Woodrow Wilson International Center for Scholars

The Project on Emerging Nanotechnologies

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NANOFRONTIERS

On the Horizons of Medicine and Healthcare

The **NanoFrontiers newsletter** reports on achievements toward realizing the immense potential of nanotechnology. It continues and updates the discussion begun at the February 2006 NanoFrontiers workshop, co-sponsored by the Project on Emerging Nanotechnologies, National Institutes of Health, and National Science Foundation. Issues will provide samplings of recent developments in selected areas—accomplishments that hint at new nanotechnology-enabled tools, products, and applications that can be used for the good of humankind and the planet. This inaugural issue focuses on *nanomedicine*, highlighting a few nanotechnology developments on the path toward improvements in human health and healthcare. Cancer-focused efforts illustrate the progress and the promise.

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NANOFRONTIERS

On the Horizons *of* Medicine and Healthcare

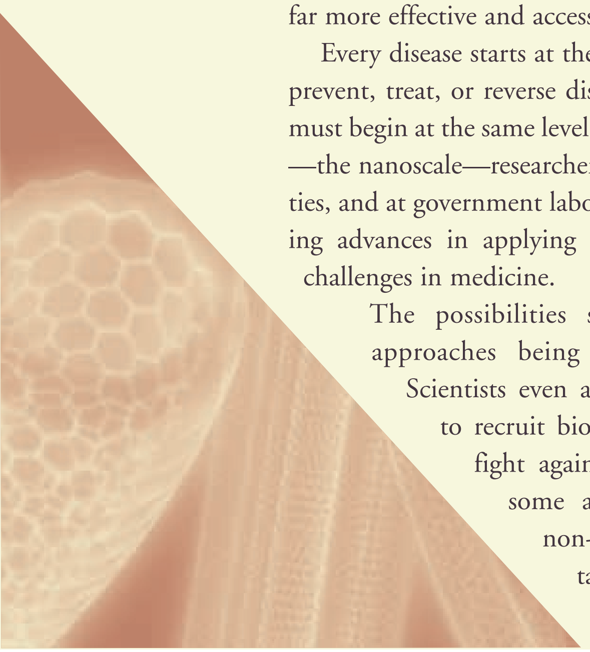
IMAGINE a barrage of tennis balls knocking the Moon out of orbit. Far-fetched, to be sure. Yet, on the scale of things, this extraordinary feat would be on a par with the collective blow struck by cold viruses when they invade your body and proceed to knock you off your feet for a spell. Compared to the average human, a virus—measuring between 50 and 100 nanometers—is roughly same relative size as a tennis ball is to the Moon.

1. Michael Holman, "Nanomaterial Forecast: Volumes and Applications." Presented at the ICON Nanomaterial Environmental Health and Safety Research Needs Assessment, Jan. 9, 2007. Lux Research.

2. Freedonia Group, *Nanotechnology in Health Care*, Feb. 2007.

Tiny as they are, viruses are formidable foes, capable of penetrating cell membranes and commandeering cellular machinery. International efforts to prevent the threat of a global bird flu pandemic attest to the fearsome destructive power of some viruses. They also suggest the incredible potential of nanotechnology—the science and technology of the incredibly small—in helping not only to thwart viruses and other infectious diseases, but also to turn the odds against cancer, to repair wounds, to restore function to damaged nerves and tissues, and, ultimately, to make healthcare far more effective and accessible, world over.

Every disease starts at the molecular level. Steps to prevent, treat, or reverse disease processes or injuries must begin at the same level. Working at nature's scale—the nanoscale—researchers in industry, at universities, and at government laboratories are making exciting advances in applying nanotechnology to meet challenges in medicine.

