The Two Faces of Nanotechnology

Concern about toxicity of nanoparticles is balanced by the potential of nanomedicine.

Omowunmi "Wunmi" Sadik

In 2010, Evelyn Sorensen, an art history professor in Arizona and a patient with stage II cervical cancer that had spread to her lymph nodes, was told by her doctor to go on vacation and say goodbye to her family, as she had a year to live. As she described in newspaper reports, rather than resign herself to this gloomy prediction, Sorensen insisted on seeing a list of clinical trials and learned of one in Cambridge, Massachusetts, where a company called BIND Biosciences was using super-small nanotechnology drones to attack tumors. She joined a trial run by Daniel Von Hoff of the Translational Genomics Research Institute in Phoenix, Arizona, and her tumors shrank 70 percent after her first treatment. Several years later, even though she was still on medication, doctors confirmed that her body still showed no evidence of cancer.

The clinical treatment Sorensen used is called BIND-014, a chemically coated nanoparticle designed to search for malignant cells and deliver potent doses of the chemotherapy drug docetaxel. The particle allows the drug to selectively collect at the cancer site, dramatically enhancing its effectiveness. Developed by Omid Farokhzad at Harvard Medical School, along with researchers at the Massachusetts Institute of Technology, BIND-014 has been in phase II trials for various cancers, and positive results have been reported in nonsmall-cell lung cancer. Results in other trials, however, were sufficiently mixed to put the company into a brief period of financial jeopardy, emphasizing the newness and potential volatility of this industry.

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Medicine is not the only area in which materials on the nanoscale have made large forays. The past two decades have seen extensive research into the design and fabrication of materials ranging in size from one to a few nanometers. This global research endeavor is commonly known as nanoscience or nanotechnology. The number of finished products that are incorporating nanomaterials is growing at a rapid pace. The Nanotechnology Consumer Products Inventory online database, published by the Woodrow Wilson International Center for Scholars, lists more than 1,600 nanotechnology-based consumer products on the market.

Scientists and investors are shifting toward broader, application-oriented areas such as healthcare and biomedical sectors. In a 2013 report, the technology market research firm Lux Research concluded that government support for nanotechnology continues to decline from a peak of $8.3 billion in 2009. Several countries have folded their nanotechnology programs and merged them into other science and technology programs. But Lux also predicted that, despite the decline in funding for nanotechnology, revenues from nanomaterials and intermediate-scale products such as coatings, memory chips, and catalysts are generating an aggregate net profit. The nanomaterials market, the report said, will continue to grow, reaching $3.2 trillion by 2018. Although toxicologists are concerned with the potentially deleterious environmental and health effects of extensive exposure to materials or particles with a diameter of less than 100 nanometers, recent commercialization successes in the nanomedicine sectors are generating excitement among biotech companies, investors, and pharmaceutical firms. Nanomedicine is starting to look like the white knight for this struggling, yet promising, field.

Defining Nanotechnology

Nanotechnology is a transformational science with the goal of building devices and structures that have every atom in the proper place. Nanoscience transcends the boundaries of traditional scientific disciplines and works at a scale where chemistry, physics, material science, and civil, electrical, biomedical, and mechanical engineering converge. We are seeing the effect of nanoscience on almost everything, including medicine, the automotive industry, energy, agriculture, consumer products, and even entertainment.

Nanotechnology is such a broad field that it defies a simple definition. Typically, it is described as a science concerned with the control of matter at the scale of atoms and molecules. *Nano* comes from the Greek word for dwarf, *nânos* or *nánnos*. A nanometer is one billionth of a meter: It's almost too small to comprehend. Scientists and engineers have described nanometers using everyday objects. For example, the National Nanotechnology Initiative equates 1 nanometer to "about 100,000 times smaller than the diameter of a human hair, or 1,000 times smaller than a red blood cell, or about half the size of the diameter of DNA." Sometimes researchers simply, and rather unhelpfully, say it's "really, really small." The late chemist Sir Harry Kroto compared the nanometer to the size of a human head in relation to the size of the planet. Even that is difficult to intuitively grasp or visualize.

Physicist Richard Feynman was one of the first to conceive of nanotechnology, describing its philosophical underpinnings in his 1959 lecture "There's Plenty of Room at the Bottom." The word *nanotechnology* was first proposed by Norio Taniguchi, who in 1974 gave an account of a new technology in which materials could be controlled and engineered beyond the micrometer scale. Scientists now have reported the existence of both naturally occurring and engineered nanoparticles. Naturally occurring nanoparticles include ocean spray, forest fire emissions, dust storms, volcanic ash, and biological particles such as proteins that have a typical size of 5 nanometers. Humans have long been exposed to naturally occurring nanoparticles resulting from combustion, and the human body is, for the most part, well adapted to protect itself from these potentially harmful intruders.

