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BIOLOGICAL APPLICATIONS OF QUANTUM DOTS: A REVIEW.

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ABSTRACT

Research on fluorescent semiconductor nanocrystals, also known as quantum dots (QDs), has evolved over the past two decades from the field of electronic materials science to biological applications. QDs have unique chemical and physical properties as a result of their size and highly compact structure. They emit light over a broad range of the electromagnetic spectrum from visible to infrared, depending on their size and chemical composition. Several researchers have shown that QD-based technology may become a promising basis for biological research. In this review, we focus on recent biological application of QDs in drug delivery and in the diagnosis and treatment of disease, including antimicrobial efficacy, screening for *sypilis*, renal clearance, and detecting cell death, among others. With the development of QD synthesis and modification, the effect of QDs on biological investigation will become increasingly important.

INTRODUCTION

Quantum dots (QDs) are semiconductor nanoparticles that greatly expand the possibilities for fluorescent imaging of cells and living animals [1]. They can be excited by a wide range of light, ranging from ultraviolet to near-infrared, and can emit different wavelengths of light depending on their size and composition. Typically, a single QD contains a total of approximately 100-100,000 atoms in its crystal core. The size of QDs ranges on the

nanometer scale, normally 2-10 nm in diameter. In the early 1990s, quantum dots were mainly prepared in aqueous solution with added stabilizing agents. This procedure yielded low-quality quantum dots with poor efficiencies in fluorescence and large size variation. From 1993 onwards, the high-temperature organometallic procedure was used for growing quantum dots [2]. Now, the use of quantum dots heralds a revolution in biological imaging; their photophysical properties have broadened their application, and they have shown great promise as imaging probes in bio-imaging, drug discovery, and diagnosis. This review of the biological applications of QDs will exclude the detection of cancer, because many research and review articles already relate to the eventual use of quantum dots to dramatically improve clinical diagnostic tests for the early detection of cancer.

Antimicrobial Efficacy of Zinc Oxide Quantum Dots in food product

Food products are rich in nutrients required by microorganisms and may become contaminated. In Particular, *Listeria monocytogenes*, *Salmonella Enteritidis* and *Escherichia coli* are considered as one of the most hazardous, potentially life-threatening, human food borne pathogens. They can contaminate many food products, such as milk, cheese, ice cream, raw vegetables, eggs, and meats [3]. Hence, the development of rapid, sensitive, and simple methods to detect these pathogens is extremely important in implementing an effective response to the prevention of food borne diseases.

Jin et al [4] reported, Zinc oxide quantum dots (ZnO QDs) are nanoparticles of purified powdered ZnO and these were evaluated for antimicrobial activity against *Listeria monocytogenes*, *Salmonella Enteritidis*, and *Escherichia coli* O157:H7. In their study, the ZnO QDs were utilized as a powder, bound in a polystyrene film (ZnO-PS), or suspended in a polyvinylprolidone gel (ZnO-PVP). Bacteria cultures were inoculated into culture media or liquid egg white (LEW) and incubated at 22°C. The inhibitory efficacies of ZnO QDs against 3 pathogens were concentration dependent and also related to type of application. The ZnO-PVP (3.2 mg ZnO/mL) treatment resulted in 5.3 log reduction of *L. monocytogenes* and 6.0 log reduction of *E. coli* O157:H7 in growth media after 48 h incubation, as compared to the controls. *Listeria* cells in the LEW control increased from 3.8 to 7.2 log CFU/mL during 8 d incubation, while the cells in the samples treated with 1.12 and 0.28 mg ZnO/mL were reduced

to 1.4 and 3.0 log CFU/mL, respectively. After 8 d incubation, the cell populations of *Salmonella* in LEW in the presence of 1.12 and 0.28 mg ZnO/mL were reduced by 6.1 and 4.1 log CFU/mL over that of controls, respectively. ZnO powder and ZnO-PVP showed significant antimicrobial activities against all 3 pathogens in growth media and LEW. ZnO-PVP coating had less inhibitory effect than the direct addition of ZnO-PVP. No antimicrobial activities of ZnO-PS film were observed. Their study suggested that the application of ZnO nanoparticles in food systems may be effective at inhibiting certain pathogens.

