NEWS

Nanotechnology Takes Aim at Cancer

The science of extremely small materials is poised to revolutionize cancer diagnostics, imaging, and treatment and could finally usher in the long-awaited era of personalized medicine

If there is a case to be made for personalized medicine, cancer is it. Every year, nearly 1.4 million Americans are diagnosed with the disease; another 600,000 die from it. Yet, although cancer is often portrayed as a monolithic illness, it is anything but. There are more than 200 types of cancers, each with many variants. Some are aggressive, some docile; some are easily treated, others are almost always fatal. Diagnosing, treating, and tracking the progress of therapy for each type of cancer has long been a dream among oncologists, and one that has grown closer thanks to parallel revolutions in genomics, proteomics, and cell biology. Now a new revolution in nanotechnology is pushing personalized cancer treatment closer than ever before.

Nanotechnology's ability to shape matter on the scale of molecules is opening the door to a new generation of diagnostics, imaging agents, and drugs for detecting and treating cancer at its earliest stages. But perhaps more important, it is enabling researchers to combine advances, creating nanosized particles that contain drugs designed to kill tumors, targeting compounds designed to home in on malignancies, and imaging agents designed to light up even the earliest stage cancers. "The future of oncology—and the opportunity to eliminate the suffering and death due to cancer—will hinge on our ability to confront cancer at its molecular level," says Andrew von Eschenbach, former director of the U.S. National Cancer Institute (NCI) in Bethesda, Maryland. Unlike previous "revolutions" in the "war" on cancer that raised hopes, nanotechnology "is not just one more tool, it's an entire field and will pervade everything in medicine," says Mauro Ferrari, a cancer nanotechnology expert at Ohio State University in Columbus.

These promises have already set off a burgeoning effort to marry nanotechnology with oncology. Most notably, in 2004, NCI launched a $144 million cancer nanotechnology initiative. As the foundation of this effort, last month NCI announced $26.3 million for the first year of funding for seven centers of cancer nanotechnology excellence designed to foster interdisciplinary work among chemists, materials scientists, and biologists. Europe and Japan are also investing heavily in nano approaches to fighting cancer, although nanotechnology funding agencies there don't break out specific programs for cancer. "It's fair to say [Europe and Japan] are putting in complementary amounts of money to the U.S. NCI," says Ruth Duncan, a nanomedicine expert at the Welsh School of Pharmacy in Cardiff, Wales. Companies are also getting in on the act: More than a half-dozen nanoparticle-based imaging agents and therapeutics are either on the market, in clinical trials, or awaiting clinical trials (see table, p. 1134).

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"The science in this area is exploding," says Gregory Downing, who heads NCI's Office of Technology and Industrial Relations. "The cancer community really gets this now." Thomas Kipps, a cancer biologist at the University of California, San Diego, agrees. "I think there is tremendous potential here," he says. "I hope it doesn't just turn out to be hype. But I don't think it will."

A softer touch

Cancer treatment has had more than its share of hype over the years. Yet despite progress in understanding cancer, its diagnosis and treatment have remained essentially unchanged for decades, and death rates from the disease are about what they were in 1950. "If you look at the everyday treatment of cancer, it's just like it was 30 years ago with just a couple of exceptions," says Michael Phelps, a cancer imaging expert at the University of California, Los Angeles. Chemotherapy, radiation, and surgery—the big three of treatments—all wreak havoc on healthy cells and tissues as well as cancerous ones. And the only way to tell whether they have worked is to wait to see whether the cancer reappears.

Nanotechnologists hope to break the log-jam by giving oncologists new tools for tracking and targeting cell surface receptors and other molecules specific to cancer cells. This push toward personalized medicine has been under way for years. For example, the cancer drug Herceptin, which homes in on a receptor called Her-2 that is overexpressed in certain cancer cells, is given only to patients whose diagnostic tests show they carry Her-2 positive cells. Nanotechnologists hope to extend that approach to numerous diagnostics, imaging agents, and medicines. "Cancer can benefit from nanotechnology in essentially every sector of the cancer enterprise," Ferrari says.

Raising red flags

Advances in diagnostics are already well under way in laboratories around the globe. In the October issue of *Nature Biotechnology*, for example, researchers led by Charles Lieber of Harvard University described using arrays of silicon-based nanowire devices (see figure, above) to electrically detect minute levels of marker proteins overexpressed in cancer cells present in blood serum. The sensors were nanowire-based field effect transistors (FETs) akin to those in computer chips. In FETs, a voltage applied to a tiny "gate" electrode controls the flow of charges between two other electrodes. Lieber and

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<<Sensitive. Nanowire devices can detect cancer proteins at femtomolar concentrations.

