QUANTUM DOTS FOR DRUG DELIVERY IN CANCER RESEARCH

Abstract

The fields of biological science, developing formulations, medical imaging, the field of nanotechnology, and oncology nanotechnology in medicine have all made significant improvements to the field of cancer nanomedicines. One of the main causes of death worldwide in the modern era is cancer, which represents a severe danger to the health of the public. Cancer encroachment cancer progression and all three are not known to occur via any known pathways. To discover the fundamental biological mechanisms of the illness, continuous surveillance is crucial as well as developing a unique way for detecting cancer. Even though several techniques have been created to reduce mortality, and chronic pain, and improve quality of life, there is still a gap in the efficacy of these cancer medications. These medications for cancer are currently lacking in several areas. Quantum dots (QDs) are among the constituents of the toolset for nanotechnology in medicine that have the highest likelihood. These nanocrystal fluorophores can be used for a range of medical applications, including photodynamic treatment, targeted drug delivery, and nano clinical imaging. Quantum dot (QD)-based nanotechnology is useful in developing a therapeutic imaging technology for studying the pathology of cancer because of the optical and chemical benefits of QDs. Quantum dots (QDs) made of nanocrystals of silicon have shown possibilities for in-situ and cellular imaging of molecules due to their exceptional photophysical characteristics. These intriguing findings have also been shown using QD-based probes. According to research, QD-based technologies may be helpful in the battle against cancer. Specifically focuses on the implementation of QD-based technology in the tumor setting research and cancer cell monitoring in situ and the laboratory, as well as the remaining obstacles and potential applications in the future.

The importance of QDs for cancer metastasis

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research will increase as QD synthesis and modification technology develops.

Keywords: cancer, nanotechnology, quantum dots, nanocarrier

I. INTRODUCTION

Cancer is the world's most serious health issue, the leading cause of mortality, and a worldwide health burden in every country. By 2018, it is expected to be 9.6 million fatalities due to cancer and 18.1 million newly identified cases of cancer [1, 2]. Several research efforts have been conducted on the alteration of cell binding as a mechanism for tumor migration and advancement in recent years [3, 4]. Rate-limiting strategies that regulate cancer progression and development include connections among protease substrates, the main signaling process, and receptor-ligand interactions, although they have yet been identified. It is now known that the complex and adaptable process of spreading cancer is significantly influenced by the stromal microenvironment of the cancer [5,6]. Several diseases affect different organs, but they are all typified by the unrestrained proliferation of aberrant cells that can spread infection. As a result of its ever-evolving interactions with the tumor, the tumor microenvironment, which is made up of host cells, tumor vascular components, and surrounding supporting tissues, is a critical element for tumor development and progression [7, 8]. Once the microenvironment of cancer reacts to the growth cells, elements such as cells from fibroblasts, endothelial cells, and monocytes may be activated and produce useful chemicals that aid or inhibit the progression of cancer [9–13]. The microenvironment is affected by these tumor cells in a way that both benefits and hinders the development of cancer [14,15]. A relevant approach to understanding the biological behavior of cancer must thus be devised. Understanding the pharmacological activity during tumor advancement is required to fully know the mechanism of cancer growth and proliferation. Quantum dots (QDs), a diverse category of produced nanoparticles with unique photographic and chemical characteristics that make them indispensable nanoparticles with a variety of potential uses ranging from energy to medicine, are one of the most fascinating advancements in nanotechnology [16]. High specificity and sensitivity cancer chemical targeting is possible using QD-based probes. This method has been demonstrated in various studies to be useful for studying the tumor microenvironment and critical for understanding the molecular mechanisms behind cancer invasion [17–19]. It focuses on the present uses of QDs in the diagnosis of tumors, such as the preliminary identification of initial tumors, including malignancies of the breast, prostate, uterus, and pancreatic cancer, as well as local lymph nodes and distant tumors. The application of QD-based nanotechnology for cancer research has made significant strides in the identification of initial cancers in vitro, cancer conception in vivo, research on the tumor microcosm for assault and growth, multimodality biomedical molecular targeting imaging, as well as significant unresolved issues and future perspectives. These are some of the major advancements that are covered in this article.

