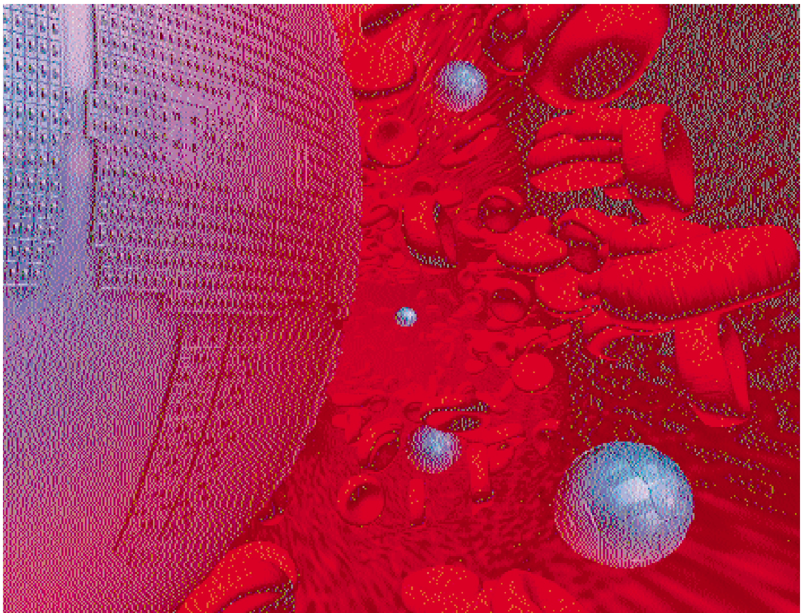
by Ineke Malsch

Biomedical Applications of Nanotechnology

Private and public research efforts worldwide are developing nanoproducts aimed at improving health care and advancing medical research. Some of these products have entered the marketplace, more are on the verge of doing so, and others remain more a vision that a reality. The potential for these innovations is enormous, but questions remain about their long-term safety and the risk–benefit characteristics of their usage.

Since 2000, when former President Bill Clinton announced the founding of the U.S. National Nanotechnology Initiative (NNI), governments in Europe, Japan, and other Asian nations have responded with competitive investments in national nanoprograms. The European Commission, a body of the European Union (EU) that funds about 24% of the publicly financed research in the EU, and the Union's 15 member nations will spend about $180 million (200 million euros) on nanotechnology in 2002. The NNI budget for fiscal year (FY) 2002 is $604 million, including $40.8 million for the National Institutes of Health (NIH). For FY 2003, proposed budgets amount to $710.2 million in the United States and between $270 and $315 million in the EU.

Definitions of nanotechnology are as diverse as the applications that are available. Rolf Allenspach, who leads research on the physics of nanoscale systems at the IBM Zurich Research Laboratory in Switzerland, defines nanotechnology as "the ability to design and control the structure of an object at all length scales from the atom up to macro scale." George Robillard, director of the Biological Materials and Devices (BIOMADE) research center at the University of Groningen in The Netherlands, has a more focused definition: "The core of nanotechnology consists of systems in the size range of nanometers," he says. "You could say a drug-delivery system is nanotechnology. We are concerned with the organization of molecules in larger functional complexes, for example a complex that can deliver a protein to a certain site in the body."



Artist's impression by www.e-spaces.com; concept by Robert A.Freitas Jr.

Figure 1. The artificial red blood cell, or "respirocyte," proposed here, is a blood-borne, spherical, 1-µm-diam pressure vessel with active pumping; an onboard, remotely reprogrammable nanocomputer; and chemical and pressure sensors.

Biomedical nanotechnology

Three applications of nanotechnology are particularly suited to biomedicine: diagnostic techniques, drugs, and prostheses and implants. Interest is booming in biomedical applications for use outside the body, such as diagnostic sensors and "lab-on-a-chip" techniques, which are suitable for analyzing blood and other samples, and for inclusion in analytical instruments for R&D on new drugs. For inside the body, many companies are developing nanotechnology applications for anticancer drugs, implanted insulin pumps, and gene therapy. Other researchers are working on prostheses and implants that include nanostructured materials.

