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Research Progress on Zinc Sulfide Quantum Dots in Tumor *in Vivo* Imaging

Han He[1], Shuhui Huang[1], Jinxiao Ma[1], Juanli Cui[1], Xusheng Zhang[1,2*]

[1]Northwest Minzu University, Lanzhou, China
[2]The Second People's Hospital of Gansu Province, Lanzhou, China
Email: *875501566@qq.com

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Abstract

This study elaborates on the application and unique contributions of zinc sulfide quantum dots (ZnS QDs) in tumor imaging, highlighting their significant potential in the field of nanomedicine, particularly in tumor imaging techniques. Zinc sulfide quantum dots are distinguished by their superior optical properties, chemical stability, and excellent biocompatibility. Our research focuses on the customization of ZnS QDs through integration with biocompatible compounds, and the use of covalent bonding and self-assembly techniques to incorporate fluorescent and bioactive groups. This significantly enhances imaging precision and efficiency for specific tumor markers. Furthermore, we explore zinc sulfide quantum dots with multimodal imaging capabilities, such as manganese-doped CdS quantum dots (Mn:CdS QDs). This novel discovery paves the way for precise tumor detection, localization, and treatment. Despite the promising applications of zinc sulfide quantum dots, challenges including toxicity, stability, and biocompatibility issues must be addressed in their clinical translation. Thus, this paper calls for future research to focus on developing safer and more efficient new fluorescent probes and to delve deeper into the stability and drug release characteristics of quantum dots to facilitate their use in clinical tumor diagnosis and treatment.

Subject Areas

Oncology

Keywords

Zinc Sulfide Quantum Dots, Tumor Imaging, Multimodal Imaging, Biocompatibility

1. Overview of Quantum Dots

Quantum dots, as zero-dimensional semiconductor nanocrystals, [1] are unique not only for their nanoscale dimensions and material diversity, such as II - VI (CdTe, CdSe), III - V (InP, GaN), or IV - VI (PbSe) semiconductors, but also for their extraordinary optical and electronic properties. These nanocrystals, typically ranging in diameter from 1 to 12 nanometers, exhibit strong quantum confinement effects due to their size being close to or smaller than the material's exciton Bohr radius. This results in optical and electrical properties that are significantly different from those of bulk materials. In particular, quantum dots have high quantum yields, noticeable Stokes shifts, and size-tunable emission wavelengths with narrow emission spectra, making them ideal fluorescent markers [2]. Moreover, the chemical stability of quantum dots and the potential to adjust their biocompatibility make them highly attractive candidates for biological imaging, especially in tumor detection and imaging. The biocompatibility and targeted imaging capabilities of quantum dots are significantly enhanced through surface modification and functionalization strategies, such as encapsulation with biocompatible polymers or targeted modification with biological binding molecules (e.g., antibodies or peptides). These strategies not only address the potential toxicity issues associated with the original quantum dots in biological systems but also expand their applications in precise tumor localization, multimodal imaging, and therapy monitoring. The pioneering work of Alivisatos *et al.* in 1996 and subsequent studies have demonstrated the immense potential of quantum dots in the fields of biological labeling and imaging [3]. With a deeper understanding of the tunable optical properties of quantum dots and continuous improvements in their biocompatibility, the application of quantum dots in biomedical research has expanded from basic scientific studies to actual clinical applications, especially in early tumor diagnosis and monitoring treatment efficacy, demonstrating unprecedented value.

Despite the relatively short history of quantum dots in biological and medical applications, they, particularly zinc sulfide quantum dots, have shown tremendous potential, especially in biomolecular labeling, cell labeling, *in vivo* imaging, and cellular immunoassays. Since quantum dots were first successfully used as biological probes in living cells in 1998, researchers have delved into techniques for binding quantum dots to biomolecules through surface functionalization. Zinc sulfide quantum dots (ZnS QDs), with their excellent photostability and resistance to photobleaching, perform exceptionally well in continuous and extensive nanocrystal laser spectra distributions, making them an ideal choice for fluorescent markers.

Compared to other quantum dots, zinc sulfide quantum dots exhibit significant advantages in toxicity and biocompatibility. They can enter cell membranes or cytoplasm more safely and be specifically recognized, allowing for rapid and sensitive detection of specific components in biological systems. This characteristic makes zinc sulfide quantum dots particularly important in tumor imaging,

as they can provide deep insights into the tumor microenvironment with minimal toxic response in surrounding healthy tissues. Another advantage of semiconductor quantum dots is their ability to absorb a broader range of light wavelengths than most organic dyes while providing a narrower range of emission wavelengths. The unique properties of zinc sulfide quantum dots, combined with their low toxicity, make them highly favored in interdisciplinary research, especially in fields such as biology (e.g., fluorescent labeling and cell imaging), analytics (e.g., detection of small molecular compounds and large protein molecules), energy, sensing technologies, and optoelectronic devices, demonstrating significant research and application potential.

