PENNSTATE

Biomedical Materials

MATERIALS RESEARCH INSTITUTE

The Gateway to Materials Research at Penn State

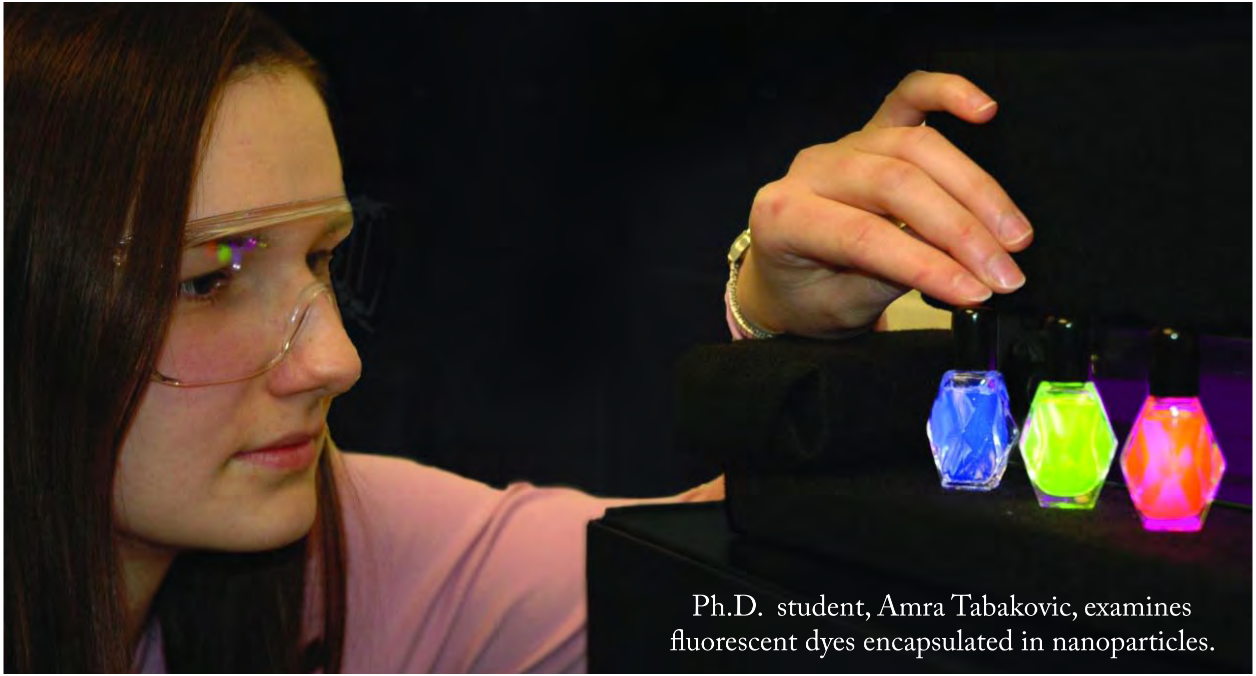
Biomedical Materials at Penn State

The interaction of the life sciences and materials research takes many forms at Penn State. From heart assist devices to artificial cells, Penn State scientists, engineers, and clinicians are breaking new paths in the study of biological systems and the integration of new materials into the body. These materials and devices could help to control the electrical storms that result in epileptic seizures, serve as cardiac stents and orthopedic implants that dissolve when their work is finished, or deliver therapeutic drugs without needles via ultrasound.

At the core of many of these discoveries are the new nano- and micro-technologies that allow for investigation and manipulation of objects at the molecular and cellular level. Tools for creating unique composite materials, for observing drug interactions within cells, for forging microscale surgical instruments, and for targeting diseases without damaging healthy tissue are all the result of advances in the ability to see and move atoms and molecules.

In 2011, Penn State will open the doors to a major research facility on the University Park campus devoted to the study of materials and the life sciences. The Millennium Science Complex will accelerate the rate of discovery in biomaterials that is already well underway at Penn State, as evodenced by the following research nuggets.

For additional information on any of these nuggets, visit www.mri.psu.edu/research/



Ph.D. student, Amra Tabakovic, examines fluorescent dyes encapsulated in nanoparticles.