Novel Quantum Dots–Based Point of Care Test for *Syphilis*

Syphilis is a chronic infectious disease caused by the spirochaete *Treponema pallidum*. Syphilis is usually transmitted by sexual contact or from mother to infant, although endemic syphilis is transmitted by non-sexual contact in communities living under poor hygiene conditions. *T. pallidum* can also be transmitted by blood transfusion. In spite of provoking a strong humoral and cell-mediated immune response, *T. pallidum* is able to survive in the human host for several decades. Syphilis causes sores mainly on the external genitals, vagina, anus, or in the rectum. Untreated syphilis in a pregnant woman can infect and possibly cause death to the unborn child.

Yang et al describe the development of a novel fluorescent POC (Point Of Care) test method to be used for screening for *syphilis*. The method was designed to combine the rapidness of lateral flow test and sensitiveness of fluorescent method. 50 *syphilis*-positive specimens and 50 healthy specimens conformed by *Treponema pallidum* particle agglutination (TPPA) were tested with Quantum Dot-labeled and colloidal gold-labeled lateral flow test strips, respectively. Results showed that both sensitivity and specificity of the quantum dots–based method reached up to 100% (95% confidence interval [CI], (91–100%)), while those of the colloidal gold-based method were 82% (95% CI, 68–91%) and 100% (95% CI, 91–100%), respectively. In addition, the naked-eye detection limit of quantum dot based method could achieve 2ng/ml of anti-TP47 polyclonal antibodies purified by affinity chromatography with TP47 antigen, which was tenfold higher than that of colloidal gold–based method. Finally they identified, quantum dots were found to be suitable for labels of lateral flow test strip. Its ease of use, sensitiveness and low cost make it well-suited for population-based on-the-site *syphilis* screening [5].

Formation of acetylcholine receptor clusters visualized with quantum dots

Geng et al [6] reported that, they provide new measurements supporting the diffusion-trap hypothesis as applied to AChR cluster formation. Consistent with published works, experiments on cultured *Xenopus* myotomal muscle cells revealed that AChRs at clusters that formed spontaneously (pre-patterned clusters, also called hot spots) and at those induced by nerve-innervation or by growth factor-coated latex beads were very stable whereas diffuse receptors outside these regions were mobile. Moreover, despite the restriction of AChR movement at sites of synaptogenic stimulation, individual receptors away from these domains continued to exhibit free diffusion, indicating that AChR clustering at NMJ does not involve an active attraction of receptors but is passive and diffusion-driven. They reveal single-molecular tracking using QDs has provided direct evidence that the clustering of AChRs in muscle cells in response to synaptogenic stimuli is achieved by two distinct cellular processes: the Brownian motion of receptors in the membrane and their trapping and immobilization at the synaptic specialization. This study also provides a clearer picture of the "trap" that it is not a uniformly sticky area but consists of discrete foci at which AChRs are immobilized.

Renal clearance of quantum dots

The field of nanotechnology holds great promise for the diagnosis and treatment of human disease. However, the size and charge of most nanoparticles preclude their efficient clearance from the body as intact nanoparticles. Without such clearance or their biodegradation into biologically benign components, toxicity is potentially amplified and radiological imaging is hindered. Choi et al using intravenously administered quantum dots in rodents as a model system, they have precisely defined the requirements for renal filtration and urinary excretion of inorganic, metal-containing nanoparticles. Zwitterionic or neutral organic coatings prevented adsorption of serum proteins, which otherwise increased hydrodynamic diameter by 415 nm and prevented renal excretion. A final hydrodynamic diameter of 5.5 nm resulted in rapid and efficient urinary excretion and elimination of quantum dots from the body. Their study provides a foundation for the design and development of biologically targeted nanoparticles for biomedical applications [7].

Imaging for embryonic stem cells

Semiconductor quantum dots (QDs) hold increasing potential for cellular imaging both *in vitro* and *in vivo*. Lin et al [8] report the successful demonstration of labeling ES cells with QDs and imaging these labeled cells *in vivo*. They have shown that it is feasible to label ES cells with QDs by Q-Tracker with high efficiency. After labeling, QDs did not affect the viability, and proliferation of ES cells, and have no profound effect on differentiation capacity of ES cells within the sensitivities of the screening assays used. They tested multiplex imaging *in vivo* using the Maestro system and showed that QD 525, QD 565, QD605, QD 655, QD 705, and QD 800 labeled ES cells can be detected *in vivo* using a single excitation wavelength (465 nm). This versatility makes them good candidates for tumor targeting, lymph node and vascular mapping, and cell trafficking in small animal imaging. Nevertheless, the use of QD in stem cells is only beginning to be explored. To their knowledge, this is the first demonstration of *in vivo* multiplex imaging of mouse ES cells labeled QDs. Upon further improvements (e.g., near-infrared QDs, better serum stability, and improved cell retention), QDs will have greater potential for tracking of stem cells within deep tissues.