The U.S. government's research agenda for nanomedical applications was defined in June 2000 at a conference organized by NIH's Bioengineering Consortium, at which about 600 scientists, physicians, and engineers identified eight topics for research in the coming years:

- Synthesis and use of nanostructures.
- Applications of nanotechnology in therapy.
- Biomimetic nanostructures, which are synthetic products developed from an understanding of biological systems.
- Biological nanostructures.
- The electronic–biological interface.
- Devices for early detection of disease.
- Instruments for studying individual molecules.
- Nanotechnology for tissue engineering.

In Europe, public research funding and networking for nanotechnology in industry tend to be more focused on applications with a time-to-market of 5 to 10 years. The international Network for Biomedical Applications of Micro & Nano Technologies (NANOMED), based in Newcastle upon Tyne (U.K.), has brought together 50 industrial and academic partners to develop biomedical applications of nanotechnology. In Germany, the Nanochem network, based at the University of Kaiserslautern, is organized in a similar public–private fashion and includes medical applications of nanotechnology. Germany has had by far the highest budget for nanotechnology research in Europe for several years; in

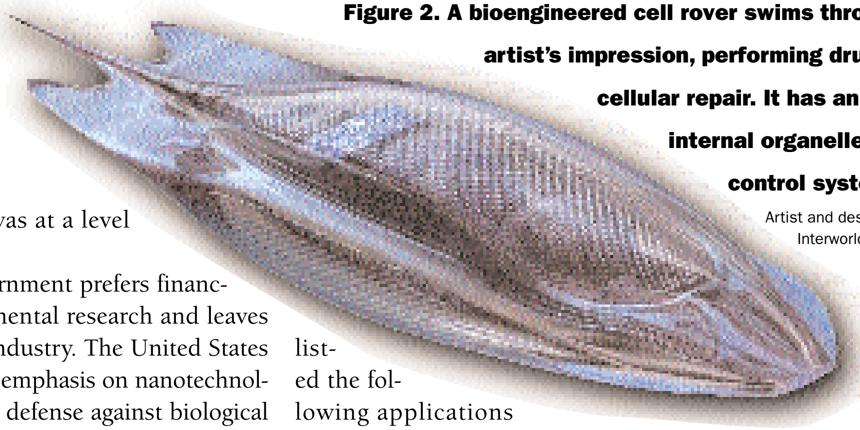


Figure 2. A bioengineered cell rover swims through the human body in this artist's impression, performing drug delivery, waste removal, and cellular repair. It has an internal frame, skin panels, internal organelles, a propulsion scheme, and a control system.

Artist and designer: Forrest Bishop, Interworld Productions

2000, funding was at a level of $56.7 million.

The U.S. government prefers financing more fundamental research and leaves applications to industry. The United States also has a strong emphasis on nanotechnology solutions for defense against biological and chemical warfare and terrorism. Since the attacks of last September 11, this effort has received even greater attention, with a new R&D focus on using nanotechnology for chemical/biological/radioactive/explosive detection and protection. Other areas of investigation include single-molecule detection and manipulation. NIH and the National Cancer Institute support the development of biomolecular sensors that can be implanted in the body to monitor and manipulate molecular processes.

Diagnostics

The Defense Advanced Research Projects Agency (DARPA) sponsors a project in which BIOMADE participates. "This project is about a biosensor to identify bacteriological infections in biowarfare," Robillard explains. "The American army wants to integrate a wearable biosensor in clothing. A soldier should be able to see within 20 minutes if he has been in contact with anthrax." (See *The Industrial Physicist*, February 2001, pp. 26–29.) The sensor can also identify other bacteria. "Our technology is general, not specified for any one disease-causing agent," Robillard says. "The principle is precise current measurement on a robust substrate. We are working on ion channels [which serve as entranceways into cells]. We collaborate with three universities in the United States: the University of Illinois at Urbana–Champaign, Rush Medical College in Chicago, and the University of Arkansas. What DARPA funds is fundamental research. We hope to have proof of principle in three years."

Other sensors for biomedical applications are closer to the market, according to a recent U.K. Foresight study that discussed the development and market entrance of applications including nanotechnologies. It listed the following applications as being close to or on the market:

- Sensors for medical and environmental monitoring and for preparing pure chemicals and pharmaceuticals.
- Light and strong materials for defense, aerospace, automotive, and medical applications.
- Lab-on-a-chip diagnostic techniques.
- Sunscreens with ultraviolet-light absorbing nanoparticles.