Human-made nanoparticles may be involved in incidental exposure. They fall into two categories. Those in the first category have no predetermined size and may exhibit undefined chemistry. Examples are combustion particulates, diesel exhaust, welding fumes, and coal fly ash. Those in the second category are known as engineered nanoparticles and range in size from 1 to 100 nanometers. They are pure materials with controlled surfaces and defined sizes and shapes. Engineered nanomaterials are comparable in dimension to the smallest naturally occurring nanoparticles, and are primarily composed of carbon, metal, metal oxides, and biological constructs, such as liposomes and viruses designed for gene or drug delivery.

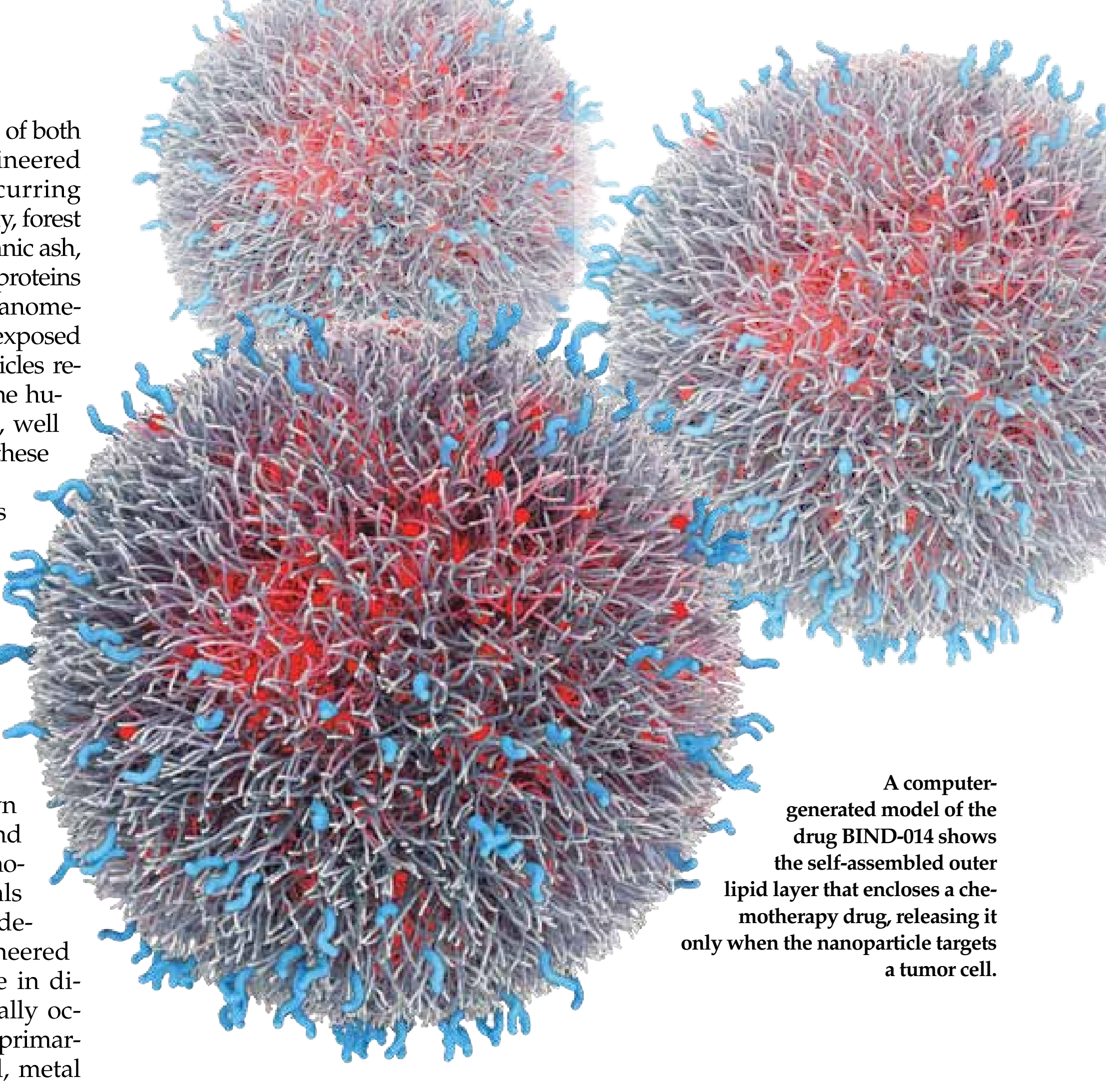


Image by Digizyme

A computer-generated model of the drug BIND-014 shows the self-assembled outer lipid layer that encloses a chemotherapy drug, releasing it only when the nanoparticle targets a tumor cell.