Single plasma membrane K⁺ channel detection

K⁺ channels are widely expressed in eukaryotic and prokaryotic cells, where one of their key functions is to set the membrane potential. Many K⁺ channels are tetramers that share common architectural properties. The crystal structure of bacterial and mammalian K⁺ channels has been resolved and provides the basis for modeling their three-dimensional structure in different functional states. This wealth of information on K⁺ channel structure contrasts with the difficulties to visualize single K⁺ channel proteins in their physiological environment. Zloy et al [9] describe a method to identify single Ca²⁺-activated K⁺ channel molecules in the plasma membrane of migrating cells. Their method is based on dual-color labeling with quantum dots and they show that >90% of the observed quantum dots correspond to single K⁺ channel proteins. Finally, their method can be adopted to label any other ion channel in the plasma membrane on the single molecule level.

***In vivo* diffusion analysis with quantum dots and dextrans predicts the width of brain extra cellular space**

Diffusion within the extracellular space (ECS) of the brain is necessary for chemical signaling and for neurons and glia to access nutrients and therapeutics; however, the width of the ECS in living tissue remains unknown. Robert G. Thorne and Charles Nicholson (Department of Physiology and Neuroscience, New York University School of Medicine) used integrative optical imaging to show that dextrans and water-soluble quantum dots with Stokes–Einstein diameters as large as 35 nm diffuse within the ECS of adult rat neocortex *in vivo*. Modeling the ECS as fluid-filled “pores” predicts a normal width of 38–64 nm, at least 2-fold greater than estimates from EM of fixed tissue. ECS width falls below 10 nm after terminal ischemia, a likely explanation for the small ECS visualized in electron micrographs. Results will improve modeling of neurotransmitter spread after spillover and ectopic release and establish size limits for diffusion of drug delivery vectors such as viruses, liposomes, and nanoparticles in brain ECS [10].

Specific detection of unamplified mycobacterial DNA

Gazouli et al present the development of a specific DNA detection method using fluorescent semiconductor quantum dots (QDs) and magnetic beads (MBs) for fast detection of *Mycobacterium* spp., dispensing with the need for DNA amplification. Two biotinylated oligonucleotide probes were used to recognize and detect specific complementary mycobacterial target DNA through a sandwich hybridization reaction. Cadmium selenite QDs conjugated with streptavidin and species-specific probes were used to produce a fluorescent signal. MBs conjugated with streptavidin and genus-specific probes were used to isolate and concentrate the DNA targets. The application of the proposed method to isolated bacteria produced the expected result in all cases. The minimum detection limit of the assay was defined as 12.5 ng of DNA diluted in a sample volume of 20 microl. In order to obtain an indication of the method's performance with clinical samples, they applied the optimized assay to the detection of *Mycobacterium tuberculosis* in DNA isolated from bronchoalveolar lavage specimens from patients with tuberculosis and *Mycobacterium avium* subsp. *paratuberculosis* in DNA isolated from feces and paraffin-embedded tissues in comparison with culture, Ziehl-Neelsen staining, and real-time PCR. The concordance of these methods

compared to the proposed method with regard to positive and negative samples varied between 53.84% and 87.23% and between 84.61% and 100%, respectively. The overall accuracy of the QD assay compared to real-time PCR was 70 to 90% depending on the type of clinical material. The proposed diagnostic assay offers a simple, rapid, specific, and cost-effective method for direct detection and identification of mycobacterial DNA in clinical samples [11].

Conclusion

Quantum dots have been received as new technology with novel characteristics that could greatly developed biological imaging and detection. It can help to improve different field of biomedical sciences. However, obtained review shows the success of QDs in biological systems and different biomedical applications. We anticipate future improvements in QDs or QD-doped particles will provide increased benefit in particular areas.

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