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Review Manuscript

FOOTSTEPS OF NANOTECHNOLOGY BY QUANTUM DOTS WITH CORNELL DOTS IN BIOLOGICAL TAGGING, IMAGING AND OPTICAL COMPUTING

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ABSTRACT

A Quantum dot is a semiconductor whose excitons are confined in all three spatial dimensions. As a result, they have properties that are between those of bulk semiconductors and those of discrete molecules. Move over, quantum dots make way for the new kids on the block brightly glowing nanoparticles dubbed Cornell dots frequently used in the field of nanotechnology for biological imaging to locate the organs and to study the biochemistry going on inside the living cell by optical computing.

Quantum dots which have been used are tiny particles of semiconductors such as cadmium selenide that behave as if they were individual atoms. They can absorb light energy, kicking their internal electrons up to higher energy levels and then release the energy by emitting light. A quantum dot fluoresces much more brightly than a dye molecule, making it a desirable marker.

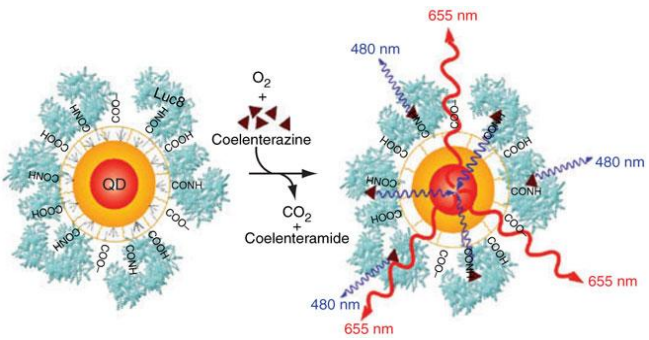
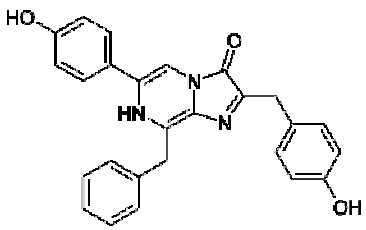


Figure-1: Coelenterazine producing quantum dots

Coelenterazine is the luciferin, the light emitting molecule, found in many aquatic organisms across seven phyla [1-3].



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A quantum dot is a particle of matter so small that the addition or removal of an electron changes its properties in some useful way. All atoms are of course, quantum dots, but multi-molecular combinations can have this characteristic. In biochemistry, quantum dots are called redox groups. In nanotechnology, they are called quantum bits or qubits. Quantum dots typically have dimensions measured in nanometers, where one nanometer is 10-9 meter or a millionth of a millimeter [4]. The fields of biology, chemistry, computer science, and electronics are all of interest to researchers in nanotechnology. An example of the overlapping of these disciplines is a hypothetical biochip, which might contain a sophisticated computer and be grown in a manner similar to the way a tree evolves from a seed [5]. In this scenario, the terms redox group and qubit are equally applicable; it is hard to classify such a chip as either animate or inanimate. The quantum dots in a biochip would each account for at least one data bit, and possibly several. In the extreme, the position of a single electron in a quantum dot might attain several states, so that a quantum dot could represent a byte of data. Alternatively, a quantum dot might be used in more than one computational instruction at a time. Other applications of quantum dots include nanomachines, neural networks, and high-density memory or storage media. Researchers have studied quantum dots in transistors, solar cells, Light Emitting Diodes (LEDs) and diode lasers. They have also investigated quantum dots as agents for medical imaging and hope to use them as qubits [6]. In an unconfined (bulk) semiconductor, an electron-hole pair is typically bound within a characteristic length called the Bohr exciton radius. If the electron and hole are constrained further, then the semiconductor's properties change. This effect is a form of quantum confinement, and it is a key feature in many emerging electronic structures [7].

Other quantum confined semiconductors include:

Quantum wires, which confine electrons or holes in two spatial dimensions and allow free propagation in the third.

Quantum wells, which confine electrons or holes in one dimension and allow free propagation in two dimensions.

