nano-ONCOLOGY

small science, big hopes

By Xianlin Li

"Nanotechnology, the study of science on a level the width of ten hydrogen atoms, is generating a great deal of attention as scientists explore the question, 'Does the future of cancer therapy lie in the hands of nanoparticles?'"

Amid images of tumor cells being vaporized in beams of colorful light, a video produced by the National Cancer Institute proclaims, "the science is at our fingertips." The science being referred to, which is 80,000 times smaller than the breadth of a single ridge of skin on a human fingertip, is cancer nanotechnology. Nanotechnology, the study of science on a level the width of ten hydrogen atoms, is generating a great deal of attention as scientists explore the question, "Does the future of cancer therapy lie in the hands of nanoparticles?" (1)

Conventional cancer therapies such as radiation and chemotherapy damage healthy cells and cause numerous unwanted side effects. To mitigate this problem, scientists are attaching antibodies, or proteins that bind to a particular molecular surface, to the outer surfaces of nanoparticles filled with anticancer drugs and imaging agents (2). When these so-called nanovectors are released into the body, they specifically target only cancerous cells. This fusion of medicine and nanotechnology maximizes the efficacy of the drugs and, at the same time, decreases the dosage required. In addition, advancements in the field of nano-oncology are improving the accuracy of methods for the early detection of cancer and giving new hope to cancer patients worldwide.

Nanoimaging and Nanodiagnostics: Seeing Small

A quick survey of the mortality statistics for cancer reveals the importance of early detection. For example, when lung cancer is detected in its early stages and surgery is performed, the five-year survival rate for patients is 60 to 80 percent. However, patients who do not undergo surgery face a drastically reduced five-year survival rate of around ten percent (3). Current methods of early detection, which include X-rays and magnetic resonance imaging (MRI), detect tumors when they are about ten billion cells large, or roughly the size of a sugar cube. Although a tumor is not considered fatal until it becomes about a thousand times as large, it is often difficult for radiologists to differentiate developing tumors from nearby structures, such as blood vessels, on imaging scans (4).

Many types of nanoparticles have been tested in an attempt to enhance the resolution of MRI scans. MRI machines generate a magnetic field that changes the alignment of protons in water molecules found in human

tissues; by detecting and processing signals caused by these changes in alignment, a three-dimensional picture of body tissues is generated. However, if protons are re-excited before fully recovering their original alignment, a weak signal is produced. Paramagnetic MRI contrasting agents amplify the imaging signal because the unpaired electrons in paramagnetic ions allow nearby protons to regain their original alignments more quickly. Angiogenesis, the process by which new blood vessels sprout from existing ones to feed regions of rapidly proliferating tumor cells, is an early indicator of tumor growth. In one experiment, nanoparticles that were carrying paramagnetic gadolinium ions and that were coated with antibodies to target emerging blood vessels were injected into rabbits implanted with tumors. As the nanoparticles pooled around tumors, a 125% increase in the signal intensity of the MRI scans was detected. This enhanced signal output allowed scientists to see small angiogenic vessels, thus detecting tumors in their earliest stages of development (5).

