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feature article

EYE ON THE FUTURE: NANOTECHNOLOGY

within a nanometer of your life

Advances in semiconductor manufacturing techniques are bringing medicine closer to cures and treatments that have eluded researchers working on the macro scale.

By Allen J. Menezes, Vik J. Kapoor, Vijay K. Goel, Brent D. Cameron and Jian-Yu Lu

Biomedical research on the nanoscale is relatively new. The entire field of nanotechnology itself can be seen as a recent offshoot of the semiconductor microelectronic revolution, which earlier spawned the development of microelectromechanical systems.

The commercial needs of electronics manufacturers have driven them to create, understand, and control objects on ever-smaller scales. In June, for instance, Intel Corp. announced that it could make a transistor 20 nanometers long containing features only three atoms thick. The company predicted that it would be producing devices that contain transistors of this size in about six years.

Advances in semiconductor manufacturing techniques and other insights are not only yielding smaller and faster means of handling information, they are also bringing the world closer to cures and treatments that have consistently eluded researchers working on the macro scale. Research is under way to design implants with nanoscale features that will promote the healing of natural tissue. Devices in development promise to meet bacteria and viruses on their own level for the detection and treatment of diseases.

The essence of nanotechnology is the creation and utilization of materials and devices at the level of atoms, molecules, and supramolecular structures, and the exploitation of unique properties and phenomena of matter at 1 to 100 nanometers. There are many nanotechnology initiatives in the biomedical engineering field, such as biomechanical materials and design related to spine research, imaging technologies, and a neurochip for the brain.

Using biocompatible materials, researchers are working toward implantable sensors and drug delivery devices that can exploit their tiny size to work effectively within the body over time. There are textured bandages with nanoscale features that accelerate healing and, in some cases, allow the repair of damage that is almost untreatable by conventional methods.

Nanomaterials are providing mechanical support in the body.

The problems of an aging spine, for example, are attributed to degeneration of soft tissue, or the disc, between the vertebrae. Spinal trauma and diseases such as arthritis or cancer can compromise the spine. When a disc deteriorates, the spacing between the vertebrae decreases and the result is painful.

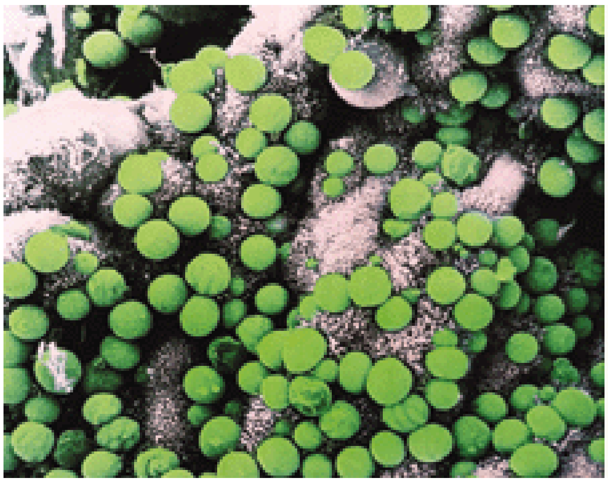
In severe cases, surgeons replace the damaged disc with an implant or bone graft that fuses neighboring vertebrae and returns them to their original spacing. The treatment sacrifices flexibility between two vertebrae in order to relieve the patient's pain.

An orthopedic implant company, Implex Corp. of Allendale, N.J., has developed spinal fusion devices for the cervical, thoracic, and lumbar spine using a novel biomaterial called Hedrocel Trabecular Metal.

Hedrocel was developed by Ultramet, a research and development company in Pacoima, Calif., that specializes in materials using chemical vapor processes, both infiltration and deposition. In the early 1990s, Implex received an exclusive license from Ultramet covering musculoskeletal applications of the material, according to Robert Poggie, Implex's director of applied research.

According to Implex, Hedrocel, which has a porous structure and mechanical properties similar to bone, can be formed or machined into complex shapes. When the material is used to fuse vertebrae, the bone can gradually infiltrate into and through the implant device, in a process similar to natural healing. The natural and artificial materials combine to reconstruct the spine and reduce the possibility of nerve compression and pain.

Implex has developed hip and knee reconstruction devices made wholly or in part of Hedrocel. The spinal implants are in commercial use in Europe and are undergoing clinical trials in the United States, Poggie said.