2. Overview of Zinc Sulfide Quantum Dots

Zinc sulfide (ZnS) is a key member of the II - VI semiconductor family and one of the earliest discovered semiconductors. It exists in two structural phases, each with its unique stacking arrangement: cubic phase (C-ZnS) with a sphalerite structure, and hexagonal phase (H-ZnS) with a wurtzite structure. The cubic sphalerite structure is composed of tetrahedral zinc and sulfur atoms arranged in an ABC ABC ABC stacking sequence, while the hexagonal wurtzite structure exhibits an AB AB AB type of close packing. The distinctive arrangements of these crystal structures not only affect their electronic structure and bandgap models but also determine their photoluminescence properties, which are crucial for tumor imaging applications. In tumor imaging, these structural characteristics mean that zinc sulfide quantum dots can optimize their optical properties, such as bandgap width and emission wavelength, by adjusting size and phase structure. The cubic ZnS is more stable at low temperatures, while the transition temperature to the hexagonal phase can be reduced by decreasing particle size, which is particularly important for synthesizing quantum dots with specific optical properties at low temperatures. Moreover, the bandgaps of zinc sulfide quantum dots are 3.72 eV (cubic phase) and 3.77 eV (hexagonal phase), respectively, [4] and both structures have large defect bands and exhibit numerous dislocations when the system is in a critical state. Under normal pressure, cubic sphalerite ZnS shows higher stability in low-temperature environments and only transitions to hexagonal wurtzite ZnS at temperatures greater than or equal to 1023˚C, making it quite challenging to obtain hexagonal wurtzite ZnS under low-temperature conditions [5]. However, the transition temperature is not constant. Studies have shown that cubic wurtzite ZnS can be obtained through a phase transition from cubic sphalerite ZnS at a temperature of 400˚C [6], indicating that the phase transition temperature of sphalerite and wurtzite decreases with the reduction in particle size [7]. Additionally, its lower lattice constant makes its band structure relatively complex and varied, which determines its unique optical and electrical properties. Therefore, by precisely controlling the structure and size of zinc sulfide quantum dots, researchers can develop new probes with optimized optical properties that improve the accuracy and effi-

ciency of tumor imaging. With a deeper understanding of the relationship between the structure and optical performance of zinc sulfide quantum dots, we can better exploit the tremendous potential of these nanomaterials in early diagnosis and therapeutic monitoring.

As research on quantum dots progresses, scientists are increasingly focusing on developing low-toxicity, high-stability, and cost-effective nanomaterials, particularly non-cadmium-based quantum dots, among which ZnS quantum dots are widely used in various fields due to their exceptional optoelectronic properties. Compared to traditional cadmium-based quantum dots, zinc sulfide quantum dots not only exhibit higher luminescence efficiency but also have lower biological toxicity, making them particularly important in the biomedical field, especially in tumor imaging [8]. However, pure ZnS quantum dots have limitations in terms of luminescence efficiency, resistivity, ease of use, optical coverage, and stability, restricting their further application [9]. Under certain specific environmental conditions, these QDs may decompose to produce harmful gases, causing damage and pollution to people and the atmosphere [10]. To address these challenges, the performance of ZnS quantum dots has been optimized through metal doping strategies. Specifically, ZnS quantum dots doped with manganese (Mn) and copper (Cu) have received widespread attention for their improved chemical inertness and biocompatibility. This doping not only expands the absorption and emission range of quantum dots, producing a variety of fluorescent effects, but also significantly improves their photoresponse efficiency and stability. Particularly in tumor imaging, doped ZnS quantum dots offer high sensitivity and specificity in recognizing tumor markers, facilitating early diagnosis and disease monitoring. For instance, Mn-doped ZnS quantum dots have been successfully applied in multimodal tumor imaging, where their unique fluorescent and magnetic properties enable them to serve as fluorescent probes for high-resolution imaging and also be used in Magnetic Resonance Imaging (MRI), providing an efficient integrated imaging solution. Furthermore, Cu-doped ZnS quantum dots have shown great potential in visual detection of specific tumor markers due to their efficient photoresponse at specific wavelengths. These advancements demonstrate the significant role of doped ZnS quantum dots in enhancing tumor imaging technology, not only greatly optimizing the performance of fluorescent probes but also facilitating revolutionary progress in early tumor diagnosis and treatment efficacy evaluation. Through these doping strategies, zinc sulfide quantum dots have emerged as a highly promising research direction in the field of tumor imaging, showcasing their immense potential in reducing environmental pollution and enhancing biomedical applications.