The report also said the following applications are expected in the next decade:

- Longer-lasting medical implants.
- The capability to map an individual's entire genetic code almost instantaneously.
- The ability to extend life by 50% from present expectations.

The Micro Electronics Material Engineering Sensors and Actuators (MESA+) research institute at the University of Twente (Enschede, The Netherlands) is engaged in high-throughput screening (HTS) research for Avantium in Amsterdam, an R&D company founded in 2000 by a consortium of chemical and pharmaceutical companies, venture capitalists, and three Dutch universities. Avantium aims to develop new strategies and equipment for screening active compounds for pharmaceuticals and other products. "We do the long-term research on the lab-on-a-chip systems," says Kees Eijkel, commercial manager of MESA+. "HTS is massive, fast, repetitive manufacturing or analyzing. If you want to do it fast, you need a small device. If you need to repeat a process step many times, you have to use laminar flows of liquids and plugs. This leads to lab-on-a-chip concepts. The scientific development in this field is magnificent."

In a lab-on-a-chip, minuscule amounts of liquids or gases are mixed in small channels, where they react. The reaction product is analyzed on the spot. One example is the field-effect flow-switching device (FLOWFET) invented by Albert van den Berg and his co-workers at MESA+. They control the electro-osmotic movement of small amounts of liquid in channels with a perpendicular electric field of 1.5×10^6 V/cm. The channels are 100 μm wide and 25 μm high. "A FLOWFET pumps liquid without fuss in controlled amounts," Eijkel explains. "That is an essential property in a network." There are more concepts for controlling the movement of a liquid through a small channel. Researchers are experimenting with principles such as peristaltic movement, electric fields, and the inclusion of inert magnetic particles in the liquid. The MESA+ researchers have a longer time horizon than the British participants in the Foresight study. Still, they don't engage in curiosity-driven fundamental research. "In the end, you will have to produce it commercially," Eijkel says.

Nanodrugs

Pharmaceutical companies do not expect nanostructured materials to become new drug compounds. However, carbon buckyballs and nanotubes might be useful as drug delivery vehicles because their nanometer size enables them to move easily inside the body. The active compound might be inserted in a nanotube or bonded to a particle's surface. Other types of nanopowders or biomolecules are also useful and are closer to the marketplace. In April 2002, American Pharmaceutical Partners (Los Angeles) presented results from an early human trial of ABI-007, a new nanoparticle delivery system for an established anticancer drug. ABI-007 is 130 nm long and consists of an engineered protein-stabilized nanoparticle that contains paclitaxel, which is used to treat breast, bladder, and more than a dozen other cancers. Such new delivery systems combine a drug with an artificial vector that can enter the body and move in it like a virus. If more advanced clinical tests are successful, ABI-007 is likely to enter the market in a few years.

Cosmetics based on quantum dots are already sold in large quantities. Nanophase Technologies Corp. (Romeoville, IL) produces nanocrystalline materials such as zinc oxide for use in sunscreens and other products. Richard Siegel started the company in 1989 as a spin-off from his research at Argonne National Laboratory. Nanophase's European competitors include Oxonica (Oxford, England), which started in August 1999 as a spin-off from the University of Oxford. “We make particles between 3 and 200 nm for different purposes,” says scientific director Peter Dobson. “We apply one type of particle in sunscreens. Our particles are protective and cause minimal damage to DNA in sunlight. That used to be a problem with earlier-generation sunscreens based on nanoparticles. We also manufacture quantum dots between 3 and 5 nm, suitable for binding specific biomolecules. The quantum dots are luminescent particles, more stable than the organic dies used today. And they are nontoxic.”