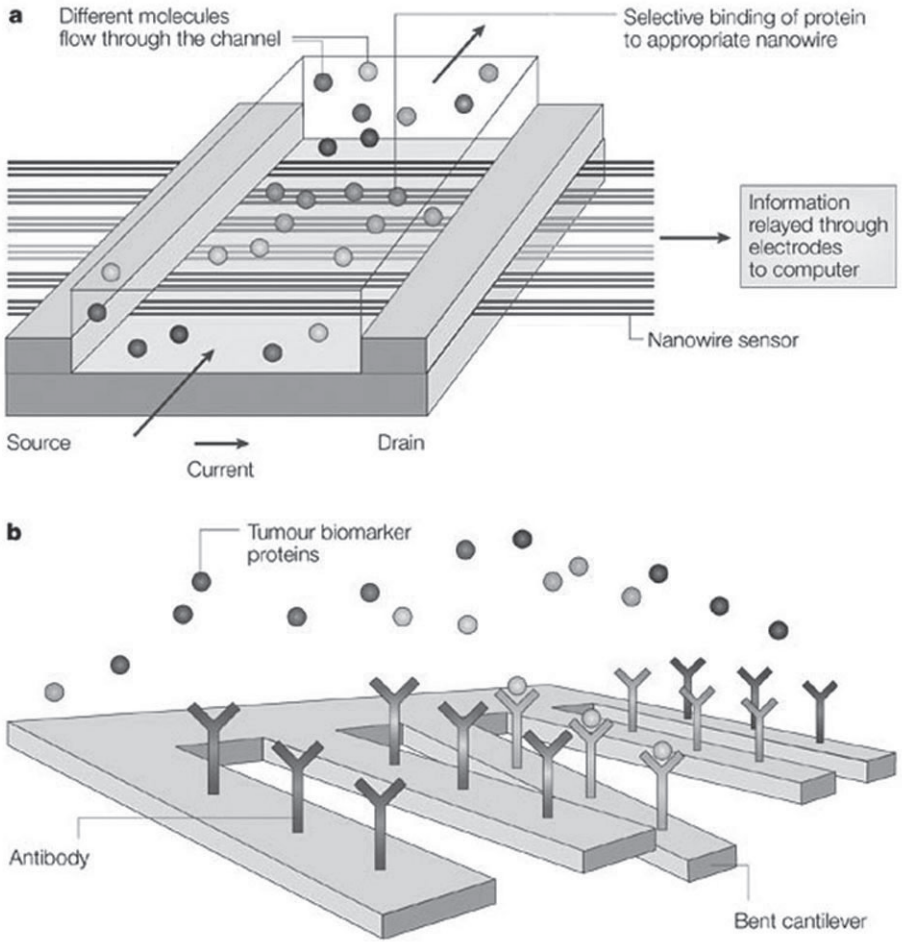

Figure 1. Arrays of (a) nanowires or (b) nanocantilevers that can bind to and detect specific molecules or biomarker proteins.

Nanodiagnostics: Biomarking Cancer

Many researchers are also using biomarkers, or molecular indicators of disease progression, to improve early detection methods. Nanocantilevers are flexible beams that can bind to molecular biomarkers through antibodies attached to their surface (Figure 1) (2). As the biomarker proteins bind to the nanocantilevers, the weight of the binding proteins causes the cantilevers to deflect. This deflection is then observed using lasers. Although this research is still in its experimental stages, scientists envision arrays of thousands of cantilevers arranged in a centimeter-sized chip that could read expression profiles of proteins in the cell (6). Similarly, nanowires are tiny, conducting wires that are coated with antibodies (Figure 1) (2). As the proteins targeted by the antibodies bind to the nanowire, their charge disrupts the current going through the wire. This disruption is detected by the wire and transmitted to a computer. Nanowires offer the unique ability of sensing a large number of protein biomarkers in real time (2).

While early detection through nanoimaging introduces artificially created nanoparticles into the body, cancer diagnosis can occur outside of the body by detecting biomarkers found in biological fluids. Using nanoparticles to identify biomarkers was limited by the fact that serum markers for most cancers were unclassified. However, recent mass spectrometry studies have revealed that a class of previously disregarded low abundance, low molecular weight (LMW) proteins found in blood may serve as a source of novel biomarker candidates (7). If this is the case, scientists could create nanoparticles with surfaces that selectively bind low abundance LMW proteins. The LMW proteins would then be separated from the nanoparticles and examined. This approach was recently used to identify potential biomarkers present in the blood of ovarian cancer patients (7).

Quantum dots—small semiconductors with a radius of a few nanometers and a polymer coating—are emerging as another class of powerful visualization tools for cancer imaging and detection. Unlike dyes, quantum dots do not pho-