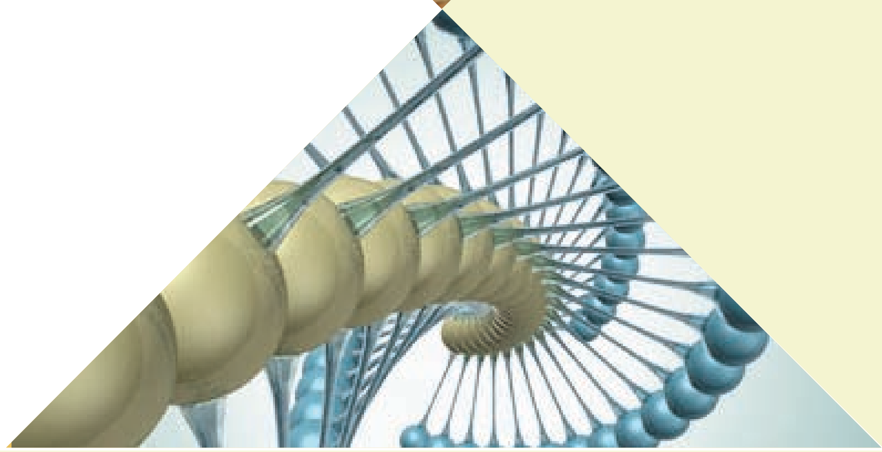


The possibilities seem endless, and the approaches being pursued can surprise. Scientists even are using nanotechnology to recruit biological adversaries in the fight against disease. For example, some are crafting viruses into non-infectious molecular containers that might be used to deliver drugs to sites inside cells. And silicon technology, the enabler of ever smaller, faster, cheaper, and more powerful integrated circuits, has been drafted as well. Silicon chips traversed by nanoscale channels and dotted with nano-sized gates, pores, and pumps are being developed for genetic and protein analyses, controlled-release drug delivery, cell transplants, and to speed the pace of drug discovery.

WHERE WE'RE AT, WHERE WE'RE HEADED

The first wave of nanotechnology products in medicine is already under way. The pharmaceutical industry, for example, sells over $1 billion worth of drugs coated with nanoparticles or encapsulated in specialized nanoscale packaging.[1] Future generations of nanotechnology applications are expected to be far more advanced and much more capable, leading to what many predict will be a revolution in personalized medicine. According to one forecast, the U.S. market for nanotechnology medical products will increase to $53 billion by 2011 and will double over the five years that follow.[2]

Looking further out, some forecasts anticipate that progress in medicine and nanotechnology will lead, for example, to internal nano-sensor networks that will monitor the total health of individuals and provide aggregated intelligence to health care providers.



"We come together at a time of the most radical transformation to ever occur in the history of medicine—the beginning of the era of molecular medicine. We now have the opportunity to completely shift the paradigm of health, the opportunity to move beyond inadequate treatment of disease to prevention and eradication."

—Andrew C. von Eschenbach, Commissioner of the U.S. Food and Drug Administration[3]

The biosensors would be small enough so that they might be inhaled, infused through the skin, or ingested. Initially, biosensor networks might be used in the care of patients with AIDS or in the advanced stages of cancer. Ultimately, this technology, used in combination with others on the horizon, could help to promote preventive approaches, constrain medical costs, increase access to care, and enable greater independence for the elderly and people with disabilities or chronic disease.[3]

SOME POTENTIAL ADVANTAGES AT THE NANOSCALE

Nano-Enhanced Drugs:		
Targeted delivery	→	Customized to patient; fewer side effects; engineered to slip through blood-brain barrier, mucus, or other obstacles
More therapeutic options	→	Expanded options for administration, such as nasal, dermal, oral, ocular
Combined detection & treatment	→	Seek-and-destroy therapy, followed by inside-the-body monitoring of patient response
Nano-Imaging and Diagnostics:		
Greater specificity	→	See and analyze at the level of individual cells
Earlier detection	→	Increases odds for effective treatment - before tumors metastasize
Less invasive	→	But yielding more definitive results
Faster, Simpler	→	More options for rapid, point-of-care diagnostics
Nano-Enabled Regenerative Medicine:		
Greater biocompatibility	→	Materials based on natural systems reduce risk of rejection

3. "The Challenges of Regulation in the World of Molecular Medicine." Prepared remarks, Inaugural International Summit, Nov. 16 , 2006

4. Nanda Ramanujam, *Commercialization of Implantable Biosensors Technology in Healthcare: Strategic Planning Using Scenario Analysis*, Aug. 25, 2006. The Wharton School, University of Pennsylvania.

CANCER'S TOLL

- Worldwide, **7.6 million people** people died of cancer in 2005, accounting for 13% of all deaths.
- **Over 70%** of cancer deaths occur in low- and middle-income countries.
- In the U.S., cancer accounts for **23.1% of yearly deaths**—the second largest cause of death and the number one killer of Americans under 85.
- In 2004, U.S. costs associated with cancer totaled **$192 billion**.
- The lifetime probability of developing any sort of cancer is **1 in 2 in men and 1 in 3 in women**.
- Breast cancer was the cause of death for **15% of cancer patients**.