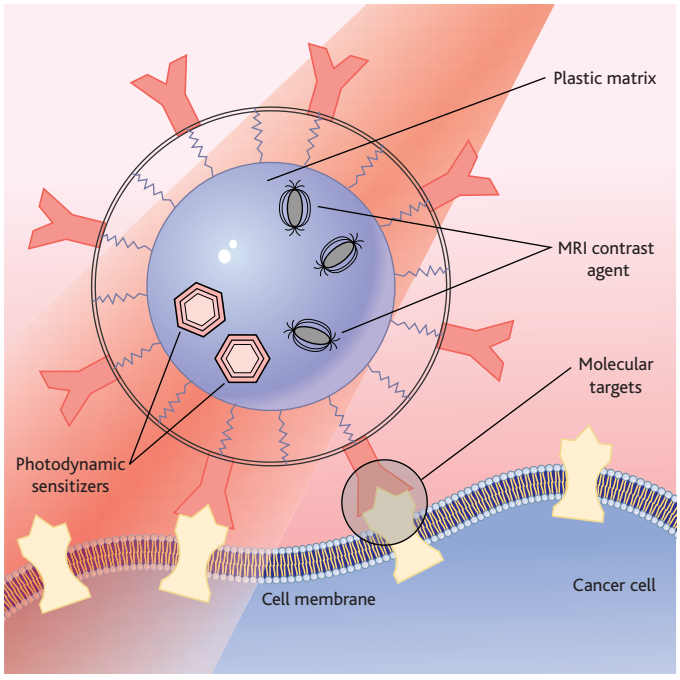
colleagues dotted charge-carrying silicon nanowires with monoclonal antibodies specific for the cancer proteins. When the proteins linked up with the antibodies, the electrical charges of the proteins changed the conductance of the silicon nanowires. This change signaled the presence and concentration of cancer markers. Lieber's team made devices that detected five cancer protein markers: prostate-specific antigen, PSA-alpha 1-antichymotrypsin, carcinoembryonic antigen, mucin 1, and telomerase.

The devices detected mere femtomolar concentrations of the target proteins without the fluorescent labels or complicated DNA-amplification procedures most often used to detect minute concentrations of biological compounds. What's more, the novel arrays contained 200 transistors that could be addressed individually, potentially opening the door to detecting scores of cancers by testing a single drop of blood.

Several other research teams have made similar progress in electrically detecting cancer-specific markers using other types of nanodevices. Last year, for example, researchers led by Hua Chen of NASA Ames Research Center in Mountain View, California, reported creating nanoelectrode arrays capable of electrically detecting single mutations in the *BRCA1* gene, which has been shown to predispose patients to several cancers including breast and ovarian cancers. First, the researchers took strands of DNA complementary to *BRCA1* DNA and bound them to electrodes made from carbon nanotubes. Then they poured a solution containing *BRCA1* over the arrays, which latched on to the target. By oxidizing nucleotides on the target, the researchers changed the conductivity of the nanotubes, which gave off a signal that could be picked up electronically.

Even further along are efforts to use tiny gold nanoparticles to help detect protein and DNA signatures for a number of diseases, including cancer. Two years ago, for example, Chad Mirkin and colleagues at Northwestern University in Evanston, Illinois, reported in *Science* a new protein-detecting technique up to a million times more sensitive than ELISA assays, the current standard (*Science*, 26 September 2003, p. 1884). The researchers start with gold nanoparticles, attach antibodies that specifically bind to proteins of interest, and tag the particles with readily identifiable DNA strands. If the target protein is in a test sample, the protein binds to the antibody on the nanoparticle. Next, the researchers add another target-seeking antibody tethered to a magnetic bead. They use a magnet to pull the beads—and everything bound to them—away from the rest of the sample, then identify their target protein by sequencing the DNA strands.

Mirkin says that clinical trials of the technique are planned for next year and that a biotech company that he co-founded called Nanosphere in Northbrook, Illinois, plans to commercialize diagnostics based on it within 2 years.



Triple threat. Multifunctional nanoparticles can combine tumor-seeking sensors, imaging agents, and toxins that kill cancer cells.

