDs properties, such as optical properties, physicochemical properties, nano sizes (2–10 nm), shape, and polymer-coated surface, allow them to be used for both *in vitro* and *in vivo* biological studies.[22-30] Regardless of above-mentioned advantages, their application in biomedicine remains minimal. Numerous types of QDs contain heavy metals (*e.g.*, cadmium), which raises concerns about: (i) higher cytotoxicity; (ii) tissue and organ toxicity; (iii) long-term accumulation; and (iv) effects on immune responses—all of which represent a significant limitation for clinical translation.

It is important to highlight that QDs enter the cancer cells through two types of targeting mechanisms. The first mechanism is passive targeting, which is based on the enhanced permeability and retention (EPR) effect—a process where leaky and disorganized blood vessels and poor lymphatic drainage of tumors allow QDs to accumulate easily in the tumor tissue. In turn, active mechanism is mainly related to surface modification and chemical connection of QDs to the specific molecules (*e.g.*, small molecules, antibodies, peptides) that easily bind to different cancer-specific proteins. the second mechanism is electroporation-facilitated delivery, which is an active, electrical pulses–driven delivery approach that is more effective than passive uptake due to the avoidance of cell membrane barriers.

4. Electro-assisted delivery of quantum dots

Traditionally, electroporation and electrochemotherapy are utilized for the cellular internalization of DNA, RNAs or drugs. Electroporation has also been used for the delivery of QDs into biological cells. Derfus *et al.*[31] were the first who applied electroporation for delivering QD/cationic liposome complexes into living cells. They also showed that QDs have colloidal stability during the application of strong electric fields and achieve the best effect without the aggregation of QDs in the cells.[31]

In another study, Chen and Gerion[32] were among the first to construct a CdSe/ZnS nanocrystal–peptide conjugate that carries the SV40 large T antigen nuclear localization signal and transfect the complex into living cells for up to a week, which demonstrated absence of detectable negative cellular effects. These findings have helped establish a new principle that focuses on applying QDs to visualize long-standing biological events in cell nucleus and provide a new nontoxic, long-term imaging platform for observing nuclear trafficking mechanisms.[31]

Sun *et al.*[22] demonstrated that electroporation with short electrical pulses induces pores in cell membranes upon the internalization of QDs, thereby proving that delivery by electroporation does not involve endocytosis or vesicular encapsulation of QD nanoparticles. The authors introduced a novel approach for intracellular targeting by establishing a stable conjugation between an anti-kinesin antibody and quantum dots (QDs). Using electroporation, they delivered the antibody-functionalized QDs into cells and tracked the single-molecule dynamics of native kinesin complexes. Their findings demonstrate that electroporation provides a simple and versatile approach for intracellular delivery of QDs, enabling the labeling and investigation of native molecules and organelles.[22]

West *et al.*[33] demonstrated that, following the application of electroporation (400V), the amount of intracellular iron oxide nanoparticle uptake by PANC-1 cells implanted on an athymic nude mouse model of pancreatic ductal adenocarcinoma (PDAC) increased significantly. The best results were observed when the nanoparticles are added 3 minutes after electro-treatment. According to the authors, formation of nanopores may take some time. This observation may appear counterintuitive, given that pore formation occurs on a millisecond timescale, whereas membrane resealing typically occurs over seconds to minutes. Further studies are needed to clarify this discrepancy.

Only two studies in the literature have investigated molecular motion during the intracellular delivery of single QDs using electrotherapy. Katrukha *et al.*[34] electro-delivered QDs-nanobodies (streptavidin-QDs) aiming to target kinesin motor protein in COS-7 in adherent cells. When nanobody-QDs were targeted to different kinesin motor proteins, their trajectories have not displayed strong actin-induced transverse displacements. Only kinesin-1 exhibited subtle directional fluctuations, which may be attributed to the undulating behavior of the microtubules along which this motor moves. These findings demonstrate

how the spatial heterogeneity of the cytoskeleton can impose substantial variations in nonequilibrium intracellular dynamics.

After electroporation and HaloTag-functionalized PEG-coated QDs, Hatakeyama *et al.*[35] proposed a low-toxicity method for monitoring intracellular proteins. The technique enabled visualization of myosin motor dynamics and F-actin organization in fibroblasts, revealing the influence of the actin cytoskeleton on myosin movement. Their work demonstrated the utility of QD labeling for single-molecule studies of intracellular protein dynamics.[35]