3. Application of Zinc Sulfide Quantum Dots in Tumor Imaging

By combining biocompatible compounds with the surface of quantum dots,

these particles are endowed with the potential for intracellular imaging. The fixation of biocompatible molecules on quantum dots through interactions such as covalent and hydrogen bonds, followed by their application as probes in the imaging of tumor tissues and organs, demonstrates this potential [11]. When these biocompatible compounds interact specifically with biomolecules in a certain region within the cell, quantum dots are capable of internalization and imaging within that specific area [12]. However, despite these strategies significantly enhancing the application potential of zinc sulfide quantum dots in biological imaging and tumor treatment, the specific interaction mechanisms and their impact on tumor imaging efficacy require further clarification. For instance, in 2003, Chen *et al*. demonstrated the application of quantum dots in tumor labeling by combining charged CdSe@ZnS quantum dots with luminescent dextran nanospheres, where the strong adhesion between glycan residues and proteins offered an effective method for studying protein-glycan interactions [13]. In 2009, Wei *et al*.'s successful preparation of CdSe@ZnS quantum dots with transcription-activating protein (TAT) functionality further evidenced the potential of surface-modified quantum dots for targeted tumor therapy and controlled drug release [14]. Nonetheless, zinc sulfide quantum dots still face a series of challenges in tumor imaging applications, such as optimization of cytotoxicity, stability, and biodistribution. The size, surface modification, and charge characteristics of quantum dots significantly influence their behavior and efficacy in biological systems. For example, variations in particle size not only affect their biocompatibility but also determine their distribution within cells, with smaller particles tending to concentrate around the cell nucleus, whereas larger particles are more distributed between the nucleus and lysosomes. Thus, precise engineering of quantum dots is key to their application in clinical tumor imaging. Facing these challenges, future research should focus on developing new strategies to improve the surface engineering of zinc sulfide quantum dots, enhancing their biocompatibility and targeting capabilities while reducing potential toxicity. With a deeper understanding of the interactions between quantum dots and biological systems, we can better design and optimize quantum dot systems for tumor imaging, driving the field towards safer and more effective directions.

Due to the outstanding luminescent properties of zinc sulfide quantum dots, they have become an important tool for high-definition cell imaging, long-term *in vivo* cell tracking, and tumor localization studies [15]. For instance, in 1999, Kang *et al*. conducted detailed imaging studies on HepG2 cells by combining Mn:ZnSe quantum dots with chitosan. They discovered that Mn:ZnS quantum dots, modified with mannose, exhibited unique and specific characteristics in cell labeling. However, the larger particle size of mannose and chitosan limited their application from a fluid dynamics perspective, highlighting the importance of optimizing particle size and surface properties when designing nanomaterials for biomedical applications [16]. In 2005, Santra demonstrated the application of Mn:CdS quantum dots in *in vivo* imaging, especially how these quantum dots,

when combined with the tetanus toxoid peptide (TAT), achieved a breakthrough in targeted fluorescence labeling [17]. This combination took advantage of TAT's specific transmembrane capability, allowing quantum dots to seamlessly cross the blood-brain barrier and selectively label cerebral vessels, which is of significant importance for research in neuroscience and oncology. Moreover, the successful preparation of water-soluble quantum dots through the encapsulation with chitosan/polystyrene nanoparticles opened new avenues for fluorescence detection of intravascular tumor markers. These applications not only highlight the extensive application potential of zinc sulfide quantum dots in the field of tumor imaging but also underscore the importance of further developing these technologies. Using polysaccharides for encapsulation in the cellular environment is an effective way to improve the biocompatibility of quantum dots, also offering a strategy to enhance their performance in clinical applications. Future research should further explore how to optimize their biodistribution, stability, and targeting by refining the surface modifications and structural design of quantum dots, to fully harness their great potential in tumor diagnosis and treatment.