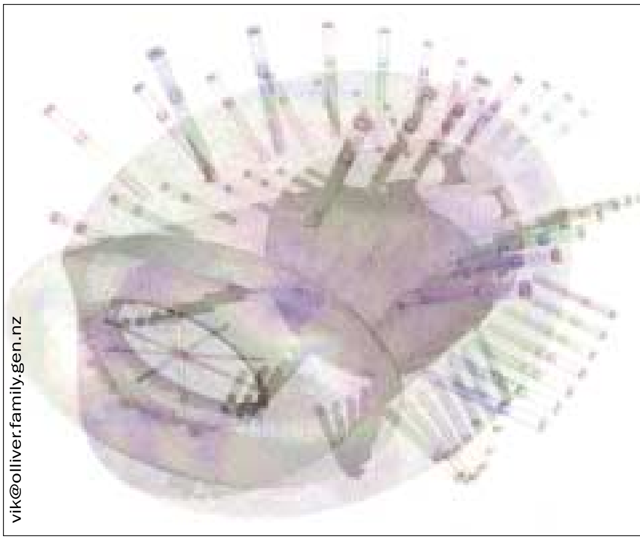


Figure 3. A nanorobotic device, called a microbivore, which eradicates blood-borne pathogens by digesting them in a similar manner to natural scavenger cells, as conceived by Robert A. Freitas Jr., in www.nanomedicine.com.

Prostheses and implants

Nanotechnology also has applications in tissue engineering. How can you help a person who needs new bones, teeth, or other tissues? In The Netherlands, dentistry professor John Jansen of the Catholic University of Nijmegen is developing new biomedical materials for such applications using tailor-made materials from MESA+: “We want to replace damaged or missing tissue by a similar equivalent material,” he says.

Jansen ranks biological and biomimetic nanostructures according to the time to market. He believes that techniques based on biological nanostructures are feasible. Researchers put a biological material in a mold—a straitjacket, as it were—which forces it to assume the shape of a body part, such as a hipbone. Biomimetic nanostructures start with a predefined nanochemical or physical structure. A nanochemical structure may be an array of large reactive molecules attached to a surface, while a nanophysical structure may be a small crystal. Researchers hope that by using these nanostructures as seed molecules or crystals, a material will keep growing by itself. Other groups want to apply nanostructured materials in artificial sensory organs such as an electronic eye, ear, or nerve. Both feats are far off.

Potential risks

Nanotechnology applications have not been marketed long enough for claims to be corroborated about risks to human health or the environment. Still, small nanoparticles can enter the human body through pores and may accumulate in cells. The health effects of such nanoparticles are unknown. Historical experience with unintended consequences of technologies, such as drug resistance to antibiotics or the persistence of chemicals such as DDT in the environment, teaches us to take precautions.

Debra Rolison of the Naval Research Laboratory (Washington, DC) points out that viruses are already nanobiotechnological objects and that humankind's history with viruses reinforces the need for continuous monitoring of the potential effects of newly designed and fabricated nanomaterials. A European Commission–National Science Foundation workshop held early this year discussed the societal aspects of nanotechnology. Participants concluded, “Nanobiotechnology could dramatically improve public health, but there is concern that technical developments could cause unforeseen adverse effects. Studies are needed to determine what environmental and health risks are associated with nanomaterials.”

Medical nanotechnologies are entering industrial production, mainly for diagnostics, drugs, and therapies. In the longer term, nanotechnology may help improve implants and even let blind people see. Nonetheless, governments must stimulate scientists to monitor possible health risks of nanoparticles that may accumulate in the body.

Further reading

Department of Trade and Industry, U.K. Foresight Conference: *Opportunities for Industry in the Application of Nanotechnology*; Institute of Nanotechnology: Stirling, U.K., 2000; 44 pp; available at www.nano.org.uk/contends.htm.

NIH Bioengineering Consortium (BECON). *Nanoscience and Nanotechnology: Shaping the Future of Biomedicine*; report of a symposium on June 25–26, 2000; http://www.becon.nih.gov/nanotechsymp report.pdg.

Other relevant Web sites: http://nanomed.ncl.ac.uk; www.nanonet.de/bindexe.php3.

Societal Implications of Nanoscience and Nanotechnology; Roco, M.; Bainbridge, W.; Eds.; Kluwer Academic. Publishers: Dordrecht, The Netherlands, 2001; available at http://itri.loyola.edu/nano/NSET.Societal.Implications/nanosi-es.pdf.

Nanotechnology: Revolutionary Opportunities and Societal Implications; report on the 3rd EC-NSF Workshop on Nanotechnology; Tomellini, R.; Ed.; European Commission: Brussels, 2002. Ω

B I O G R A P H Y

Ineke Malsch, a consultant in technology and society (postbus@malsch.demon.nl), is director of Malsch TechnoValuation in Utrecht, The Netherlands (www.malsch.demon.nl).