Microchip technology that can detect Cryptosporidium in drinking water (shown in a colorized microphoto) is being marketed for cancer research and diagnosis.

Ultramet composes various materials using chemical vapor deposition, the process that produces Hedrocel. During chemical vapor deposition, a continuous thin film of metals such as rhenium or tantalum, or compounds such as silicon carbide can be distributed throughout the interior of a construct. The films lend certain thermal or tensile properties to a carbon foam substrate and to the structure as a whole. The resulting product is characterized by low cost, low density, high chemical purity, controlled thermal expansion, and high thermal stability.

Ultramet's president, Andrew Duffy, said the nanomaterial can be made to withstand temperatures of up to 6,000°F.

Hedrocel consists of 99 percent tantalum over a vitreous carbon matrix, and the final product is about 80 percent porous, with a pore size of 550 micrometers and a modulus of elasticity of 3 GPa.

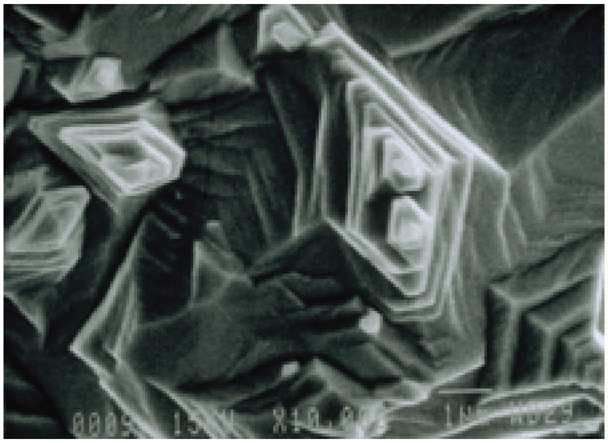
During the chemical vapor deposition process, the tantalum metal crystallizes from tantalum pentachloride gas onto the three-dimensional lattice structure of the Hedrocel. The result is a nano-textured surface, representing the crystallized tantalum metal.

Nanotechnology may teach us more about collagen, an important protein constituent of the body's connective tissues. Any deviation in the molecular structure of collagen causes its properties to vary, and leads to complications such as excessive joint laxity, poor ligament healing, abnormal fracture healing, tendon adhesion, soft tissue degeneration, and abnormal wound healing.

Until now, only major anatomical structures containing collagen have been studied. A recent paper titled "A Method for the Determination of the Stiffness of Collagen Molecules," published in Biomedical and Biophysical Research Communications, No. 232, describes a new method involving the use of an optical LaserTweezers system commercially available from Cell Robotics Inc. in Albuquerque, and a binding technique for gripping the collagen molecule termini for micromechanical testing.

The authors, Zong-Ping Luo, Mark E. Bolander, and Kai-Nan An, work for the Division of Orthopaedic Research at the Mayo Clinic in Minnesota. The test involves the stretching of single collagen molecules using the optical tweezer system, which is designed to manipulate cells by using the momentum of laser beams.

Polystyrene beads—one small, 490 nm in diameter, and one large, 3,150 nm—are placed onto a coverglass. A single collagen molecule has one end attached to the small bead and the other to a large bead. This is achieved by coating the beads with heparin, used to bind the collagen molecule to the bead. Equal numbers of beads are mixed with an equal number of collagen molecules in an appropriate solution. A high incidence of single-molecule attachment onto a small bead at one end and a large bead at the other is achieved by estimating the number of beads and molecules before coupling them. The beads are examined by optical microscopy.



A scanning electron micrograph of Hedrocel reveals the nanoscale texture of the 3-D lattice created as tantalum crystallizes from tantalum pentachloride gas during the chemical vapor deposition process.

The molecule is stretched through the beads by optical force microscopy using the optical tweezer system. The deformation of the bound collagen molecule is measured as the displacement of the small bead center from the large bead center. The method provides a novel technique for the measurement of the mechanical properties of collagen molecules.

Meanwhile, research at the University of Wales in Bangor has developed a microchip technology that can diagnose diseased or damaged cells in body fluids or bacteria in water supplies.

Ron Pethig and Julian Birt, professors associated with the university's Institute of Bioelectronic and Molecular Microsystems, have collaborated on the development of what they call biofactories on chips. Pethig has become the university's envoy to the business world and has raised the money to start a company, Aura Oncology Systems in Palo Alto, Calif., to commercialize the technology.