Biology

In modern biological analysis, various kinds of organic dyes are used. However, with each passing year, more flexibility is being required of these dyes, and the traditional dyes are often unable to meet the expectations. To this end, quantum dots have quickly filled in the role, being found to be superior to traditional organic dyes on several counts, one of the most immediately obvious being brightness (owing to the high quantum yield) as well as their stability (allowing much less photodestruction). For single-particle tracking, the irregular blinking of quantum dots is a minor drawback. The usage of quantum dots for highly sensitive cellular imaging has seen major advances over the past decade. The improved photostability of quantum dots, for example, allows the acquisition of many consecutive focal-plane images that can be reconstructed into a high-resolution three-dimensional image. Another application that takes advantage of the extraordinary photostability of quantum dot probes is the real-time tracking of molecules and cells over extended periods of time. Researchers were able to observe quantum dots in lymph nodes of mice for more than 4 months. Semiconductor quantum dots have also been employed for in-vitro imaging of pre-labeled cells. The ability to image single-cell migration in real time is expected to be important to several research areas such as embryogenesis, cancer metastasis, stem-cell therapeutics, and lymphocyte immunology. Scientists have proven that quantum dots are dramatically better than existing methods for delivering a gene-silencing tool, known as small interfering RNA, into cells. First attempts have been made to use quantum dots for tumor targeting under in vivo conditions [8]. There exist two basic targeting schemes: active targeting and passive targeting. In the case of active targeting, quantum dots are function with tumor-specific binding sites to selectively bind to tumor cells. Passive targeting utilizes the enhanced permeation and retention of tumor cells for the delivery of quantum dot probes. Fast-growing tumor cells typically have more permeable membranes than healthy cells, allowing the leakage of small nanoparticles into the cell body. Moreover, tumor cells lack an effective lymphatic drainage system, which leads to subsequent nanoparticle-accumulation. One of the remaining issues with quantum dot probes is their in vivo toxicity. For example, CdSe nanocrystals are highly toxic to cultured cells under UV illumination. The energy of UV irradiation is close to that of the covalent chemical bond energy of CdSe nanocrystals. As a result, semiconductor particles can be dissolved, in a process known as photolysis, to release toxic cadmium ions into the culture medium. In the absence of UV irradiation, however, quantum dots with a stable polymer coating have been found to be essentially nontoxic [9]. Then again, only little is known about the excretion process of polymer-protected quantum dots from living organisms. These and other questions must be carefully examined before quantum dot applications in tumor or vascular imaging can be approved for human clinical use. Another potential cutting-edge application of quantum dots is being researched, with quantum dots acting as the inorganic

fluorophore for intra-operative detection of tumors using fluorescence spectroscopy [10].

Applications

Quantum dots are particularly significant for optical applications due to their theoretically high quantum yield. In electronic applications they have been proven to operate like a single-electron transistor and show the Coulomb blockade effect. Quantum dots have also been suggested as implementations of qubits for quantum information processing. The ability to tune the size of quantum dots is advantageous for many applications. For instance, larger quantum dots have a greater spectrum-shift towards red compared to smaller dots, and exhibit less pronounced quantum properties [11-17]. Conversely, the smaller particles allow one to take advantage of more subtle quantum effects. Researchers at Los Alamos National Laboratory have developed a wireless device that efficiently produces visible light, through energy transfer from thin layers of quantum wells to crystals above the layers. Being zero dimensional, quantum dots have a sharper density of states than higher-dimensional structures. As a result, they have superior transport and optical properties, and are being researched for use in diode lasers, amplifiers, and biological sensors. Quantum dots may be excited within the locally enhanced electromagnetic field produced by the gold nanoparticles, which can then be observed from the surface Plasmon resonance in the photo luminescent excitation spectrum of (CdSe)ZnS nanocrystals. High-quality quantum dots are well suited for optical encoding and multiplexing applications due to their broad excitation profiles and narrow/symmetric emission spectra. The new generations of quantum dots have far-reaching potential for the study of intracellular processes at the single-molecule level, high-resolution cellular imaging, long-term in vivo observation of cell trafficking, tumor targeting, and diagnostics [18].

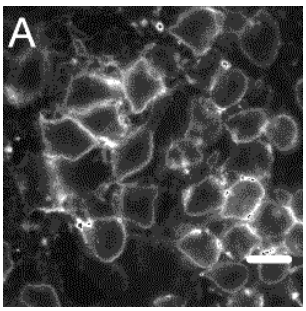
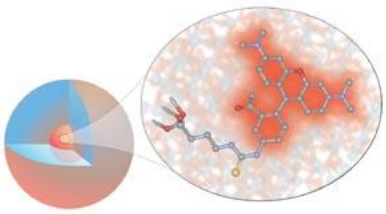


Figure-2: Schematic representation of a Cornell Dot, with several molecules of a fluorescent rhodamine dye encapsulated in the center. The dye has been modified with a group that links to the encapsulating silicon.