1. What Are Quantum Dots? Nanoscale semiconductor particles known as quantum dots have distinctive electrical and visual features as a result of quantum entanglement processes. Due to their characteristics, nanoparticles are useful in a variety of applications, such as electronics, optoelectronics, medical imaging, and quantum computing [16]. QDs (CdSe–ZnS core–shell nanoparticles) produce light at certain wavelengths in a variety of colors when UV light strikes them (fig.1). Alexey I. Ekimov, a Russian physicist, discovered semiconductor nanoparticles known as quantum dots in 1981 [20].

Figure 1: Quantum Dots

QDs have atom counts between 200 and 10,000 and have a diameter between 2 and 10 nm [16]. Quantum phenomena set a limit on the energy when semiconductor particles are produced tiny adequately. Because energy and wavelength (or color) are inversely related, it is possible to precisely adjust a particle's spectral properties based on its physical dimensions (fig. 2) [20]. QDs are excellent options for illuminating nanoprobes and carriers in biological applications due to their unique optical properties. Pharmaceuticals may be loaded into QD nanocarriers for therapy using a variety of techniques, including dissolving, dispersion, adsorption, and coupling [21, 22]. It is anticipated that QD fluorescence imaging technology and therapy-based multipurpose nano-drugs would be used to diagnose and treat cancer [23].

- **2. Properties of QDs:** The size, shape, composition, and structure of a quantum dot define its attributes. Ideal QDs have a variety of properties:
	- Quantum dots, often known as "designer atoms," have a wide range of optical and electrical features that allow them to overcome the limitations of standard semiconductors
	- Excellent encapsulation effectiveness and medication loading efficiency
	- Useful cleaning and pretreatment procedures
	- Low toxicity $&$ high biocompatibility
- An acceptable particle form and dimension, as well as a certain degree of structural durability and rigidity
- In vivo, a longer duration of residency
- No adverse medication reactions
- Quantum dots are made up of thousands of microscopic metal particles the size of a human hair
- Quantum dots may be formed into a variety of forms and loaded with a variety of nanomaterials
- Ouantum dots produce UV light, and the dimensions of the dots impact the hue. For example, 2 nm Quantum dots' luminescence of radiant green and 5nm Quantum dots' luminescence of red are two examples of quantum dots
- Luminous quantum dots are often made from chemicals in classes II to VI and III to V, such as Ag, Cd, Hg, Ln, P, Pb, Se, Te, and Zn
- The wavelength generated through quantum dots diminishes as their size decreases
- There are many strategies for activating quantum dots
- The spectra of numerous fluorescence emissions do not overlap because quantum dots emit at a distinct wavelength (24, 25).

3. Advantages of QDs

The advantages of ideal QDs are as follows:

- QDs modified antibodies, aptamers, folic acid, and other biological molecules to target medicine delivery to specific organs.
- QDs control and release medications in a rather unique way. The style of managing and releasing pharmaceuticals of QDs is usually a prevalent assertion at first, and then it exhibits a consistent release for an extended period.
- Drug QDs can dramatically increase drug efficacy at low concentrations, transport at shorter interludes and minor doses, and lessen side effects.
- QDs increase medication contact area and improve oral drug absorption and bioavailability.
- In the process of imparting increased medication stability and use, QDs can avoid rapid drug breakdown by digestive enzymes in the body.
- Pharmacological-loaded nanoparticle transporters can alter membrane transport routes and improve drug permeability in biofilms, enhancing medicine uptake in cells.
- The original medicine can be enhanced by using nanoparticles as carriers to increase its solubility in water or to produce a controlled and prolonged release function, boosting chemotherapeutic treatment efficacy and lowering side effects [26, 27].

II. FORMULATION AND CLASSIFICATION OF QUANTUM DOTS

1. Formulation of Quantum Dots: Synthesizing semiconductor materials at the nanoscale is necessary for the creation of quantum dots. Group II-VI (like CdSe, CdTe) and III-V (like GaAs) compounds are the most popular semiconductor materials utilized for QD production. The optical and electrical qualities of the Quantum Dots that are needed will determine the material choice [28].