As an innovative imaging approach, multichannel imaging has garnered widespread attention in the scientific community for its ability to provide comprehensive biological data beyond traditional single-mode methods. Particularly, nanoscale multichannel imaging probes that combine Magnetic Resonance Imaging (MRI) with optical imaging have shown great application prospects. In recent years, researchers have developed various nanomaterials with unique functionalities, including metal-organic compounds, semiconductors, graphene, and other inorganic nanoparticles, to meet the complex needs of clinical diagnostics. In 2006, Yang *et al*. successfully synthesized Mn:CdS quantum dots with dual MRI and fluorescence imaging functionalities, opening a new chapter in multimodal imaging techniques [18]. Building on this, a novel type of quantum dot was further designed and prepared, which not only incorporates nuclear magnetic resonance and fluorescence imaging but also adds photoacoustic imaging capabilities, significantly expanding its application range. These quantum dots were first coated with silica oxide, then captured $Gd3+. $ through functionalized polymers. This structure not only ensured that the fluorescent nanoparticles produced strong optical signals when activated but also triggered a series of biochemical reactions targeting the tissue, effectively improving the accuracy and efficiency of imaging. Due to their significant proton relaxation effects, $Gd3 ± Mn-CdS $QDs demonstrated potential as live-cell MRI contrast agents, becoming an excellent molecular probe for magnetic resonance. This multifunctional imaging probe, combining the deep penetration ability of MRI with the high resolution of fluorescence and photoacoustic imaging, offers a new efficient and precise tool for future biomedical research and clinical applications.

CdSe@ZnS quantum dots, through covalent bonding with so-called "photosensitizer" molecules acting as electron donors, possess the capability to oxidize

or reduce oxygen, especially at the molecular edges of molecular oxygen and water. This property enables them to generate reactive oxygen species (ROS) and phototoxicity, offering a potential pathway for photodynamic therapy. In 2009, Mei demonstrated a method for preparing quantum dots and gold nanoparticles coupled via PEG, which not only enhanced their resistance to environmental changes but also facilitated their application in bioanalysis and live cell imaging [19]. Additionally, in 2009, Susumu showcased the role of ligand exchange techniques in enhancing the water solubility and biocompatibility of quantum dots by preparing DHLA-PEG ligands with terminal functional groups [20]. Cooper in 2010, using dopamine as a photosensitizer, studied the generation of ROS in solution and within cells, providing important foundational data for the application of quantum dots in photodynamic therapy [21]. In 2011, Wang and colleagues introduced $Mn2+ in $CdSe@Mn-doped ZnS QDs successfully combining the optical properties of quantum dots with magnetic resonance imaging capabilities for multimodal imaging [22]. These quantum dots could not only visually mark macrophages through fluorescence imaging but also facilitate contrast imaging using MRI technology, demonstrating their potential in tumor diagnosis and therapy. Furthermore, the introduction of Fe_3O_4 nanoparticles expanded the application of quantum dots in intracellular drug transport imaging [23]. These advancements not only reveal the broad application prospects of quantum dots in the field of tumor therapy but also show that through functional doping, such as the introduction of cancer inhibitors, folic acid, and polyethylene glycol, it is possible to prepare nanoprobes that possess both optical and MRI imaging capabilities and can achieve targeted drug release. These probes provide new tools for precise diagnosis and treatment of tumors, showcasing the continuously expanding potential of quantum dots in the biomedical field.

The potential toxicity of quantum dots is a major barrier to their clinical application. Therefore, developing new fluorescent probes that are both low in toxicity and highly efficient is particularly crucial for tumor imaging. In this context, Mn:ZnS and Mn:ZnSe quantum dots are considered promising candidates in the field of biological imaging due to their relatively low cytotoxicity. In vitro experiments have shown that even at a concentration of 100 mM for 48 hours, Mn:ZnS quantum dots exhibit no significant toxicity to cells, a characteristic that may originate from their inherent good water solubility. Furthermore, after treating cells with SiO_2-S-Mn-ZnS quantum dots, the morphology and vitality of the cells remained essentially unchanged, further indicating that the toxic effects of these quantum dots are negligible. Recent studies, using Mn:ZnSe quantum dots for imaging human prostate cancer cells, have shown that these quantum dots have relatively low toxicity to cells, suggesting their potential for tumor targeting. Due to the low cytotoxicity, bright multicolor luminescence, high specificity to cancer cells, and excitability by biologically friendly visible light of Mn:ZnS quantum dots, they have become a highly regarded biological probe in the field of cancer cell imaging. Given the low cytotoxicity of ZnS or

ZnSe quantum dots themselves, transition metal-doped ZnS quantum dots have shown great application potential in areas such as drug transport. In 2011, Xu and colleagues demonstrated the multifunctionality and broad potential of these materials in medical applications by using a mixture of manganese and ZnS quantum dots modified with glycopeptides for the loading and release of ibuprofen [24].