By surrounding fluorescent dyes with a protective silica shell, Cornell University researchers have created fluorescent nanoparticles with possible applications in displays, biological imaging, optical computing, sensors and microarrays such as DNA chips. These are all applications for which quantum dots have been used or are being considered. But the new Cornell nanoparticles offer an appealing alternative because of their greater chemical inertness and reduced cost. People have done superb experiments with quantum dots that were not previously possible. Hopefully Cornell dots will serve the same purpose and offer new possibilities. There are also some interesting physics questions about how the new dots work. Since optical microscopes can't resolve individual molecules, and electron microscopes can't be used on living organisms,

Cornell dots, also known as CU dots, are nanoparticles consisting of a core about 2.2 nanometers (nm) in diameter containing several dye molecules, surrounded by a protective silica shell, making the entire particle about 25 nm in diameter. The researchers call this core-shell architecture. (A nanometer is one-billionth of a meter, about three times the diameter of a silicon atom.) Like quantum dots, CU dots are many times brighter (20-30 times) than single dye molecules in solution and resist "photobleaching," a process by which dyes in solution rapidly lose their fluorescence. CU dots can be made with a wide variety of dyes, producing a large assortment of colors [19].



biologists often tag organic molecules with fluorescent dyes in order to track their movements through biological processes, such as the action of enzymes inside a living cell. While it can't see the molecules, an optical microscope can track the bright light given off by the dye [20]. The manufacture of CU dots and early experiments with them are described in a paper, "Bright and Stable Core-Shell Fluorescent Silica

Figure-3: Cornell Dots bound to Immunoglobulin-G antibodies attached to the surface of leukemia cells, demonstrating a possible use in biological tagging

Nanoparticles," in the journal Nano Letters (Vol. 5, No. 1) by Wiesner and his Cornell colleagues Hooisweng Ow, Daniel R. Larson, Mamta Srivastava, Barbara A. Baird and Watt W. Webb.

Unlike quantum dots, CU dots are mostly chemically inert. The silica shell is silicon dioxide: essentially glass. For use as biological markers, quantum dots are encased in a polymer shell: a process that adds to their already high manufacturing cost. Quantum dots also contain heavy metals like cadmium that can leach through the polymer shell and disrupt the chemistry being observed. However, silica is benign, cheap and easy to attach, and it is totally compatible with silicon manufacturing technology. That opens enormous possibilities in the life sciences and in information technology. The Cornell researchers tested the use of CU dots as biological markers by attaching an antibody, immunoglobin E (IgE), and observing how this combination attached to cell receptors on leukemia mast cells. The dots also offer an intriguing physics question:

Why do they fluoresce so brightly? In effect, the whole is brighter than the sum of its parts. We have this enormous brightness, and we don't know exactly where it's coming from. Several explanations have been offered. One is that the silicon shell protects the dye molecules from the solvent. A second is that dye molecules floating free can lose energy by actions other than emitting photons, but in the packed core of the particle those other actions are diminished [21].

According to research at Memorial Sloan-Kettering Cancer Center (MSKCC), Cornell dots, also known as C dots, are biologically safe and stable and small enough to be easily transported across the body's structures and efficiently passed through the kidneys and out in urine. A single dot consists of several dye molecules encased in a silica shell that can be as small as 5 nanometers in diameter (a nanometer is one-billionth of a meter, about three times the diameter of a silicon atom). The silica shell, essentially glass, is chemically inert. Coating the dots with polyethylene glycol, a process called PEGylation, further protects them from being recognized by the body as foreign substances, giving them more time to find targeted tumors. The outside of the shell can be coated with organic molecules that will attach to such desired targets as tumor surfaces or even locations within tumors. The cluster of dye molecules in a single dot fluoresces under near-infrared light much more brightly than single dye molecules, and the fluorescence will identify malignant cells, showing a surgeon exactly what needs to be cut out and helping ensure that all malignant cells are found. According to MSKCC researchers, the technology also can show the extent of a tumor's blood vessels, cell death, treatment response and invasive or metastatic spread to lymph nodes and distant organs [24].

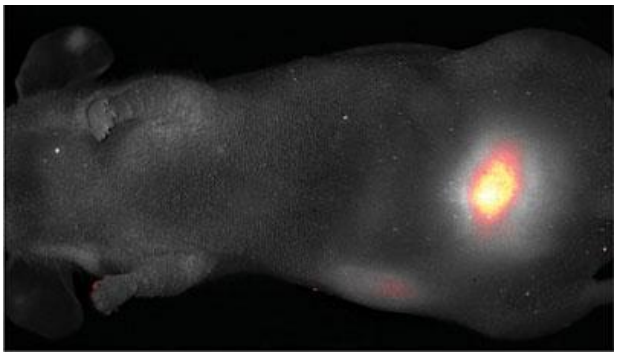


Figure-4: Cornell Dots fluoresce brightly enough to be seen through the skin of a mouse (faintly visible in this photo). Dots coated with polyethylene glycol have all reached the bladder in 45 minutes, demonstrating that C dots will be harmlessly excreted after they do their job [23]. (Reference: Memorial Sloan Kettering Cancer Center)