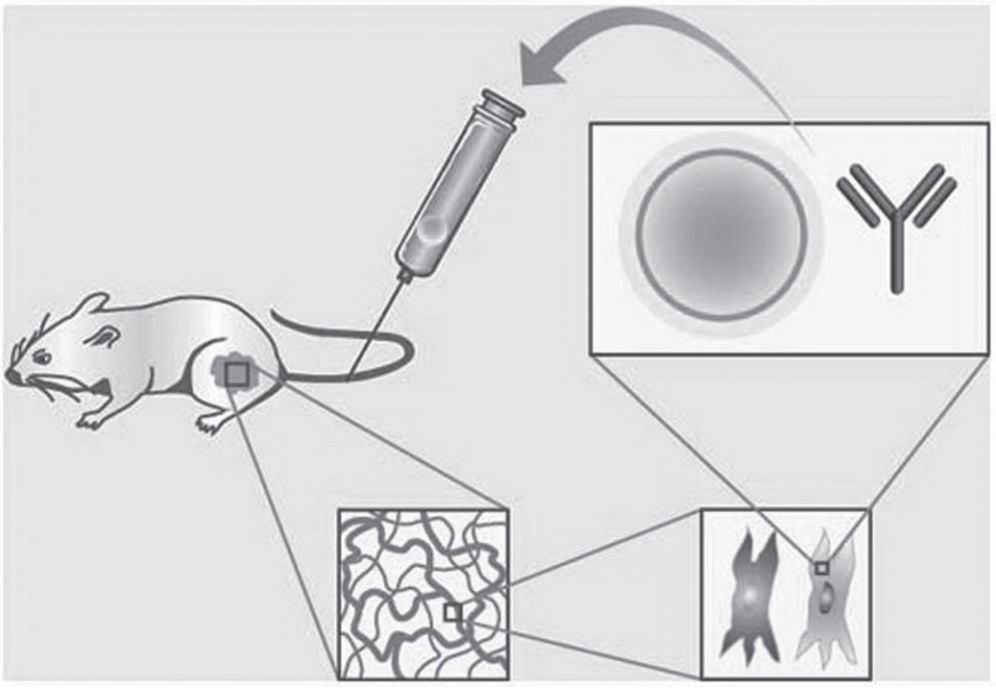

Figure 2. Quantum dots are used to characterize the abnormal blood vessel network of tumors in mice. Using antibodies, quantum dots can target specific cellular components or entire cells. Quantum dots are distinct in their ability to label different types of cells with different colors of quantum dot. All tagged species can then be differentiated with one wavelength of light.

tobleach or lose their signal intensity with time. Each color in a population of quantum dots can be conjugated, or coated, with antibodies that have different molecular targets. When these quantum dots are hit with light of a single wavelength, they generate a spectrum of colors that can serve as a barcode to identify molecular targets within the cell (2,6).

Nanoparticle Drug Delivery: Bullets, Bombs and Then Some

Nanovectors are platforms for delivering imaging enhancements and cancer therapeutics, but in techniques involving thermal ablation, the nanoparticle can also serve as the therapy. Nanoshells, nicknamed "nano-bullets," are made of semiconductors such as silica surrounded by a gold shell that absorbs near-infrared (NIR) light. The inert, non-toxic gold surface allows for the assembly of antibodies and other agents for targeted particle delivery (8). Nanoshells are harmless in the body on their own, but when tissue embedded with nanoshells is irradiated with NIR light from a laser, the light is converted into heat. The heat given off by the nanoshells leads to the photothermal destruction of cancerous cells (7).

Experiments have shown that solid tumors in mice treated with nanoshells and NIR light reached temperatures high enough to cause cell shrinkage and loss of nuclear staining, two signs of cell death (8). Another technique involving a similar strategy uses 30 to 40 nanometer-wide solid round gold particles to target breast cancer cells (9). As the nanoparticles accumulate on the membranes of these cells, they self-assemble into nanoclusters. These nanoclusters are described by researchers as "nanobombs" because their structure enhances NIR-induced damage to cancerous cells (9). However, precise timing is necessary, as the NIR cannot be applied until the physician is certain that the majority of nanoshells has reached the targeted tumor.

"In a recent experiment, 30 to 40 percent of the mice given the methotrexate attached to the dendrimer survived, while all of the mice treated with methotrexate alone died. In effect, the dendrimer with methotrexate delayed tumor growth for 30 days in mice or the equivalent of about three years in humans (10)."

While bullets and bombs are not subtle in their destruction of malignant cells, scientists have created a nano-sized "Trojan Horse" to smuggle chemotherapeutic drugs into tumor cells. Folic acid is a vitamin required by all cells to maintain their normal function. However, the folate receptor is overexpressed on the membranes of many types of cancerous cells, including those in lung, brain, breast, and ovarian cancers (10). Folic acid and methotrexate, a powerful anticancer drug, are attached to a dendrimer, a small, branched synthetic molecule that is used for drug delivery (10). Because of their rapid rate of cell division, cancer cells take in larger quantities of folic acid and, by extension, of the methotrexate that is also attached to the dendrimer. Normally, drugs like methotrexate have to diffuse across the cell membrane to get inside cancer cells. But since cancer cells demand folic acid, the dendrimers allow the drug to be transported concomitantly into the cells. This decreases the sever-