Pethig's work has developed a chip that can detect Cryptosporidium and Giardia in water supplies. More recent developments are microchips that can detect damaged cells, viruses, and bacteria in body fluids.

The chips contain electrodes 1 to 2 microns across that are made using microfabrication techniques. The edges of the electrodes are defined to 50 nanometers, using electron beam lithography with a spot size of 20 nm. The result is a precise electric field geometry.

Researchers are able to use the electric field to identify cells, viruses, and proteins by looking at their dielectric properties.

The microchip allows faster and earlier detection of diseases such as HIV and cancer. Pethig said a test of a small volume of blood, for instance, can take a minute or two. Culture tests for some diseases currently take days.

By studying fluid samples at the cellular level, the system can diagnose the physical and chemical status of cells to detect disease at an early stage.

The technology also can be used to study the effects of drugs on cells.

Specialized cells, known as neurons, compose the human nervous system. The neurons form complex networks that are the basis of the brain circuitry that gives us our intelligence and a host of other abilities, including motor control and sensing.

Nanotechnology-based transistors can be designed and fabricated that can mimic the function of an individual neuron. Therefore, it is possible to fabricate a neurobiochip containing many of these transistors to simulate the function of part of the brain neurons. This can one day replace part of the damaged or malfunctioning brain circuitry, as in the case of Alzheimer's and other neurological disorders. The neurochip would be a prosthetic device for the brain, much like an artificial heart, prosthetic hip, or knee.

Two of the authors, Vik J. Kapoor and his graduate student, Allen J. Menezes, of the Nanotechnology Research Center at the University of Toledo in Ohio, are investigating the feasibility of the design and fabrication of such a neurochip.

About one-third of the operations carried out to repair severed tendons are unsuccessful because the regenerating natural tissue sheathing attaches itself to the tendon, making it unable to move. An article published in 1999 in Foresight Update by the Foresight Institute in Palo Alto, Calif., reported on a smart bandage with the ability to aid in tendon healing.

The Foresight Institute describes itself as "a nonprofit educational organization formed to help prepare society for anticipated advanced technologies." The group concentrates on nanotechnology.

The smart bandage, developed by Chris Wilkinson and Adam Curtis of the Nanobiology Center at the University of Glasgow in Scotland, is made of biodegradable plastic designed with grooves that have been fabricated using lithography and dry etching. The bandage is wrapped around the tendon.

The macrophages, which are cells 10 microns wide that promote adhesion of the tendon to the rest of the tissue, grow into the grooves in the bandage, which are about the same width. The tendon grows on the bandage separated from the sheathing.

The shape of the groove causes the macrophage cells to grow long and thin. The cell undergoes internal changes and the agents that hold the cell together are aligned in the direction of the groove, which promotes healing.

Wilkinson has undertaken further development of this technology, the use of 50-nm-diameter plastic dot mesh bandages for directed growth of tissue. Thus, any pattern of tissue can be grown for use in reconstructive surgery.

The smart bandage is currently undergoing clinical trials.

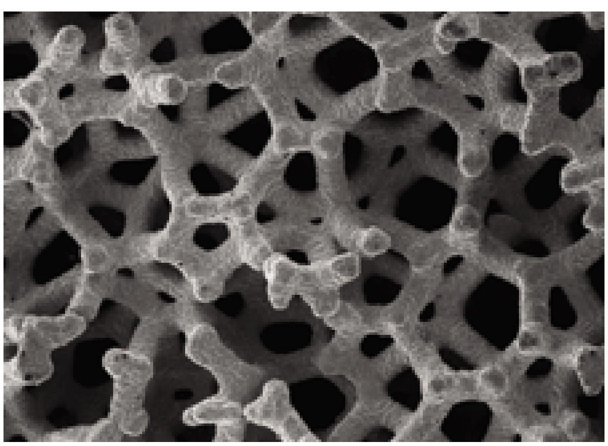
The ability to fabricate and machine components on a nanoscale level is providing an avenue for the development of optical sensors in the areas of biomedical diagnostics, sensing, and therapeutics. In the past decade, considerable progress has been made in biomedical optics. This area has received attention in part because of the potential advantages optical sensors can offer compared with electrical and electrochemical sensing technologies.