5. Experimental and *in vivo* studies

Atanasova *et al.*[36] studied the QDs and QD-loaded nano-hydrogels (polymersomes) electro-assisted internalization in Colon-26 cell line (visualized by confocal microscopy) and investigated their influence on cell viability. The authors reported that electroporation significantly enhanced nanoparticle uptake by Colon-26 cells under *in vitro* conditions. Delivery of QD705 (Qdots® 705 ITK™ non-targeted quantum dots, Invitrogen, USA) was performed using 16 biphasic rectangular pulses, each consisting of two 50 μs phases separated by a 20 μs interval and an 880 μs pause between consecutive pulses. Parallel stainless-steel electrodes with a 1 cm gap were employed, and electric-field strengths of 200, 500, and 1000 V/cm were evaluated. The results demonstrated a voltage-dependent increase in nanoparticle internalization, while cell viability remained largely unaffected. Furthermore, the study showed that QD705-loaded nanosomes could be successfully delivered into cancer cells and retained intracellularly for at least 24 hours, supporting the potential of electroporation as an efficient nanoparticle delivery strategy. Lately, Skorupska and Grabowska–Jabach[37] investigated the cytotoxicity of QDs using the electrical pulses in three human lines: A 549 (human lung cells), MRC-5 (normal lung fibroblasts), and HaCaT (normal skin keranocytes). They found that the larger QDs (CdTe from Pharma Chem, Germany) accumulated and nano-clustered in lysosomes, but not in the cell nucleus. The increased cytotoxicity of QDs for all tested lines were observed only when particles are delivered into cytoplasm after electro-treatment.

Yoo *et al.*[38] have shown that, through electroporation, QDs (NIR-near infrared fluorescence quantum dots CdTeSe) could be successfully delivered into lung cancer cells (NCI-H460) and ovary cancer cells (SK-OV-3), and that the QDs could be retained within the cancer cells for a period of up to more than 1 month. The visualization was achieved by using a multiphoton confocal laser scanning microscope (MCLSM, LSM 510, Carl Zeiss, Germany). The study used single cells pre-electroloaded with QDs to implant tumors in mice. Subsequent multispectral imaging allowed *in vivo* assessment of cancer development and progression in the xenograft mouse tumor model for more than 1 month, providing a powerful means to learn more about the biology of cancer and metastasis.

Previous studies from our group[39-42] have demonstrated that electroporation can improve the intratumoral accumulation and retention of QD-based nanocarriers in experimental tumor models, supporting the feasibility of this strategy for localized delivery. However, further investigations involving clinically relevant tumor models and larger animal studies are required to validate these findings and define the optimal treatment conditions.

Based on recent reviews by Shukla *et al.*[43] and Guo *et al.*,[44] metal QDs enter the cell by non-specific endocytosis, and with good optical properties and stability, they provide a powerful tool for biomedical diagnostics, therapy, and drug delivery in the oncological contexts. QDs boast advantages for cancer imaging, but owing to their toxicity, they have limitations for universal nano-diagnostics. Therefore, QDs have only been investigated in four clinical trials.[28] Nevertheless, active delivery, *i.e.*, the delivery of QDs by electroporation, could be useful for early cancer detection.

A preliminary search of the PubMed database using the keywords "quantum dots" and "electroporation" over the past 20 years identified fewer than 40 publications. This limited body of literature highlights the relatively unexplored relationship between electroporation and quantum dots and motivated us to write this review. Here, we summarize the available studies on the use of electroporation-assisted QD delivery in tumor models, including animal models, to evaluate therapeutic outcomes and explore the potential of this approach for cancer therapy.

6. Challenges and limitations

Despite substantial progress in both electroporation technology and QD-based nanomedicine, their combined application for cancer theranostics remains at an early experimental stage. Several fundamental challenges continue to limit translational development.

A primary concern is the intrinsic toxicity and long-term safety of QDs, particularly those containing heavy metals such as cadmium, selenium, or tellurium. Although surface coatings, polymer encapsulation, and PEGylation can reduce acute cytotoxicity, nanoparticle degradation under physiological or oxidative conditions may still lead to the release of toxic ions. In addition, chronic exposure effects and long-term biodistribution profiles remain

insufficiently characterized.

A second major limitation is uncertain biodistribution and clearance behavior. Following systemic administration, QDs tend to accumulate in organs of the mononuclear phagocyte system, particularly the liver and spleen. This non-specific retention raises concerns regarding long-term toxicity and limits clinical applicability. Moreover, clearance pathways for different QD formulations remain incompletely understood, particularly for larger or surface-modified constructs.

From the electroporation perspective, optimization of electrical parameters remains critical but highly non-standardized. Pulse amplitude, duration, frequency, and electrode geometry strongly influence both membrane permeabilization efficiency and cell viability. However, across the literature, there is considerable variability in experimental protocols, making cross-study comparison difficult and limiting reproducibility.

In vivo applications introduce additional complexity due to tissue heterogeneity and electric field distribution constraints. Variations in tissue conductivity, tumor vascularization, and extracellular matrix composition can lead to uneven electric field exposure, resulting in heterogeneous nanoparticle delivery within tumors.

Overall, while experimental evidence supports the feasibility of electro-assisted QD delivery, these limitations highlight the need for standardized protocols, improved nanoparticle design, and deeper mechanistic understanding before clinical translation can be achieved.