A New Approach to Metal Implants

Cardiac and orthopedic implants offer great hope to millions of patients with blocked arteries and deteriorating joints. Some 700,000 stents are surgically implanted in patients each year. A similar number of patients receive artificial joints. But in many cases, an implant is only required for long enough for damaged tissue to heal. A metal stent or metallic bone implant that dissolved harmlessly over time would make further stenting much easier or avoid unnecessary joint surgery.

Barbara Shaw and her research associate **Elzbieta Sikora** have developed a process using electron beam physical vapor deposition (PVD) to create a magnesium alloy material that can be controllably and safely dissolved in the body. Vapor deposition allows them to create chemistries in the alloy that wouldn't be possible using the more conventional methods of making alloys. Vapor deposition also allows them to get around some of the solubility issues encountered when alloys are mixed.

Perhaps most importantly, PVD allows them to control surface effects on the magnesium alloy. By manipulating the surface, coatings with drugs can be introduced, either on the surface or at different layers of the alloy. Used for orthopedic implants or coronary artery stents, these drug-eluting materials could reduce the inflammation over time as the magnesium dissolves. By manipulating its composition, the alloy can be made to corrode at a predetermined rate, from weeks to a year or more in the case of certain orthopedic implants.

Barbara Shaw, Ph.D., is professor of engineering science and mechanics. Her collaborators in biomedical research include Ian Gilchrist, Henry Donahue, and Wallace Greene at Penn State Milton S. Hershey Medical Center, and departmental colleagues Steven Schiff and Bruce Gluckman in the Center for Neural Engineering. A patent is pending for the medical applications of their process.

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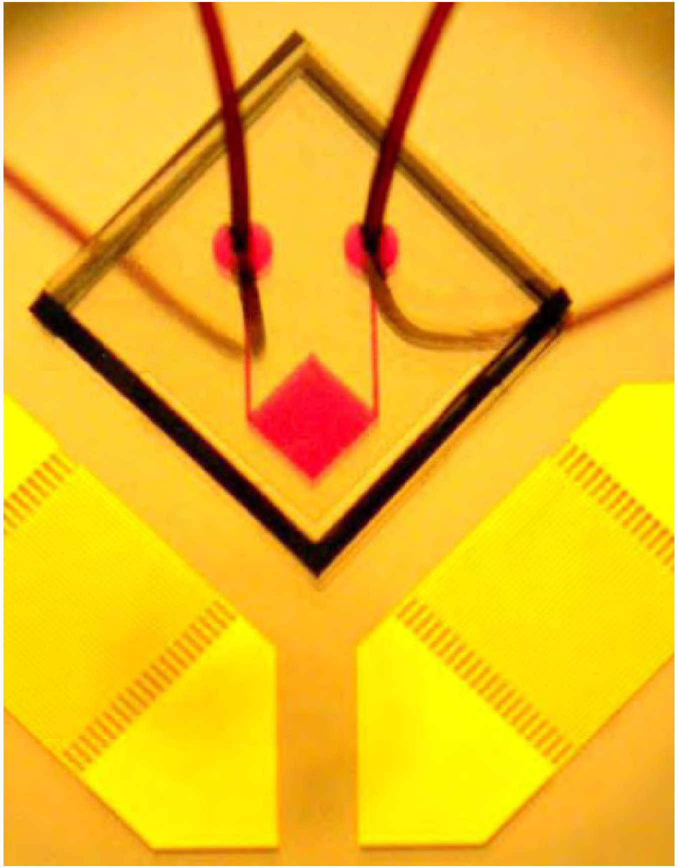


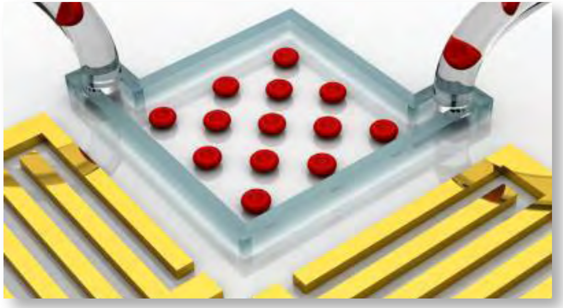
Acoustic Tweezers

A versatile, low-power tool for drug screening and tissue engineering

A new and simple method for manipulating small objects, including living cells, without damage has been developed by a team led by **Tony Huang**, an assistant professor in the Department of Engineering Science and Mechanics at Penn State. Called acoustic tweezers, these tiny devices small enough to fit on a computer chip use sound waves to push small objects into "troughs," created when two sound waves of the same frequency cancel each other out. These acoustic tweezers are capable of pushing large numbers of cells or nanoparticles into precise locations simultaneously to form patterns that could be useful for biological applications, such as placing stem cells on a grid for testing or growing new tissues.