A Range of Applications

Through the new skill sets of nanofabrication, it is now possible for scientists and engineers to precisely build almost any nanomaterial. Such materials can be used to convert energy efficiently, deliver medical nanocapsules or drugs, target crops with herbicides and pesticides, and improve drug solubility and bioavailability. Applications of precisely built nanostructures have also included nanochip components in computers and radio-frequency tags, used to automatically identify and track food products and animals. Researchers at IBM, Hewlett Packard, and elsewhere are assembling nanoscale logic circuits between individual carbon nanotubes and nanowires, nanotransistors, and nanoswitches. They can fit in much less space than current silicon transistors, and are faster and cooler.

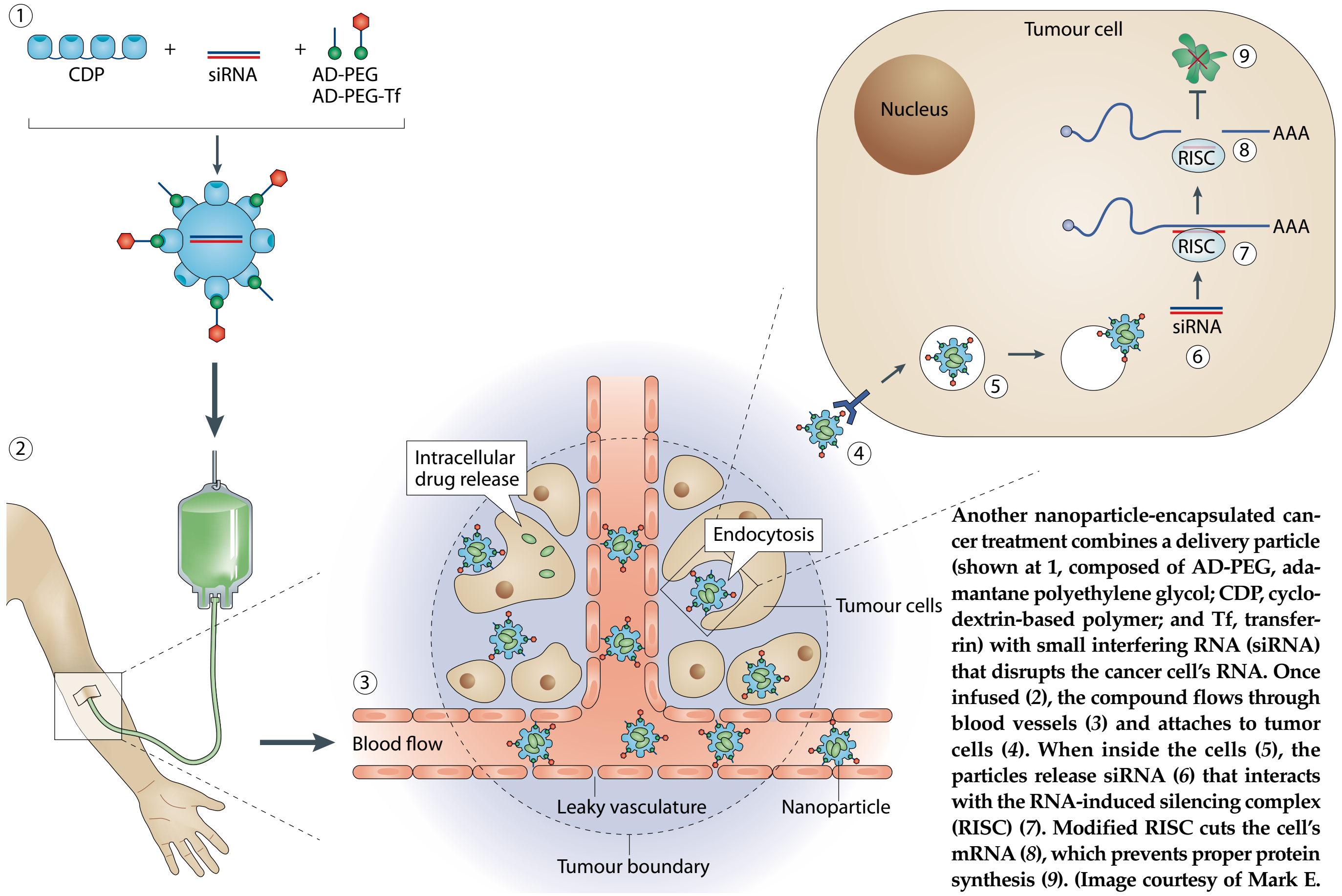
Nanotechnology-enabled sensors are found in personal health monitors and environmental detectors capable of detecting contaminants, toxins, and pathogens. NanoMarket, an industry analytic firm, predicts continued growth for nanosensors in a myriad of applications. The firm expects key growth drivers to be improved sensitivity and the ability to concurrently detect multiple chemical compounds. NanoMarket also predicts continuous development of nanotechnology tools. Gaining insights into nanoscale phenomena will be crucial to improving the performance of existing nanosensors. Not only would this affect the sensor market, it could also support researchers in the development of nanosensors that are based on innovative mechanisms. Transformational opportunities for nanotechnology are expected in novel sensing applications. Such biochemical sensors will take advantage of unusual phenomena at the nanoscale to assess disease markers.