ILLUSTRATION: C. BICKEL/*SCIENCE*

In sight

Researchers are also making quick progress in using nanotechnology to spot cancer in its earliest stages inside the body. Last year, for example, researchers led by oncologist John Frangioni of Beth Israel Deaconess Medical Center in Boston reported that they had used semiconductor particles called quantum dots to image cancer cells in the sentinel lymph nodes of animals as large as pigs. The sentinel lymph nodes are typically the first to show signs of metastatic cancer cells shed by nearby organs. Oncologists check them for cancer through surgical biopsy—a tricky procedure, as the sentinel nodes are small and hard to locate.

Frangioni's group teamed up with quantum-dot experts led by Moungi Bawendi of the Massachusetts Institute of Technology in Cambridge. Bawendi's team synthesized nanosized onionlike structures composed of an inner cadmium-tellurium core surrounded by a cadmium-selenium layer and then capped with an organic compound to make the particles water-soluble. The particles are strong absorbers and emitters of infrared light. When the researchers injected animals with tiny amounts of the quantum dots, lymphatic cells quickly cleared the dots and routed them to the lymph nodes. As the researchers reported in the January 2004 issue of *Nature Biotechnology*, they could light up the lymph nodes even through centimeters of skin simply by shining near-infrared light from a halogen lamp. If the approach works in humans, it could guide surgeons to the lymph nodes of biopsy patients.

The notion of using cadmium-based quantum dots in humans has long come under fire, because the heavy metal is toxic. As an alternative, in the 3 August issue of the *Journal of the American Chemical Society*, the researchers reported creating indium-based semiconducting dots that also worked for mapping sentinel lymph nodes. These dots contained arsenic, another toxin, but the authors say the dose required to light up lymph nodes may be small enough to keep the toxicity low.

Infrared light–emitting nanoparticles are likely to prove most useful in spotting tumors near the skin surface. For tissues deep within the body, many groups are turning to magnetic nanoparticles that can be used as contrast agents for magnetic resonance imaging (MRI) machines. In May, for example, Carola Leuschner, a biochemist at the Pennington Biomedical Research Center in Baton Rouge, Louisiana, told attendees of the Nano Science and Technology Institute (NSTI) meeting in Anaheim, California, that her group has developed iron oxide nanoparticles capable of revealing the presence of breast cancer cells in mice. Leuschner's team targeted their iron oxide particles to tumor cells by covalently linking them to copies of a short peptide called LHRH, which seeks out and binds to receptors overexpressed on a wide variety of tumor cells. In mice inoculated with human breast cancer cells that caused them to develop tumors, the researchers imaged tumors just half a millimeter wide—far smaller than can be seen by conventional mammography and ultrasound techniques. "The potential for nanoparticles to improve tumor imaging is really very great," says Leuschner.

Search and destroy

Of course, finding cancer cells is only the first step. Nanotechnologists are developing a

number of particles designed to wipe out tumors as well. Many use targeting agents such as LHRH to direct toxic compounds to tumor cells. For example, Vladimir Torchilin and colleagues at Northeastern University in Boston are linking chemotherapeutic-containing nanoparticles to an antibody called 2C5, which homes in on the surface of human cancer cells. They have shown that the approach slows the growth of a variety of tumors, in part because the nanoparticles can ferry large amounts of the chemotherapeutic drugs to the tumor.

Moving to Market

Product	Type of nanomaterial	Indication	Phase	Company
VivaGel	Dendrimer	Topical microbicide for HIV	Phase I	StarPharma
MRX-952	Branching block copolymer self-assembled nanoparticulate formulation of irinotecan metabolite	Oncology	Preclinical	ImaRx Therapeutics
Abraxane	Nanoparticle albumin	Non–small cell lung cancer, breast cancer, others	NDA filed	American Pharmaceutical Partners
Cyclosert-camptothecin	Cyclodextrin nanoparticle	Metastatic solid tumors	IND filed	Insert Therapeutics
TNT AntiEpCAM	Polymer-coated iron oxide	Solid tumors	Preclinical	Triton BioSystems
Verigene platform	DNA-functionalized gold nanoparticles	Diagnostics	On market	Nanosphere
INGN-401	Liposome	Metastatic lung cancer	Phase I	Introgen
Combidex	Iron oxide nanoparticle	Tumor imaging	NDA filed	Advanced Magnetics

In the pipeline. Several nanotech cancer treatments are being tested or have been approved.