Acoustic tweezers are made by building sound producing transducers onto a piezoelectric chip. The tweezers require very little power to operate, which is not the case with other devices, such as optical tweezers. Huang believes his versatile new device will have applications not only in biology, but also in physics, chemistry, and materials science.

Their experiments manipulating single cell E. coli bacteria, 1.9 micrometer polystyrene beads, and cow red blood cells was reported in the journal Lab on a Chip.



In addition to Huang, the authors were Jinjie Shi, Daniel Ahmed and Sz-Chin Steven Lin, graduate students, engineering science and mechanics; Xiaole Mao, graduate student in bioengineering, and Aitan Lawit, undergraduate in engineering science and mechanics. The work is supported by the National Science Foundation. Source: Penn State Live

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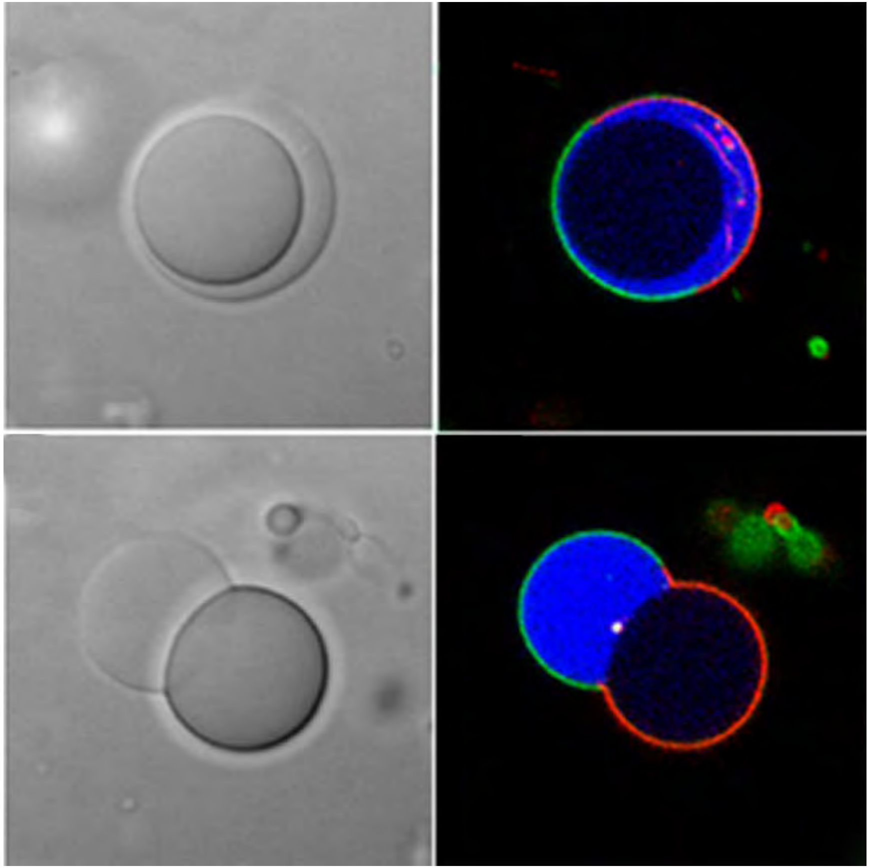

A Simple Model Cell Reveals Complexity of Cellular Function

The model cell developed in the lab of Christine Keating at Penn State uses as the cytoplasm a solution of two different polymers, PEG and dextran. The blue area is the PEG-rich region. This new structure exhibits polarity both in the membrane and in the aqueous interior of the model cell.

A team of Penn State researchers has developed a simple artificial cell with which to investigate the organization and function of two of the most basic cell components: the cell membrane and the cytoplasm—the gelatinous fluid that surrounds the structures in living cells. The work could lead to the creation of new drugs that take advantage of properties of cell organization to prevent the development of diseases.