Biochemical sensors can take advantage of phenomena at the nanoscale to assess disease markers.

Nano Versus Chemical Structures

When small-scale devices such as computer chips are created, they are etched out of a bulk silicon substrate. In contrast, nanostructured materials are built by adding one substance to another to alter or improve various qualities. So whereas silicon micromachining works in the range of 0.2 micrometers, basic sizes in nanotechnology are about an atomic diameter of 0.0008 micrometers.

Molecules designed for a specific function have always been a familiar part of modern chemistry. But unlike chemistry, nanotechnology is not limited to the attraction and association of molecules and ions in solution. Once a specific "bottom-up" process for building atomically precise structures has been worked out, the design of new nanomachines and nanofabrication systems closely resembles mechanical engineering. The method can be applied to both small individual parts and large systems.



Another nanoparticle-encapsulated cancer treatment combines a delivery particle (shown at 1, composed of AD-PEG, adamantane polyethylene glycol; CDP, cyclodextrin-based polymer; and Tf, transferrin) with small interfering RNA (siRNA) that disrupts the cancer cell's RNA. Once infused (2), the compound flows through blood vessels (3) and attaches to tumor cells (4). When inside the cells (5), the particles release siRNA (6) that interacts with the RNA-induced silencing complex (RISC) (7). Modified RISC cuts the cell's mRNA (8), which prevents proper protein synthesis (9). (Image courtesy of Mark E. Davis, from *MRS Bulletin* 37:828–835.)

In a conventional chemical reaction, bonds hold atoms together, and reactants are thus held in accurate orientations that promote the lowest level of free energy. Every reactant has a discrete amount of energy. The rearrangement of atoms that occurs in a chemical reaction is always accompanied by the liberation or absorption of heat. Breaking a bond uses energy, and forming a bond gives off energy. In nanotechnology, the same reactions are performed by a "molecular mill," in which the reactants are held in accurate orientations by jigs on belts and then pressed together at the proper angle and force. The belts move as the reaction occurs, such that a single station catalyzes more than a million reactions per second.

However, the rapid development of nanotechnology and the increasing production of nanomaterial-based products and processes present both great opportunities and challenges. There are a number of unresolved questions about free, uncontained nanoparticles. Researchers are looking for ways to distinguish between anthropogenic, incidental, and naturally occurring sources of nanoparticles. Other challenges are linked to the fact that many existing nanotechnologies are not sustainable because they require the use of large quantities of energy, water, and solvents. In addition, some existing nanomanufacturing processes use nonrenewable materials, and further, their impact on human health is not clearly understood. Researchers are studying safe and sustainable alternatives, but they have unanswered questions regarding the safety of some nanomaterials.

Potential Nano Poster Child

As the nanomedicine industry continues to grow, it is expected to have a significant effect on the economy, particularly in the medical field.

Nanomedicine employs various nanoparticles, particularly to diagnose and treat cancer. Most anticancer drugs in clinical trials have been hindered by their general toxicity and lack of selectivity, as they kill both normal and cancerous cells. Significant efforts are underway to find anticancer drugs that can selectively target cancerous cells and tissues, leaving healthy tissues untouched.

Nanomedicine presents an alternative approach to improving the delivery of anticancer drugs by enhancing targeted drug delivery. Anticancer compounds that are attached to nanoparticles, such as quantum dots and carbon nanotubes, are efficiently being carried through cells and tissues to be taken up by cells. When nanoparticles are within the relatively large size range of 10 to 100 nanometers, they can't cross or pass through tightly packed cell linings into the neighboring tissues. However, when drug molecules are attached to the particles, they retain stability in the bloodstream while maintaining their integrity until they reach the targeted tumor. These nanoparticle-drug conjugates are able to target only cancer cells because of their size, shape, and surface characteristics. Ultimately, their selectivity maximizes the drugs' effects on cancer cells, leaving healthy cells intact and producing fewer side effects for patients.