2. Several Methods for Synthesizing Quantum Dots:

- **Colloidal Synthesis:** This method involves the biochemical combination of quantum dots in a colloidal solution. It typically utilizes precursors containing semiconductor materials such as cadmium, lead, or indium. By carefully controlling the reaction conditions, including temperature, reaction time, and precursor concentrations, quantum dots of desired size and properties can be obtained. The colloidal synthesis method is widely used due to its simplicity and versatility [28].
- **Sol-Gel Method:** The sol-gel method is another technique used for quantum dot formulation. In this approach, metal alkoxides or organometallic complexes are hydrolyzed and condensed to form a gel. The gel is then calcined or annealed to yield the desired quantum dots. A relevant reference for sol-gel synthesis of quantum dots is the study [29].
- **Electrochemical Synthesis:** Electrochemical methods offer a versatile approach to quantum dot synthesis. In electrochemical synthesis, an electrode is used to initiate and control the reaction between precursors, which allows for precise control over the quantum dot properties. Key references for electrochemical synthesis techniques include the works [30,31].
- **Molecular Beam Epitaxy (MBE):** Molecular Beam Epitaxy is a vapor phase depositing technique used to increase atomically tinny layers of various materials, including quantum dots. MBE allows for the precise control of growth parameters, resulting in high-quality quantum dots with tailored properties. Notable references for quantum dot synthesis using MBE include the studies [32,33].
- **Plasma Synthesis:** Plasma synthesis involves the generation of plasma, which is a high-energy, ionized gas, to produce quantum dots. In this method, precursor gases containing the desired semiconductor materials are introduced into a plasma reactor, where they are broken down and condensed to form nanoparticles. The use of plasma allows for efficient and rapid synthesis of quantum dots, through control over shape, and composition [34].
- **3. Characterization of Quantum Dots:** Quantum dots (QDs) are nanoscopic semiconductor crystals that exhibit unique optical and electrical properties. Due to their size-dependent properties and potential use in various applications, it is crucial to characterize QDs accurately. In this guide, we will explore the different techniques used for the characterization of quantum dots, providing proper references along the way.
	- **X-ray Diffraction (XRD):** XRD is widely used to determine quantum dot quartz structure and size. It allows scientists to study the exact location and magnitude of the X-ray diffraction peaks, which provides information about the lattice parameters and crystal structure [35].
	- **Transmission Electron Microscopy (TEM):** TEM offers detailed information on quantum dots' size, shape, and morphology. Nanoparticles' sizes and shapes were studied using a high-resolution JEOL 7550 scanning electron microscope equipped

with a TEM detector. Samples were made by drop-coating 10 microlitres of material on carbon-coated grids 200 mesh Cu (100). High-resolution TEM enables atomicscale imaging, which assists in determining the structure of nanocrystals [36].

- **Scanning Electron Microscopy (SEM):** SEM offers valuable information about the surface morphology and size distribution of Quantum Dots [36].
- **Photoluminescence (PL) Spectroscopy:** PL spectroscopy is widely used to study the light emission properties of quantum dots. It measures the intensity and wavelength of the emitted light, providing information about the bandgap, energy levels, and quantum efficiency. At room temperature, the photoluminescence of the films was measured with a spectrophotometer. The films' emission spectra were determined before and after stabilization [37].
- **Absorption Spectroscopy:** UV-Vis absorption spectroscopy measures the absorption spectrum of Quantum Dots, revealing their bandgap energy. PL spectroscopy measures the emission spectrum, providing information about their luminescent properties [38].
- **Energy-Dispersive X-ray Spectroscopy (EDS):** EDS is utilized for determining the elemental composition of Quantum Dots [39].
- **Fourier Transform Infrared Spectroscopy (FTIR):**FTIR helps identify the organic ligands or surface capping agents on the Quantum Dots [40].
- **Dynamic Light Scattering (DLS):**DLS provides information about the hydrodynamic size and size allocation of Quantum Dots in solution [41].