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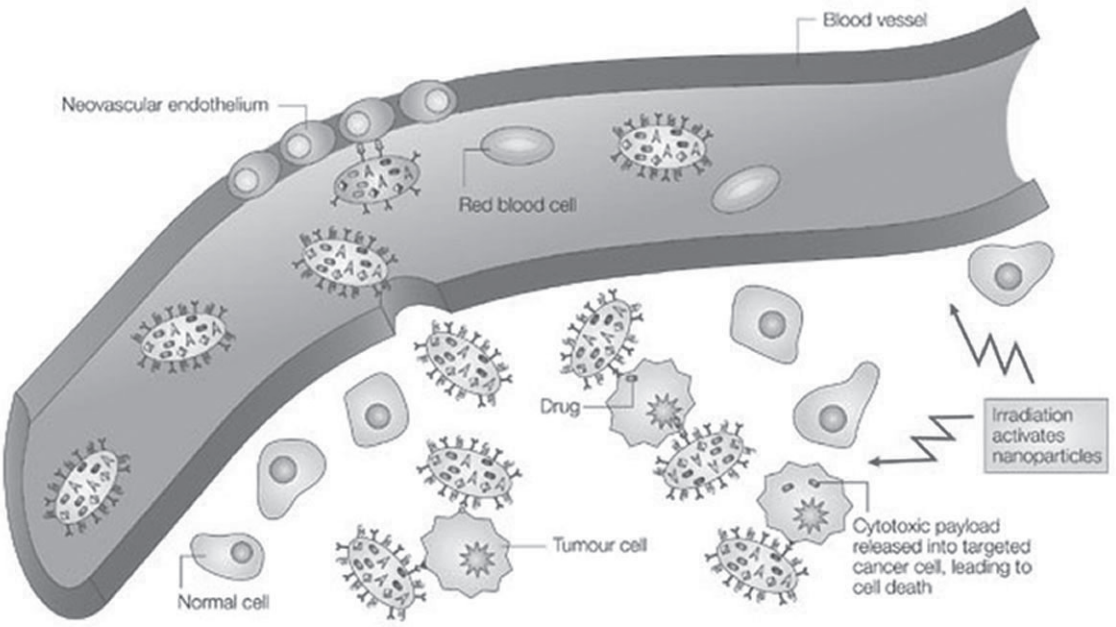

Figure 3. Nanoparticles, with antibodies to specifically target tumor cells, travel through the bloodstream. They are activated to deliver and release their cytotoxic payloads when irradiated with external energy.

ity of the side effects associated with methotrexate; ordinarily, a high concentration of the drug is required for diffusion to occur, resulting in damage to healthy cells. In a recent experiment, 30 to 40 percent of the mice given the methotrexate attached to the dendrimer survived, while all of the mice treated with methotrexate alone died. In effect, the dendrimer with methotrexate delayed tumor growth for 30 days in mice or the equivalent of about three years in humans (10).

A New Nanoworld

Methotrexate is not the only drug to get a nanotechnology makeover. In 2005, Abraxane, a treatment for severe cases of breast cancer, became the first "protein-bound particle" drug to be approved by the U.S. Food and Drug Administration (FDA) (11). Each dose of Abraxane contains millions of nanoparticles consisting of paclitaxel, the generic name for the world's best-selling chemotherapy drug, taxol, bound to albumin, a protein that is naturally found in blood. In clinical trials, metastatic breast cancer patients treated with Abraxane showed a response rate of 33% versus a response rate of 19% in patients treated with ordinary paclitaxel. Abraxane not only enhanced the efficacy of paclitaxel, but it also decreased its toxicity. The solvent used to dissolve paclitaxel often caused severe allergic reactions in patients and the steroids used to treat these reactions often led to more side effects. Since Abraxane does not need to be dissolved in solvent, it can be administered at higher doses with fewer side effects (1).

"Small in size but large in possibilities, nanotechnology is a new frontier in the fight for the cure for cancer."

People have dreamed small for decades since the release of the classic film, *Fantastic Voyage*, which was based on an Isaac Asimov novel and which describes the journey of a group of miniaturized surgeons who are injected into the body of dying man. Small in size but large in possibilities, nanotechnology is a new frontier in the fight for the cure for cancer. However, with research initiatives underway in major universities worldwide and with the National Cancer Institute declaring that it aims to eliminate cancer death and suffering by 2015, it is clear that cancer nanotechnology is no longer science fiction. H

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