"Today, medicine is one size fits all. Diseases and patients are heterogeneous and, therefore, treatments need to be individualized. Personalized medicine means the right medicine for the right person at the right time."
—Christine Cote, Vice President for Emerging Technologies and New Ventures, Johnson & Johnson[11]

TARGETING CANCER

Sequencing of the human genome, completed in 2003, was a tremendous scientific accomplishment. Yet, the race to decode the genome, as one healthcare industry executive has put it, "was merely the race to the starting line."[5] In effect, it was a qualifying heat for a higher-stakes race to develop powerful new tests and therapies, based on human DNA sequences.

Fortunately, the strengthening connection between molecular biology and nanotechnology—sometimes referred to as nanobiotechnology—has the potential to deliver highly effective treatments for cancer, heart disease, infectious diseases, and other devastating illnesses. These treatments will be tailored to individuals, thanks, in large part, to rapid, inexpensive DNA-sequencing tools. Advances in nanotechnology, motivated by the quest for the "$1,000 Genome," a research program supported by the National Human Genome Research Institute, are moving us closer to the capability to identify and address all of the many factors involved in the onset and progression of disease.

After considering limitations of today's pharmaceutical treatments, motivations to pursue this nanotechnology-enabled approach become clear. For example, adverse drug reactions are responsible for more than 100,000 deaths, placing it among the top 10 killers in the United States. Traditional cancer drugs are not effective in 20 to 40 percent of patients. Of those cancer patients who do benefit, many—about 40 percent of human tumors[6]—eventually develop resistance to once-effective drug treatments. Damage to the liver and other organs and tissues outside the diseased area is a common side effect of cancer therapy. Early detection—before a tumor has 1,000 cells—improves prospects for effective treatment of cancer patients, but today's standard techniques, such as mammography, require more than a million cells for accurate diagnosis.[7]

TAKING AIM

A handful of nanotechnology-enabled drugs and diagnostic tools, such as biomarkers that "flag" genetic and cellular abnormalities or nanoparticles that enhance images captured with X-rays, ultrasounds, MRIs, and other equipment, already are on the market. Early applications provide a hint of the possibilities yet to be realized.

A growing array of nanoparticles—from dendrimer "starbursts" to nanocrystals—and nanoscale packaging—such as nanoshells, nanotubes, and membrane-bound spheres called liposomes—provide numerous possibilities for delivering drug treatments at the disease site. Nano-enabled drugs already in use include Doxil, a liposome-borne treatment for metatastic ovarian cancer, and Abraxane, a nanoparticle-bound formulation of taxol, which eliminated the need for a toxic solvent in a treatment for advanced breast cancer.

Herceptin, a nanotechnology-enabled treatment for breast cancer, illustrates the advantages of personalized therapy—therapy tailored to the individual patient, which eliminates repeated rounds of trial-and-error testing. The drug can significantly benefit the 25 to 30 percent of breast cancer patients with a gene that codes for a particular protein. This protein makes these women vulnerable to a more aggressive form of cancer, and they are more likely to suffer a recurrence of disease. Thanks to a diagnostic test, these patients can now be identified as candidates for treatment with Herceptin. The drug bonds to receptors on the membranes of tumor cells and neutralizes the cancer-promoting protein.[8]

In March 2007, the Food and Drug Administration approved Tykerb, a new targeted therapy for the same group of patients in the advanced stages of breast cancer. Orally administered at home, the drug can infiltrate the membranes of cancer cells and deliver a double whammy—interfering with internal communication signals traced to two genes that play a role in cancer progression. Research also indicates that Tykerb is small enough to enter the brain, resulting in fewer and smaller brain metastases.[9]

NEXT-GENERATION TOOLS

Early-stage applications of targeted treatments have added, on average, months to the lives of patients in advanced stages of cancer. The benefits attest to the merits of the approach, but they also suggest that there is much more to be gained. Fortunately, the ongoing convergence of nanotechnology and biotechnology greatly increases options and opportunities for combating cancer.