III. APPLICATIONS OF QD-BASED NANOTECHNOLOGY IN CANCER RESEARCH

1. Cancer of the Ovaries: Ovarian cancer is the second most common cervical cancer in women and is the main cause of death among gynecological malignancies. CA 125 is an epithelial antigen that can be used as a tumor marker in the identification and treatment of ovarian cancer [42-44]. Clinical diagnostic applications require the capacity to observe native processes in living organisms, but this is challenging to do in reality because of the limits of traditional imaging and the dearth of fluorescent markers that are suited for the task. QDs are interesting fluorophores for in vivo fluorescence imaging due to their unique photophysical properties, which can overcome many of the drawbacks of traditional dyes. QDs with a maximum emission wavelength of 605 nm (QD605) to detect CA125 in ovarian cancer specimens of various kinds (fixed cells, tissue slices, and xenograft tumors) with good specificity and sensitivity [45]. The labeling signals from QDs were brighter, more specific, and more persistent as compared to fluorescein isothiocyanate (FITC). Biocompatible QDs coated with the natural protein silk fibroin (SF) and utilized these QD conjugates as a fluorescent marker for effective bioimaging of HEYA8 ovarian cancer cells [46]. Furthermore, QD signals are more photostable than traditional organic dyes [47]. Photoluminescence that is pH-dependent CdSe/ZnSe/ZnS QDs was generated in SKOV-3 human ovarian cancer cells, hinting at implications for intracellular pH sensors. In human ovarian epidermal carcinoma cells, effectively targeted EGFR single molecules (A431) [48,49]. The characteristics of QDs have created new opportunities for improved molecular and cellular imaging, as well as ultrasensitive bioassays for ovarian cancer detection.

S. no.	Type of QDs	Type of human ovarian cancer cell	Outcomes	Reference
	QD605	CA125	Labeling signal more specific and stable	[45]
	QDsSF(QDs conjugates)	HEYA8	Better photostability	[46, 47]
3.	CdSe/ZnSe/ZnS	SKOV-3	Enhanced molecular or cellular imaging for ovarian cancer diagnose	[48, 49]

Table 1: Development of QDs-based nanotechnology for ovarian cancer research

2. Breast Cancer: Wu et al. [50] examined a novel method for labeling HER2 (human epidermal growth factor receptor 2, HER2) on the breast cancer cell membrane, also known as c-erbB-2 or HER2/neu, which is overexpressed in 25-30% of breast cancer that is invasive [49,50] and plays an important role in breast cancer prognosis and treatment selection [50-53]. Other studies utilizing QDs to detect HER2 for breast cancer detection followed [54,55]. Yezhelyev et al. [56] used intact breast cancer cells and tumor specimens to examine the use of multicolor QDs for quantitative and concurrently identifying of several biomarkers, as well as a comparison of the new QDs-based genetic profiling technology with standard western blotting and fluorescence in situ hybridization (FISH).

The multicolor bioconjugates were utilized to detect five clinically relevant tumor markers at the same time in breast cancer cells MCF-7 and BT474, including HER2 (QD-HER2), ER (QD-ER), PR (QD-PR), EGFR (QD-EGFR), and mTOR (QD-mTOR). The use of QD-Abs profiling revealed a quantifiable link between HER2 gene amplification and HER2 protein expression. The current research implies that conjugated QDs might be used to detect low levels of HER2 protein expression, although the therapeutic implications of this discovery need to be examined further. To get around the research's practical drawbacks, we recently used QDs coupled with antibodies to detect HER2 status in breast cancer [57]. Our study included 700 individuals with advanced breast cancer, including 3 men and 697 women. Our QD immune histochemistry (QDs-IHC) analytical approach was used to analyze the expression of HER2 in breast cancer in an automated, quantitative, sensitive, and easy manner. The QDs-based methodology is more sensitive, accurate, and cost-effective than traditional IHC, especially in cases of IHC $(2+)$, signaling that this unique method has therapeutic promise, particularly in nations with poor infrastructure [24].