BIND-014, the drug that helped Evelyn Sorensen, is one of the most promising of the nanoparticles used in targeted drug delivery. Having cleared the safety testing of phase I clinical trials, it is now in phase II trials to test its efficacy in treating lung and prostate cancer. BIND-014 is assembled from polymeric strings that spontaneously fold to form a particle. The polymers are interspersed with targeted molecules or ions, which bind to another molecule and are designed to link the particles to cancer cells. This self-assembly process makes it easier to reproduce the molecule in batches and may ultimately provide unique advantages for translating the technology for clinical applications.

Another promising anticancer drug is CALAA-01, a combination of the delivery particle RONDEL and the small interfering RNA (siRNA) molecule, which inhibits tumor growth by affecting the function of the cancerous cell's RNA. The siRNA in CALAA-01 is protected from degradation within a stabilized nanoparticle and has been in phase Ib clinical trials.

Nanotoxicology

It can be challenging to define all the distinctive physical, chemical, or biological features of nanoscale particles. That difficulty only adds to the concern that these new materials could have a number of potential causes of toxicity. Nanostructures have electronic, optical, and magnetic properties that are related to their physical dimensions, and when these nanostructures break down, they could develop toxic effects that are difficult to predict. Nanostructured surfaces can get involved in catalytic and oxidative reactions and be more toxic than similar but larger-scale materials because of their higher area-to-volume ratio. Moreover, some nanostructured materials contain toxic metals or compounds that can be released as the parent material breaks down.

One class of engineered nanoparticles of major concern is carbon nanotubes. More than 5,000 patents have already been issued for carbon nanotubes, and there are about another 50,000 varieties of them overall. The most common categories are either those that have several concentric walls, called *multiwalled*, or those that are made from one layer, called *single-walled*. Carbon nanotubes are highly desirable for applications in electronics, structural engineering, and medicine because of their unique electrical conductivity, mechanical strength, and the ease of derivatization for custom applications in drug delivery. In chemical terms, *derivatization* is a technique in which a compound is transformed into a product of similar chemical structure. The resulting material is then called a *derivative.*

However, regulators, health personnel, environmentalists, health advocates, and even the general public have increasing concerns about exposure to carbon nanotubes. Numerous studies have found that their introduction into the lungs of mice, rats, and guinea pigs may result in granuloma, inflammation, and fibrosis. Multiwalled carbon nanotubes have been shown to exhibit increased toxicity when inhaled, ingested, or exposed to the skin. Carbon nanotubes are particularly troublesome because their length-to-width ratio is similar to that of asbestos, whose fibrous crystals cause lung cancer, mesothelioma, and asbestosis. However, many of these studies possess no supporting epidemiological data, indicating a significant gap in research.

While advances in nanomedicine are allowing tailored drug delivery, other developments are generating health and environmental concerns.

While advances in nanomedicine are allowing scientists to tailor drug delivery chemistry and identify various nanoparticle constituents, other developments in the field are generating health and environmental concerns. The 8th International Nanotoxicology Congress, or Nanotox2016, was held in Boston last year with the theme *Decade of Nanotoxicology: Impact on Human Health and the Environment.* With dozens of talks on the schedule, the meeting was one of the largest congregations of nanotoxicologists in the world. Critically examining the past decade of nanotoxicology, panels of experts argued in favor of two significant successes. The first is the evolution of nanotoxicology as a truly interdisciplinary field outside of its traditional core disciplines. Second, the congress attributed this evolution to the increased awareness of past mistakes when commercializing new technologies, and the commitment of the community to the safer development of nanotechnology.

The congress also acknowledged that some aspects of the science could have been done differently. For example, measuring the dose range used in nanotoxicology research is challenging. Sometimes the dose used in a study is so high that it has no relevance in the real world, leading to findings of questionable value. There are other unanswered questions related to the development of standard methods of assessing nanotoxicity. To this end, the congress set up the Sustainable Nanotechnology Organization (http://www.susnano.org) to establish the economic, ethical, and societal benefits of nanotechnology. Overall, the researchers in this field recognize the need to develop characterization parameters, metrological tools, novel instrumentation, and protocols that can provide information on the interactions of engineered nanomaterials with biological and environmental systems.

In this proactive environment, although debate continues regarding concerns and new biomedical applications, it is clear that the two faces of nanotechnology remain divided between benefits and risks.

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