One of the main advantages is the ability to sense or measure biological parameters in a noninvasive manner. The majority of optical techniques are based on observing and quantifying the effect or changes in light as it interacts with the sample. Most sensing-based techniques that use light are reagentless, which is a clear advantage in the development of other techniques that may be invasive, implanted in the body over long periods of time.

More specific medical applications of recent focus and interest in the field of optics and bioengineering are in the areas of diabetic glucose sensing, cancer diagnostics, and genetic research. Although the number of optical techniques being applied to these areas is large, some of the more common modalities include optical polarimetry, interferometry, and a number of spectroscopic techniques, such as Raman, absorption, and fluorescence spectroscopy.

Regardless of the optical technique, to date, these methods have already demonstrated the ability or potential to sense physiological glucose levels noninvasively, distinguish between normal and cancerous tissue and cells noninvasively, and provide real-time genetic screening for multiple diseases in a single measurement.

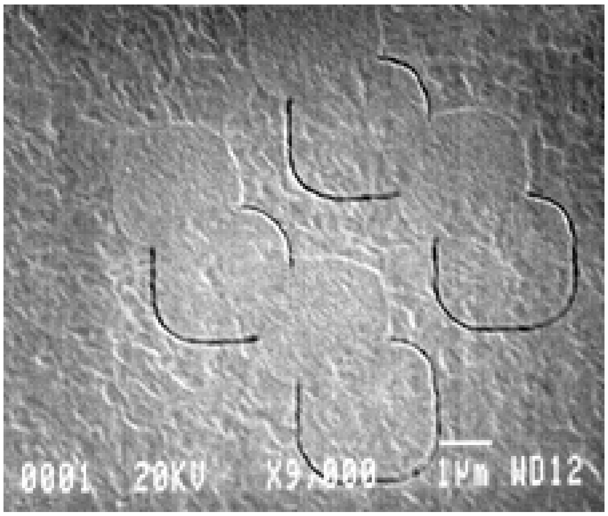
The focus in the upcoming decade will be on realizing this technology in the commercial marketplace. Therefore, the ability to integrate and miniaturize current prototype benchtop optical setups and support electronics into a single unit through advances in nanotechnology will indeed play a crucial role in making devices based on this technology commercially feasible and cost effective. For example, consider a nano-optical device that can enter the body to observe individual cells.



Implex Corp. has developed spinal fusion devices of Hedrocel Trabecular Metal with structural properties compatible with bone. After surgery, natural bone eventually infiltrates the porous scaffold.

A report titled "Nanosensor Probes Single Living Cells," in a 1999 issue of ORNL Review from Oak Ridge National Laboratory in Tennessee, described an experimental device developed by Tuan Vo-Dinh and his coworkers, Guy Griffin and Brian Cullum. The ORNL researchers demonstrated the ability to probe cells for carcinogenic chemicals with a nanoscale needle.

The nanoneedle is a 50-nm-diameter silver-coated optical fiber carrying a helium-cadmium laser beam. BPT (benzopyrenetetrol), for instance, is a product of a chemical reaction between benzopyrene, a cancer-causing environmental pollutant, and cellular DNA. Monoclonal antibodies that attach and bind to BPT are attached to the tip of the nano-needle, which is inserted into a tissue sample. The laser light, at a wavelength of 325 nm, excites the antibody-BPT complex at the fiber tip, causing the complex to fluoresce. The fluorescent light travels up the fiber to an optical detector. A layer of silver deposited on the fiber wall prevents the laser light and the fluorescence emitted by the antibody-BPT complex from escaping.



An experimental insulin-delivery system at Ohio State University uses a membrane containing channels that are 50 nm wide.

According to Vo-Dinh, the system can detect carcinogens and DNA adducts, the damaged DNA with carcinogens attached, and can recognize the presence of carcinogens even when there is no damage to the cell's DNA.

Nanoscale devices may one day be introduced into the body to deliver treatment.

In diabetes mellitus, for example, the cells called the islets of Langerhans, which produce insulin in the pancreas, malfunction. A possible cure would be to implant fresh copies of the cells into the body.

The replacement tissue can be harvested from a compatible nonhuman species such as a pig, whose islet of Langerhans cells produce insulin very close in chemical composition to a human's. The porcine cells would replace malfunctioning pancreatic cells and restore the body's feedback loop.

One of the major problems in developing such a treatment is the body's immune reactions. A foreign organism in the body triggers an immune system response, the release of antibodies to attack the intruder. Implanted replacement cells are foreign to the body and would be attacked by the immune system, with detrimental results.