3. Pancreatic Cancer: Pancreatic cancer patients have a median survival time of about 6 months, and only about 5% of those diagnosed with the disease live longer than 5 years [58,59]. Because of a lack of specific symptoms and diagnostic restrictions, the majority of patients are diagnosed at an advanced stage. [56]. QDs can be used to target the purpose of early diagnosis of pancreatic cancer [61], even at an early stage of development (uPAR), by using proteins/peptides directed against overexpressed surface receptors on cancer cells/tissues such as the transferrin receptor, antigen claudin-4, and urokinase plasminogen activator receptor. Qian [63] employed CdSe/CdS/ZnS QDs with enhanced photoluminescence efficiency and stability as an optical agent for imaging pancreatic cancer cells with transferring and anti-Claudin-4 antibodies. The anti-Claudin-4 monoclonal antibody is also utilized to demonstrate pancreatic cancer-specific uptake. This tailored QDs technology will be improved further to provide an imaging tool for pancreatic cancer early detection. Yong et al. [64] used non-cadmium-based QDs to scan live pancreatic cancer cells effectively and safely. Bioconjugation of functionalized InP/ZnS QDs with pancreatic cancer-specific monoclonal antibodies, such as anti-claudin 4, resulted in pancreatic cancer cell line targeting in vitro. The discovery of poor targeting in nonpancreatic cancer cell lines missing the claudin-4 receptor validated in vitro receptor-mediated transport of bioconjugates. These findings suggest the use of InP/ZnS QDs as noncadmium-based, safe, and effective optical imaging nanoprobes in imaging for diagnosis.

4. Prostate Cancer: Yong et al. [64] used non-cadmium-based QDs to scan live pancreatic cancer cells effectively and safely. Bioconjugation of functionalized InP/ZnS QDs with pancreatic cancer-specific monoclonal antibodies, such as anti-claudin 4, resulted in pancreatic cancer cell line targeting in vitro. The discovery of poor targeting in nonpancreatic cancer cell lines missing the claudin-4 receptor validated in vitro receptormediated transport of bioconjugates. These findings suggest the use of InP/ZnS QDs as noncadmium-based, safe, and effective optical imaging nanoprobes in diagnostic imaging. Shi [70] discovered that QDs outperformed IHC for detecting androgen receptors (AR) and PSA in prostate cancer cells. Both of these investigations [71] highlight why QDs are attractive nanoparticles for diagnostic applications by demonstrating their diagnostic tool potential. Because antibodies coupled to QDs are typically full-length antibodies, their binding ability is significantly reduced [72]. A recent study revealed that using single-chain antibody fragments (scFvs) in combination with QDs has various benefits in terms of solubility, activity, ease of production, and ease of structure-based genetic editing, all of which were proven by detecting prostate cancer cells [73].

5. Gastrointestinal Cancer: Bostick et al. [75] used QD-based combinatorial imaging to uncover five biomarkers on the same tissue slide, which allowed them to evaluate additional biomarkers using numerous slides stained with the five different biomarkers. And also advised creating a workflow for each biomarker's quantitative analysis. The technology was effective and convenient, taking only 7 hours to test six biomarkers, which was beneficial for clinical use.

IV.PATENTS OF QDs

To evaluate and categorize current work in the field of sickness treatment, patents, and associated searches were conducted on the World Intellectual Property Organization's official website.

Patent No.	Assignee Issue		Reference
US 4637988	Eastman Kodak Company	1987	[24]
US 6114038	BioCrystal Ltd	2000	[24]
US 6274323	Quantum Dot Corporation	2001	[24]
US 7181266	Massachusetts Institute of Technology, Beth	2007	[24]
	Israel Deaconess Medical Center		
CN 200810041133	Shen Bo Crane	2009	[24]
CN 201010185953	Mao Quan, Chu Hou Sen	2012	[24]
CN 201410239033	Im Kwon, Yang Xudong, Chen Jie, Chen Yang,	2014	[24]
	Sun Yang, Xue Qing, BaiYang, Dongfeng Xia		
EP 3073728A1	Nokia Technologies Oy	2016	$[76]$
EP2603935B1	Samsung Electronics co Ltd.	2018	$[77]$
US10630927B2	Nokia Technologies Oy	2021	[78]

Table 5: Shows a list of Quantum Dots patents

V. QUANTUM DOTS IN CANCER DIAGNOSIS AND THERAPY

Quantum dots (QDs) are photovoltaic nanostructures. that glow when stimulated by light. They offer outstanding optical features, including as high brightness, photobleaching resistance, and a wavelength that may be adjusted. QDs can now be used in cancer imaging thanks to recent advances in surface modification. Combining QDs with biomolecules such as peptides and antibodies may enable in vivo cancer targeting. We propose future potential for enhancing QD technology to identify metastatic cancer cells, count the quantity of specific biological targets, and prescribe tailored cancer therapy by giving biomechanical indicators for target suppression [82].