Other nanoparticle drugs take a less direct targeting approach. Because tumors grow so quickly, the blood vessels that form around them tend to be porous, leaking out small molecules around the tumor. Several groups hope the leakage will help them bombard tumors with tiny packages of toxins. Northeastern University pharmaceutical scientist Mansoor Amiji, for example, reported at the NSTI meeting that his team has loaded the anticancer compound paclitaxel (known more commonly by its trade name, Taxol) into tiny hollow polymer nanospheres, which release their cargo when exposed to the relatively low pH of tumor cells. Because the plastic spheres shield healthy cells from the drugs, the researchers can deliver higher concentrations of the drugs. In ongoing studies, Amiji reported, animals receiving the nanoparticle-based delivery systems have all survived longer than controls that received the drugs by themselves.

At the same meeting, Giulio Paciotti of CytImmune, a biotech company in Rockville, Maryland, reported a similarly effective strategy for delivering the highly toxic chemotherapeutic agent tumor necrosis factor to tumors by linking it to nanosized gold particles, which are good at escaping through leaky blood vessels. Because more of the drug accumulates in the target tissue, "it allows you to lower the dose and increase the safety," says Paciotti. "Nanoparticle drugs may block collateral damage so often due to chemotherapy," Downing says.

Jennifer West and Naomi Halas of Rice University in Houston, Texas, have pioneered another damage-control strategy in which they target tumors with gold-coated nanoparticles, which then become tiny heaters that cook tumor cells to death. To turn on the heat, the Rice researchers hit the nanoparticles inside tumors with infrared light. The light passes harmlessly through normal tissue, but the nanoparticles readily absorb it and warm up to more than 40°C. In the 11 November 2003 issue of the *Proceedings of the National Academy of Sciences*, the Rice researchers reported that their nanoscale heaters wiped out tumors in both cell culture and animal studies. Since then, other groups have reported similar success in heating tumors with carbon nanotubes and magnetic nanoparticles.

Such treatments, Ferrari notes, have a great potential to improve the safety of cancer treatment, because they kill cells only when they are activated by an external source.

Putting the pieces together

Nanotechnology's greatest advantage over conventional therapies may be the ability to combine more than one function. "Even though we think of nanoparticles as small, they are large compared to molecules. So you can decorate them with all kinds of bells and whistles to carry out multiple functions," Mirkin says. Chemist Raoul Kopelman of the University of Michigan, Ann Arbor, and colleagues, for example, have recently created three-component nanoparticles that target, image, and destroy tumors in the brains of rats. The particles consist of an iron oxide core that serves as an MRI contrast agent. Attached to them are copies of a cancer-targeting peptide called F3, as well as a light-absorbing compound called photofrin that kills cells when hit with red light. When Kopelman's team used their combination particles to treat rats previously injected with cancer cells inside their brains, animals receiving the combination nanoparticles survived more than twice as long as control animals receiving the nontargeted photofrin compound.

Another Michigan team, led by pathologist James Baker, achieved equally enticing results by targeting tumbleweedlike organic molecules called dendrimers designed to ferry large concentrations of traditional chemotherapeutic drugs and imaging agents inside cancer cells. Ferrari predicts that countless examples will come: "There are several thousand particle types and many vector types. What we are seeing is the tip of the iceberg."

Despite such progress, nanotechnology products face unique hurdles in making it to the clinic. Researchers must find ways to prevent immune cells from clearing nanoparticles before they reach their targets and must also overcome tumors' acquired ability to spit out cancer drugs that get inside cells. Even more challenging may be designing clinical trials for particles that perform more than one function. Trials for imaging agents are typically very different from those for drugs. "Do you have to design separate trials?" asks Downing. "We've been struggling with this."

A more general concern, Downing says, is the pharmaceutical industry's preference for blockbuster drugs with massive sales. "Cancer as a whole presents a challenge to the blockbuster drug model. It represents a fragmented market," Downing says. That prospect, he says, has slowed major pharmaceutical companies from jumping into nanotechnology research.

Finally, the toxicity of nanoparticles remains unclear. As a result, environmental health and safety agencies around the world continue to grapple with how best to regulate these novel materials (*Science*, 18 June 2004, p. 1732). "Those are very, very important concerns," Ferrari says. But over time, he says, patients will likely clamor for the novel therapies: "It is going to be very, very hard to come up with a nanoparticle drug that will be more toxic than the drugs out there today." If true, nano-based drugs will at least be less harmful than today's cancer fighters. But if they work as intended, they should also prove far more effective.

–ROBERT F. SERVICE

SOURCE: M. FERRARI AND G. DOWNING, *BIODRUGS* 19, 203 (2005)