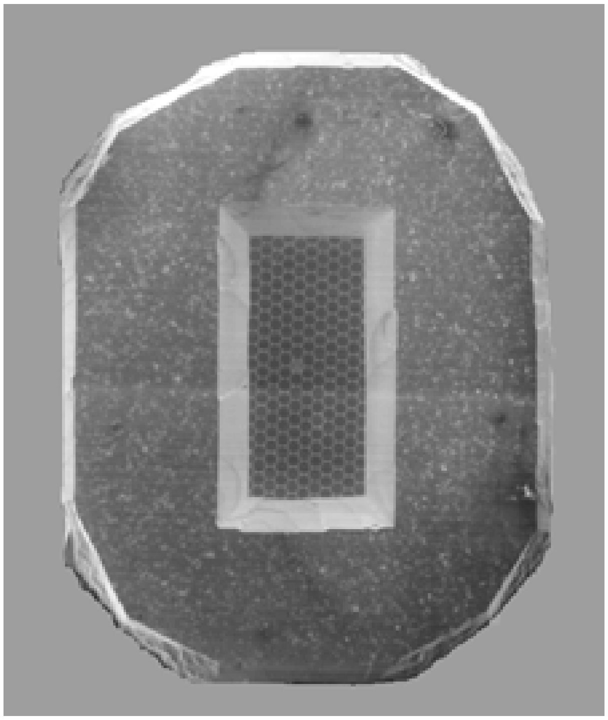
Clinical trials of replacement therapy so far have required that the patients take drugs to suppress the immune response. The strategy leaves a patient dangerously susceptible to infection.

Mauro Ferrari, director of the Biomedical Engineering Center at Ohio State University in Columbus, leads a research team that is experimenting with a novel technique to counter the effect of the immune system by using nanotechnology.

The Ohio State researchers are working on an artificial barrier that will keep the immune system from reach-ing the transplanted cells. The team's method is to fabricate a silicon capsule with a membrane barrier containing pores small enough to block antibodies and large enough to let desirable molecules flow in and out.

Silicon capsules with nanoscale pores could hold the healthy pancreatic cells and be implanted beneath a diabetic patient's skin.

Antibodies have the capability of penetrating any orifice larger than about 18 nanometers. The exact size is still unknown. State-of-the-art photolithography techniques for integrated circuits are good for features as small as a few hundred nanometers.



A capsule with a nanoporous membrane (at center) can protect replacement cells from antibodies.

According to a research team member, Derek Hansford, an assistant professor at the Biomedi-cal Center, manufacture of the nanopore structure doesn't use the conventional cure-and-etch method of photolithography. Instead, a sacrificial layer is grown as a thin film that defines the channel size, only a few nanometers wide.

The smaller glucose molecules can stream easily through the nanopores into the capsule to activate the cells and the insulin can trickle out, controlling the blood chemistry. At the same time, the cells are shielded against attacks by natural antibodies.

Hansford said research has progressed as far as in vivo tests of the technique involving animals.

Tejal Desai, a bioengineer at the University of Illinois, is pursuing a similar approach for use in treating patients with Alzheimer's. Patients with Alzheimer's have dysfunctional neurons that are unable to release neurotransmitters. Nanopore fabrication technology is used to make microcapsules for implanting neurons in the brain. Once the capsules are implanted, the neurons are electrically stimulated to release neurotransmitters. Disorders where basic neurosecretory cells (cells that release neurotransmitters, which are chemicals that influence the functioning of neurons) are missing or damaged can be treated using nanopore technology.

The limits of nanotechnology have not been established, and no one can state authoritatively what is out of reach. Biomedical nanotechnology will make it possible to build nanorobots having cellular dimensions with the ability to eliminate infections, unclog arteries, and a range of other applications. A lab on a chip would be developed that would be able to test for a host of conditions with a single drop of blood and thus replace entire laboratories.

Who can say? Biomedical nanotechnology's future may one day eliminate old age, or at least ease its symptoms.

Vik J. Kapoor, Vijay K. Goel, Brent D. Cameron, and Jian-yu Lu are faculty members in the Department of Bioengineering at the University of Toledo in Ohio. Allen J. Menezes is a graduate student there. All five are associated with the university's Nanotechnology Research Center.

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