Consider that many existing drug formulations are greatly diluted by the time they reach the site of disease in the body. For example, drugs incorporating monoclonal antibodies—identical disease-fighting proteins that may have the potential to be magic bullets in the fight against cancer and other diseases—can shed more than 99.99 percent of their therapeutic contents while in transit.[10]

The ability to make specially designed nanoparticles and other nanosized carriers creates opportunities to improve this therapeutic delivery record and improve the overall specificity and effectiveness of treatment and diagnostic tools. One reviewer estimates that several thousand different types of nanocarriers have been reported in the scientific literature, a strong indication of future innovation.

For example, long nanocylinders modeled after the string-like shape of viruses have proved to be

5. Tony L. White, Prepared text for keynote address at "Personalized Medicine: A World of Opportunities," November 28–29, 2006.

6. Christopher F. Huggins, "Multiple molecular mechanisms for multidrug resistance transporters," *Nature*, April 12, 2007.

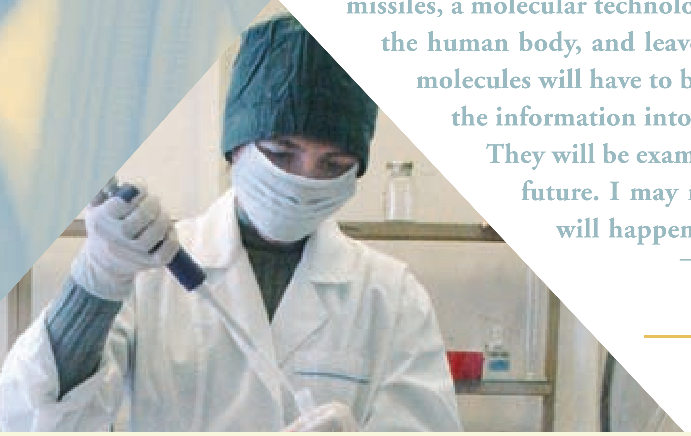
7. 2006 NSTI Nanotechnology Conference and Trade Show-Nanotech 2006, "Technology for Medical Diagnostics and Treatment Workshop."

8. PriceWaterhouseCoopers Global Technology Center, *Personalized Medicine: The Emerging Pharmacogenomics Revolution*, Feb. 2005.

9. Bernadine Healy, "Closing in on a Cure," *U.S. News & World Report*, Oct. 15, 2006.

10. See, for example, Mauro Ferrari, "Cancer Nanotechnology: Opportunities and Challenges," *Nature Reviews, Cancer*, March 2005.

11. *Knowledge @ Wharton*, "Personalized Medicine and Nanotechnology: Trying to Bring Dreams to Market," March 7, 2006.



"Twenty years ago, without even this crude chemotherapy I would already be dead. But 20 years from now, I am confident we will no longer have to use this blunt tool. By then nanotechnology will have given us specially engineered drugs which are nanoscale cancer-seeking missiles, a molecular technology that specifically targets just the mutant cancer cells in the human body, and leaves everything else blissfully alone. To do this these drug molecules will have to be big enough—thousands of atoms—so that we can code the information into them of where they should go and what they should kill. They will be examples of an exquisite, human-made nanotechnology of the future. I may not live to see it. But, with your help, I am confident it will happen."

—Congressional testimony of Nobel Prize-winning chemist Richard Smalley, who died of non-Hodgkin's lymphoma on October 28, 2005.[13]

12. Yan Geng, Paul Dalhaimer, Shenshen Cai, et al. "Shape effects of filaments versus spherical particles in flow and drug delivery," Nature Nanotechnology, April 2007.

13.Testimony prepared for U.S. House of Representatives hearing on creating a National Nanotechnology Initiative, June 22, 1999.

long-lived drug carriers in studies done in mice implanted with human lung tumor tissue. Measuring as small as 20 nanometers in diameter and as long as the size of a red blood cell (8 micrometers), cylinder-shaped polymers were stocked with the anticancer drug paclitaxel. They remained in circulation for one week after injection, compared with a few hours for spherical nanocarriers. The nanocylinders delivered a more effective dose, killing more cancer cells and shrinking the tumors to a much greater extent. This discovery also may point the way to improvements in treatments of other illnesses, such as cardiovascular disease and other types of cancer.[12]

Nanotechnology will be instrumental in the multicomponent systems that many experts believe will define the future of cancer treatment. "Nanotech is the notion of incorporating more tasks into something the size of a molecule or small sub-cellular organism," explained Mauro Ferrari, head of the Alliance for NanoHealth, a collaboration of seven Houston area research institutions.