Despite promising experimental findings, several important challenges continue to limit the development of electro-assisted quantum-dot delivery for cancer theranostics. First, the long-term safety of many conventional QDs remains a major concern because they frequently contain heavy metals such as cadmium, selenium, or tellurium. Although encapsulation and surface engineering can reduce toxicity, potential degradation of the nanoparticle core may result in the release of toxic ions. Second, the biodistribution and clearance of QDs remain insufficiently understood, particularly following repeated administration. Accumulation in the liver, spleen, and other organs of the reticuloendothelial system may limit clinical applicability. Third, electroporation parameters must be carefully optimized to balance efficient nanoparticle delivery with preservation of tissue viability. Finally, regulatory approval of combined nanotechnology–electroporation platforms present additional challenges because both the nanoparticle formulation and the delivery device require extensive safety validation.

7. Future perspectives

Despite the remarkable progress achieved in the electro-assisted delivery of QDs, several scientific, technological, and translational challenges remain before this strategy can be routinely implemented in clinical oncology. Future research should concentrate on several complementary directions that together will determine the successful development of QD-based electro-assisted theranostic systems.

7.1. Engineering next-generation QD nanocarriers

The design of QD-based nanocarriers should be further optimized to improve tumor selectivity, intracellular delivery, and long-term biosafety. Future studies should focus on tailoring nanoparticle size, morphology, surface charge, and surface chemistry to maximize tumor accumulation while minimizing off-target distribution. Surface functionalization by PEGylation, biodegradable coatings, targeting ligands, antibodies, or peptides may prolong circulation time and improve selective recognition of tumor-associated biomarkers. The development of heavy-metal-free or biodegradable QDs will also be essential for reducing toxicity and facilitating future clinical translation.

7.2. Optimization of electroporation technology and delivery mechanisms

Further optimization of electroporation protocols remains a major priority. Electric field strength, pulse duration, pulse number, treatment timing, and electrode geometry should be systematically optimized according to the physicochemical characteristics of the nanocarriers and the biological properties of individual tumors. Future investigations should also clarify the relative contributions of membrane permeabilization, electrophoretic transport, transient tumor blood-flow reduction, electrosensitization, and nanoparticle retention to the overall efficiency of electro-assisted delivery. A better mechanistic understanding will support the establishment of standardized treatment protocols and improve reproducibility across laboratories.

7.3. Understanding nanoparticle–cell interactions

The interactions between QDs and cancer cells remain incompletely understood. Future research should investigate how the electrical properties of tumor cell membranes, including ζ-potential, membrane composition, and tumor microenvironment, influence nanoparticle adsorption and internalization following electroporation. Additional attention should be devoted to active targeting strategies using antibodies, peptides, or

other ligands directed against tumor-specific biomarkers, such as HER2 or CD44. Moreover, the possible influence of the semiconductor properties of QDs on local electric field distribution and electroporation efficiency represents an intriguing hypothesis that warrants experimental validation.

7.4. Integration into multifunctional theranostic platforms

One of the most promising future directions is the development of multifunctional QD-based theranostic systems capable of combining molecular imaging, targeted drug delivery, and therapeutic monitoring within a single platform. The integration of electroporation with fluorescence imaging, magnetic resonance imaging, photoacoustic imaging, immunotherapy, gene editing, and precision oncology could enable real-time monitoring of treatment response while improving therapeutic specificity and minimizing systemic toxicity.

7.5. Translation toward clinical application

Successful clinical implementation will require comprehensive investigations of long-term biosafety, biodegradation, pharmacokinetics, immunogenicity, and regulatory compliance. Future studies should include standardized preclinical models, larger animal studies, and well-designed clinical trials to establish the safety and efficacy of electro-assisted QD delivery. Close collaboration among materials scientists, engineers, biophysicists, chemists, and clinicians will be essential for translating these promising laboratory technologies into clinically applicable cancer theranostic platforms.

Taken together, QDs conjugated with drugs or antibodies for delivery under suitable electrical pulses (electrochemotherapy) serve as a good therapy for human tumors and oral squamous cell carcinoma.

8. Conclusion

In conclusion, electro-assisted delivery of QDs represents a promising strategy for improving intracellular nanoparticle delivery and expanding the capabilities of cancer theranostics. However, the field remains at an early stage of development, with relatively few dedicated studies and no established clinical applications. Future progress will depend on advances in nanoparticle safety, targeted delivery, biodistribution control, and standardized electroporation protocols. Addressing these challenges will determine whether electro-assisted QD platforms can ultimately transition from experimental systems to clinically relevant theranostic technologies. While electro-assisted delivery of QDs is still at a preclinical stage, it represents a compelling platform for next-generation cancer theranostics. Its future success will depend on bridging the gap between experimental proof-of-concept studies and clinically robust, standardized therapeutic systems.

Acknowledgments

The authors thank the Bulgarian Ministry of Education and Science for the support provided via Scientific Infrastructure on Cell Technologies in Biomedicine (SICTB) D01-105/2025 and the National Center for Biomedical Photonics (NCBP) D01-101/2025, part of the Bulgarian National Roadmap for Scientific Infrastructures 2020–2027, COST Action - CA21140 INTERCEPTOR.

Funding

National Science Fund of Bulgaria Grant KP-06-COST/30.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Conceptualization: All authors
Writing–original draft: All authors
Writing–review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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