Researchers detail the evolution of quantum dot imaging in the journal Science

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New imaging tool may change the way cancer is diagnosed and treated

The evolution over the last two decades of the nanocrystals known as quantum dots has seen the growth of this revolutionary new tool from electronic materials science to far-reaching biological applications that will allow researchers to study cell processes at the level of a single molecule and may result in new and better ways to diagnose and treat cancers.

Fluorescent semiconductor quantum dots, or qdots, also hold promise for high-resolution cellular imaging and the long-term observation of individual molecules and their movement within cells, according to a UCLA-led team of chemistry and biochemistry researchers that includes scientists from Stanford University. The researchers assess this emerging field and highlight two recent advances in the Jan. 28, 2005, issue of the peer-reviewed journal Science.

"Qdots as biological probes have lived up to the hopes of their initial promoters," said the article's senior author, Shimon Weiss, a Jonsson Cancer Center researcher, UCLA professor of chemistry, biochemistry and physiology and a member of the university's California NanoSystems Institute (CNSI). "This paper presents an objective view and perspective of what we can do now and what we may be able to do in the future. Undoubtedly, biologists will catch on to these exciting developments and find as yet unforeseen applications for this new physiology toolkit, enhancing their existing arsenal of imaging tools."

The work outlined in Science is the first result of a new joint effort between UCLA's Jonsson Cancer Center and the CNSI. The creation of the UCLA Cancer Nanotechnology Partnership signals a long-term commitment and investment into nanotechnology and its applications in cancer research, said Judith C. Gasson, cancer center director.

"The environment at UCLA makes it possible for researchers from diverse disciplines – physicists, cell biologists, chemists, immunologists - to work side by side," said Gasson, a professor of medicine and biological chemistry. "This new partnership has enormous potential and I'm very excited to see the advances in cancer diagnosis and treatment to come."

Qdot molecular imaging is a new way of seeing biologic processes at work within cells and in small animals. Probes can be attached to a given protein or receptor to monitor it and see what other molecules it interacts with, what part of the cell it is in and what signaling pathways the protein may use for performing normal cell functions and abnormal functions that may result in cancer. Qdots are much more resistant to degradation than other optical imaging probes, allowing them to track cell processes for longer periods of time and shed new light on molecular interactions. Additionally, because they are nanocrystals – tiny pieces of rock one-billionth of a meter in size – qdots provide good contrast for imaging with an electron microscope. Based on recent advances in UCLA laboratories, researchers hope that qdots might be used one day as a one-two punch to both diagnose and treat cancer (see attached figure). The qdot technology will enable researchers to locate a tumor within the body, look at it very precisely at the cellular level to determine what type of cancer it is and then perhaps arm it with toxic therapies designed to kill the disease, said physicist Xavier Michalet, the first author of the article.

"It would be a big advantage to use the same tool to not only locate and identify the cancer, but also to treat it," Michalet said. "This technology is likely to explode in the very near future."

Qdots have such potential because they can be color encoded, with different colors used to label

different cell processes, different cancers or different stages of the same cancer, Michalet said. Currently, a positron emission tomography (PET) scan can tell doctors the locations of tumors throughout the body, based on targeting the PET probe to a single tumor marker. With qdots, however, several different markers of the same tumor could be simultaneously "painted," generating a color barcode for real-time "optical biopsy" and diagnosis.

"Humans have close to 40,000 genes," Weiss said. "A large group of these genes operates at every moment, in every single cell of our body, in very complicated ways. By color encoding a subset of proteins in the cell with different color quantum dots, we can follow molecular circuitry, the dynamic rearrangement of the molecular interactions and interactions that re-program cells to gain and lose function in disease - in short, oversee the 'molecular dance' that defines life itself."

Two new advances are highlighted in Science, including proof of principle in animal models that qdots can be used to image processes at the cellular level, work done at the UCLA Crump Institute for Molecular Imaging. In the study, qdots were labeled with a positron-emitting isotope and injected into mice. Using PET scanning, researchers were able to watch over time as the qdots made their way through the vascular system and to the liver.

The same technique may be used on patients, who could be injected with a cocktail of different colored qdots that would "label" the cancerous cells. Once they're gathered at the tumor site, the positrons emitted from the qdots could be imaged with PET scanners now in use in clinics throughout the country. The scan would indicate the presence and location of a tumor. An "optical barcode" of the different colored qdots could help doctors identify tumor type and stage by allowing them to see differing levels of various tumor markers. This detection could be achieved by infra-red optical imaging directly through the tissue or by inserting into the patient a catheter carrying an optical fiber that would be guided using PET scanning directly to the tumor, allowing for detection and a real-time optical biopsy. This procedure could result in a diagnosis without tissue removal and analysis because of the selective recognition by qdots of the multiple molecular features of the tumor. A doctor could determine tumor type, provide an immediate diagnosis and administer treatment such as surgical resection or irradiation.

"This works helps pave the way for further use of nanoparticles in molecular imaging and cancer therapy applications. Researchers in the labs of Weiss, Anna Wu and myself have been working together for more than three years and are committed to advancing the routine use of quantum dots for preclinical and clinical studies," said Dr. Sanjiv Gambhir, director of the molecular imaging program at Stanford. "Our unique partnership is leading to many new discoveries and the best is yet to come."

The other advance outlined in Science details how Weiss and his colleagues were able to track receptors on a cell surface and watch them interact. As the receptors move around on the cell membrane, researchers will be able to determine their function and test whether or not they may be sensitive to outside molecules. Such studies would provide new clues about molecularly targeted therapies that could be effective in fighting cancer. Before qdots, researchers were able to track individual receptors and proteins on cell surfaces for seconds only, and were unable to view their interactions. Weiss and his colleagues were able to view the cell processes for many minutes using this new technology, shedding light on processes that had been theorized, but not actually seen.

Weiss and his team developed a unique peptide coating for the qdots that disguises them with a protein-like costume that allows them to target specific molecules. This coating – UCLA's Fabien Pinaud led the team in this advance – allows researchers to track individual molecules participating in cell processes. Using the color encoding, researchers could label many proteins and receptors on a cell surface and monitor in real time how they interact and the results of those interactions.

Weiss' team includes UCLA researchers Pinaud, a biochemist; Michalet, a physicist; Wu, a tumor

immunologist and Jonsson Cancer Center member; Soeren Doose, a physicist; Laurent Bentolila, a cell biologist; and Jack Li and James Tsay, physical chemists; and molecular imaging experts Gambhir and Gopal Sundaresan, both from Stanford.

Nanotechnology is likely to have a significant impact on the way cancer will be diagnosed and treated. UCLA researchers believe this powerful and far-reaching technology promises further advances in the near future.

"Nanobiotechnology is a very demanding field, since many areas of expertise have to be brought to bear," said Fraser Stoddart, CNSI director. "This new partnership allows scientists from different disciplines to jointly develop better ways to detect, diagnose and treat cancers."

Source: UCLA