The National Cancer Institute (NCI) is supporting efforts to assemble a "toolbox" of methods to translate the discovery of protein biomarkers to novel therapeutics and diagnostics. Built mostly with nanoscale components, these hybrid tools will consist of:

- Carrier/delivery system,
- Targeting agent,
- Therapeutic agent, and
- Imaging agent for detecting disease and then monitoring response to therapy.

With all of four elements in hand, physicians will be able not only to deliver therapeutic drugs at the right place, but also at the right time and in the right amount, with no collateral damage.

In animal and cell culture studies, various research teams have used all or combinations of these components to steer and deliver their "Trojan horse" payloads to tumor cells associated with cancers of the brain, prostate, colon, liver, skin, and other tissues and organs. In addition to biological and chemical agents, exploding bubbles, magnetically guided and activated capsules, and laser-triggered nanoparticle heaters are among the prospective agents that nanomedicine researchers are evaluating for their effectiveness in destroying cancer cells, while sparing neighboring tissue.

TOWARD PREVENTION

Of course, the ultimate aim of cancer researchers and their nanotechnology partners is to prevent the more than 100 forms of the disease or, at least, to attack in the very early stages, when chances of treatment success are best. This will require nanotechnology-enabled advances in cancer imaging capabilities and in biomarkers. These indicators have a variety of uses, from indicating cancer risks and detecting early signals of the disease to revealing variations in genes that affect how drugs are broken down and used in the body.

Considerable work remains to be done. An NCI official estimates that there may be up to a million proteins that play a role in cancer. To date, a total of about 1,200 of these potential biomarkers have been identified in research and, of these, 12 have been approved for clinical use.[14]

NCI and its partners have launched an effort to accelerate the process of discovering, developing, and approving cancer biomarkers for use in patient care. The vision is to use nanotechnology to build the equivalent of tiny platforms filled with selected assortments of biomarkers. These tools will perform the health-related surveillance needed to subvert the onset of cancer.

"Biomarkers are going to be used for all kinds of things in the future," Dr. Anna Barker, NCI's deputy director, explained recently. "They're going to be used to detect diseases early, they're going to be used hopefully, to even detect diseases early enough to prevent the disease. They're going to be used to inform drug discovery, so you can actually develop therapies targeted to these biomarkers."

The quest to prevent cancer is poised to make steady gains over the coming years and decades. It will take on even greater urgency. The International Agency for Research on Cancer predicts that the number of people living with cancer, worldwide, will increase from 25 million in 2000 to 75 million in 2030. Much of this increase is expected to occur in poorer countries, according to the agency.[15]

ADDITIONAL RESOURCES

Project on Emerging Nanotechnologies, Nanotechnology and Medicine (includes a list of current nanotechnology-enabled medical applications): **www.nanotech project.org/86**

Project on Emerging Nanotechnologies, Using Nanotechnology to Improve Health in Developing Countries (webcast of an event held on Feb. 27, 2007): **www.nanotech project.org/106**

Project on Emerging Nanotechnologies, *Trips to the NanoFrontier*, podcast series, **www.nano techproject.org/114**

National Cancer Institute (NCI) Alliance for Nanotechnology in Cancer, an initiative to harness the potential of nanotechnology in detecting, treating, and preventing cancer: **http://nano.cancer.gov/**

Personalized Medicine Coalition, non-governmental, non-profit group, dedicated to advancing the understanding and adoption of personalized medicine concepts and products: **http://www.personalizedmedicine coalition.org/**

14. The Online News Hour, "Extended Interview: Dr. Anna Barker Discusses Cancer Biomarker Research," aired on March 28, 2007.

15. Carley Petesch, "Agency: Cancer Cases to Double by 2030," Associate Press (April 4, 2007, Forbes.Com.).

THE PROJECT ON EMERGING NANOTECHNOLOGIES was launched in 2005 by the Wilson Center and The Pew Charitable Trusts. It is dedicated to helping business, governments, and the public anticipate and manage the possible human and environmental implications of nanotechnology.

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