VI. FUTURE CHALLENGES AND PROSPECTS

1. Nanotoxicity: Although QDs have great potential for biomedical imaging and detection, toxicological and pharmacological difficulties, mostly due to heavy metal and colloidal instability, have hampered breakthroughs in cancer diagnosis and therapy [79, 80].

These difficulties may not stymie application development in vitro, but they pose significant obstacles to human in vivo cancer imaging. Efforts have been undertaken to create novel QDs based on their components, sizes, surface coatings, and valences to minimize toxicity and enhance detection efficiency. However, issues such as QD modification-induced coating shell deterioration should be taken into account [81-83]. Nonspecific RES buildup should be evaluated, including the liver, spleen, and lymphatic system [79, 84]. There have also been instances of immunological reactions and genotoxicity [85]. According to several studies [86], QDs smaller than 5 nm can be eliminated by the kidney. When addressing biosafety for in vivo applications, long-term toxicological and pharmacokinetic studies involving QD breakdown, excretion, persistence, and immune response should be extensively assessed. Due to the toxicity of Cd, Se, Zn, Te, Hg, and Pb, numerous low-toxicity QDs have been produced [87, 88]. Reduced toxicity can be accomplished, for example, by swapping Cd for Zn. Temperature, chemical, and photochemical disturbances, for example, are also less vulnerable to such QDs. Because of their excellent quantum efficiency and color tunability, these doped QDs are intriguing candidates for future attempts to reduce QDbased cytotoxicity. Because of their narrow emission spectra (45 nm to 65 nm whole width at half maximum), they can also cover the bulk of the visible spectral window. Doped QDs emitting in the near-infrared spectrum will be available shortly. Before QDs can be employed in any medical activity, they must go through thorough testing and study on their toxicity profiles.

2. Design and Manufacture of Biocompatible and Biodegradable Nanoparticles: QDbased in vivo imaging and targeting research is hampered by their relatively large size (15 nm to 30 nm) and short circulation half-life in the blood vascular system. Various current groups are aiming to increase the circulation time of QDs by adding passivating compounds such as PEG to the particles and controlling the overall charge of the particles to avoid adsorption to plasma proteins [89-91]. On the other hand, any contrast agent must be eliminated from the body before being employed in a therapeutic setting. A recent study discloses a size barrier of 5 to 6 nanometers in diameter below which QDs are unable to exit the liver and be removed through the kidneys [92,93].

3. Reproducibility, reliability, and comparability of QDs: The present clinical uses of QDs are significantly hampered by a lack of data on their repeatability and comparability, as well as their quantification capabilities. varied functionalized QDs from diverse sources will have varied fluorescence quantum yields due to differences in materials and surface chemistry. As a result, the first step is to formulate and establish quality standards for these distinct functionalized QD materials [94-96].

VII. CONCLUSION

Nanotechnology has shown a great deal of promise in cancer treatment throughout the years. Nanomaterials (QDs) have improved cancer diagnosis and therapy due to their superior pharmacokinetic and pharmacodynamic features. Nanotechnology, because of its unique properties, allows for targeted drug delivery in injured tissues with minimum systemic toxicity. QDs are technical marvels with qualities that have the potential to revolutionize cancer detection and therapy. Nowadays, QDs are frequently utilized in vitro for a variety of purposes, including determining cancer biomarkers in molecular pathology, revealing cancer invasion, focusing on the tumor environment, and providing a new approach to better understanding tumor heterogeneity, diagnosis, classification, and cancer treatment. The future of nanomedicine will be multifunctional nanoplatforms that combine medicinal components with multimodality imaging. The ultimate objective is for nano platform-based medicines to enable efficient and selective in vivo targeted drug delivery without systemic toxicity, with dosage and therapeutic effectiveness monitored noninvasively throughout time. Inadequate administration, potential toxicity, and the absence of monitoring are all significant barriers to QD clinical implementation.

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