Multimodal imaging contrast agents, possessing unique magnetic resonance and optical imaging functions, demonstrate vast potential in disease detection and treatment. In 2008, Chen combined alpha-fetoprotein (AFP) monoclonal antibodies (Ab) with CdSe@ZnS quantum dots (QDs-AFP-Ab) aiming to detect AFP levels in human liver cancer cell lines (HCC LM6). Both *in vivo* and in vitro studies confirmed that QDs-AFP-Ab exhibited high stability, specificity, and biocompatibility in the liver cancer model system for ultrasensitive fluorescence imaging of molecular targets [25]· Currently, quantum dots that are water-soluble, biocompatible, and chemically stable are considered unsuitable for subcellular component labeling or staining due to their large size. In 2011, Lim developed a dual-mode contrast agent called perfluorodecalin (PFD)/InGaP@ZnS nanocomposite microemulsions, which possess F magnetic resonance imaging characteristics [26]. Studies showed that this dual-mode contrast agent could easily be transported into both phagocytic and non-phagocytic immune cells. The multifunctional PFD/InGaP@ZnS nanomicroemulsions can be absorbed into immune therapeutic cells, allowing marked cells to be imaged by magnetic resonance or fluorescence imaging with relatively minimal impact on cell survival and function.

Transferrin and anti-Claudin-4 labeled CdSe@ZnS quantum dots can serve as optical contrast agents for in vitro pancreatic cancer cell imaging. Besides in vitro confocal microscopy, cell-free co-precipitation analysis also verified the transferrin-mediated labeling, and the use of monoclonal anti-Claudin-4 demonstrated the specific extraction of pancreatic cancer. Furthermore, it was found that quantum dots themselves do not affect the proliferative activity of cancer cells but can enhance the tumor tissue's sensitivity to chemotherapeutic drugs, thereby increasing therapeutic efficacy. Semiconductor quantum dots, due to their photophysical superiority over organic dyes, are considered high-quality markers in biomedical applications. Since quantum dots inherently lack immunogenicity and tumor selectivity, they have unique advantages in targeted therapy. Folic acid (FA), a common receptor on cancer cells, has been linked to Mn:ZnS QDs. By specifically recognizing the high expression of folate receptors on tumor cell surfaces, precise quantification of cancer cells was successfully achieved [27]. Manzoor utilized doping quantum dots, harmless to cells and biocompatible under visible light excitation, to successfully detect folate receptor-positive human oral epidermoid carcinoma cells (KB). Given the multiple crucial roles of Zn^{2+} in biological systems, the detection of intracellular Zn^{2+} has attracted widespread attention. In 2009, Ren and others successfully assembled Mn:ZnS QDs

modified with SiO_2 containing S^{2-} and imaged intracellular Zn^{2+} [28].

4. Conclusions

Zinc sulfide quantum dots, as materials with nanoscale structures, have shown great potential and promising prospects in tumor *in vivo* imaging. Their unique optical properties, excellent chemical stability, and good biocompatibility make them one of the most promising nanomaterials in the current development of the biomedical field. Particularly in the realm of tumor imaging, quantum dots have been endowed with the ability to image specific biological markers through the combination of biocompatible compounds with their surface. Researchers have utilized this technology to successfully study the functional status of tumor tissues, drug delivery mechanisms, and treatment effects, achieving significant milestones by covalently binding or using self-assembly techniques to combine quantum dots with specific bioactive groups or fluorescent groups.

Furthermore, quantum dots with multimodal imaging capabilities have been developed, such as Mn:CdS quantum dots that combine MRI and fluorescence imaging characteristics, and multimodal imaging contrast agents with both magnetic resonance and optical imaging functions. These advanced multimodal imaging techniques offer more choices and possibilities for tumor diagnosis and treatment, and are expected to play an important role in future clinical applications. However, despite the significant potential of zinc sulfide quantum dots in the field of tumor imaging, their application still faces several challenges and limitations. Among them, toxicity issues related to quantum dots are a major obstacle, limiting their widespread use in clinical settings. Therefore, future research efforts need to focus on developing new types of low-toxicity, high-efficiency fluorescent markers to address this critical issue. Moreover, further research on the stability, biocompatibility, and drug release characteristics of quantum dots will provide a more solid scientific foundation and technical support for their clinical application in tumor therapy and imaging.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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