Cornell dots were developed in 2005 by Hooisweng Ow (pronounced "Hoy-sweng-Oh"), then a graduate student working with Ulrich Wiesner, Spencer T. Olin Professor of Materials Science and Engineering at Cornell. Their refinements of the dot design and experiments in mice at MSKCC are reported in the January 2009 issue of the journal Nano Letters (Vol. 9 No. 1) by Wiesner, Dr. Michelle Bradbury, a physician-scientist specializing in molecular imaging and neuroradiology at MSKCC, and colleagues. The dots were created by Ow, then Wiesner's graduate student. Webb, the S.B. Eckert Professor in Engineering, and Larson, a graduate student in applied and engineering physics now at Albert Einstein College of Medicine, studied their photophysical properties. Baird, director of the Cornell Nanobiotechnology Center, and Srivastava, a postdoctoral researcher, studied the dots as labels on living cells. The research was supported by the National Science Foundation, the state of New York and Phillip Morris USA. Quantum Dot Corp. supplied quantum dots used for comparison. Brightly glowing nanoparticles known as "Cornell dots" are a safe, effective way to "light up" cancerous tumors so surgeons can find and remove them [22].

Highly sensitive and specific probes and molecular imaging strategies are critical to ensure the earliest possible detection of a tumor and timely response to treatment [25]. Findings may now be translated to the investigation of tumor targeting and treatment in the clinic, with the goal of ultimately helping physicians to better tailor treatment to a patient's individual tumor. Since creating the Cornell dots, Wiesner, Ow and Kenneth Wang '77 have co-founded the company Hybrid Silica Technologies to commercialize the invention. The

dots, Wiesner said, also have possible applications in displays, optical computing, sensors and such microarrays as DNA chips. The latest research was supported by the Clinical and Translation Science Center at Weill Cornell Medical College and the Cornell Nanobiotechnology Center. The original research was funded by the National Science Foundation, New York state and Phillip Morris USA.

Glowing 'Cornell dots' can show surgeons where tumors are C dots fluoresce brightly enough to be see through the skin of a mouse (barely visible in these photos). At left, dots accumulated in the liver and bladder 45 minutes after injection. At right, dots coated with polyethylene glycol have all reached the bladder in 45 minutes. These experiments demonstrate that C dots will be harmlessly excreted after they do their job. Image: Memorial Sloan Kettering Cancer Center.

(PhysOrg.com) -- Brightly glowing nanoparticles known as "Cornell dots" are a safe, effective way to "light up" cancerous tumors so surgeons can find and remove them.

The outside of the shell can be coated with organic molecules that will attach to such desired targets as tumor surfaces or even locations within tumors. The cluster of dye molecules in a single dot fluoresces under near-infrared light much more brightly than single dye molecules, and the fluorescence will identify malignant cells, showing a surgeon exactly what needs to be cut out and helping ensure that all malignant cells are found. According to MSKCC researchers, the technology also can show the extent of a tumor's blood vessels, cell death, treatment response and invasive or metastatic spread to lymph nodes and distant organs [26].

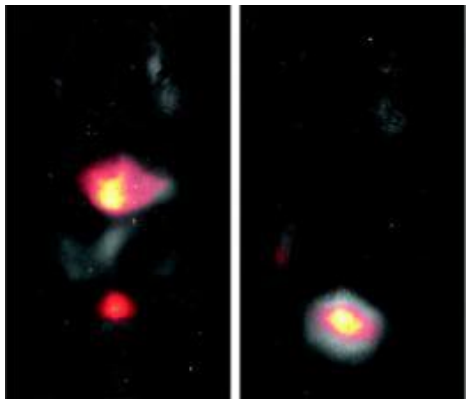


Figure-5: (PhysOrg.com) Brightly glowing nanoparticles known as "Cornell dots" are a safe, effective way to "light up" cancerous tumors so surgeons can find and remove them. (Image: Memorial Sloan Kettering Cancer Center)

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Conclusion: Newer technology in modern life is embedded thoroughly in such a way that every device cannot think to keep their footsteps towards the horizon of latest technology without nanotechnology. Any molecule either it is macro or micro in structure has the chemical design on nano-world. Quantum dots and Cornell dots are one of the most important examples. Detection and diagnosis of any disease can be easily

done in this new era by the help of nanotechnology by molecular tagging, imaging and then by optical computing. Drug-receptor compatibility and binding can be done by this newer technology to learn about the toxicological and pharmacological profile of the chemical molecule. So nanotechnology is very diverse, ranging from extensions of conventional device physics, to completely new approaches based upon molecular self-assembly, to developing new materials with dimensions on the nanoscale, even to speculation on whether we can directly control matter on the atomic scale.

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