"We aren't trying to generate life here. Rather, we want to understand the physical principles that govern biological systems," said **Christine Keating**, associate professor of chemistry. "For me the big picture is trying to understand how the staggering complexity observed in biological systems might have arisen from seemingly simple chemical and physical principles."

The research team includes Ann-Sofie Cans, a former postdoctoral researcher in the Department of Chemistry who is now at Chalmers University of Technology in Sweden, and M. Scott Long and Meghan Andes, both graduate students in the Department of Chemistry. The work was primarily supported by a grant from the National Science Foundation and by the Arnold and Mabel Beckman Foundation.
Source: Eberly College of Science

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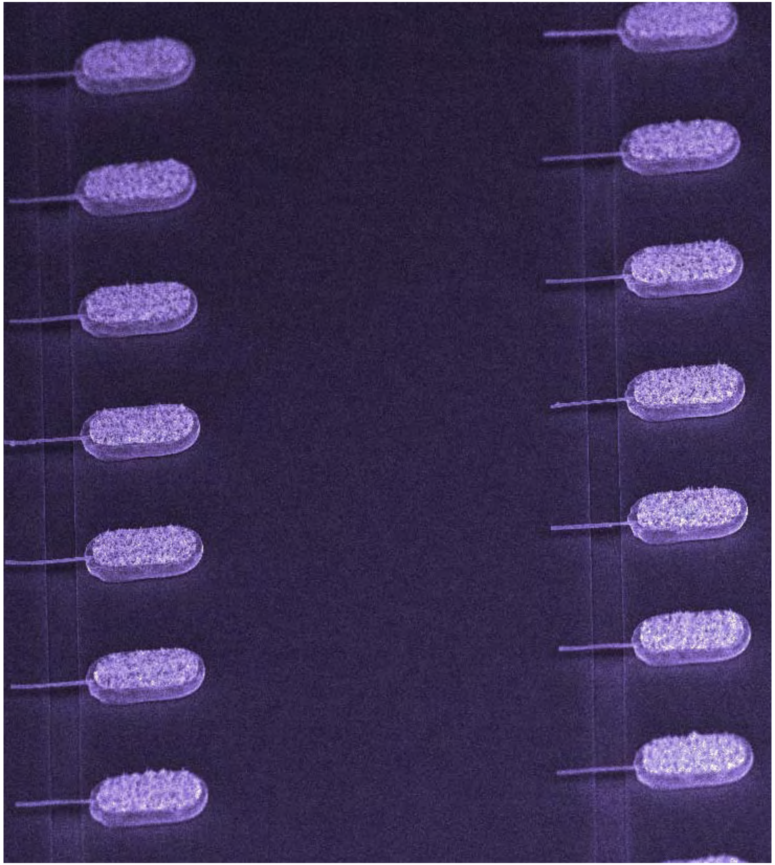

An Early Detection Sensor for Cancer

Unassembled nanowires.

Left: FE-SEM image of a nanowire array positioned on a silicon chip. Nanowires can be functionalized off-chip with cancer-specific molecular sensors.

Carcinomas shed cells into the vascular system before they metastasize. What if you could detect those malignant cancer cells in the blood before they had a chance to spread? That's what **Theresa Mayer** and her collaborators **Christine Keating** and **Gary Clawson** are trying to achieve. They are developing highly specific and highly sensitive RNA sensors built on a CMOS semiconductor chip that are expected to make the detection of early cancers easier and more effective.

Researchers have incorporated functionalized single crystal silicon and metal nanowires that have been optimized to detect cancer cells onto lithographically patterned chips. In a process unique to the Penn State team, the nanowires are optimized chemically off the chip and then incorporated onto the chip through electrofluidic assembly, a process that can precisely control their placement. Mayer's group uses chemical vapor deposition techniques to make silicon nanowires. The single crystal structure results in high quality sensors. Arrays of silicon nanowires that have been optimized with various cancer-specific oligonucleotides will attach to circulating tumor cells from breast, prostate, and melanoma cancers. "If successful, this biosensing strategy will enable early diagnosis of these cancers and improve treatment success," Dr. Mayer says.

Theresa Mayer is professor of electrical engineering and director of the Nanofabrication Facility. Christine Keating is associate professor of chemistry. Gary Clawson, MD, is professor of pathology in the College of Medicine.

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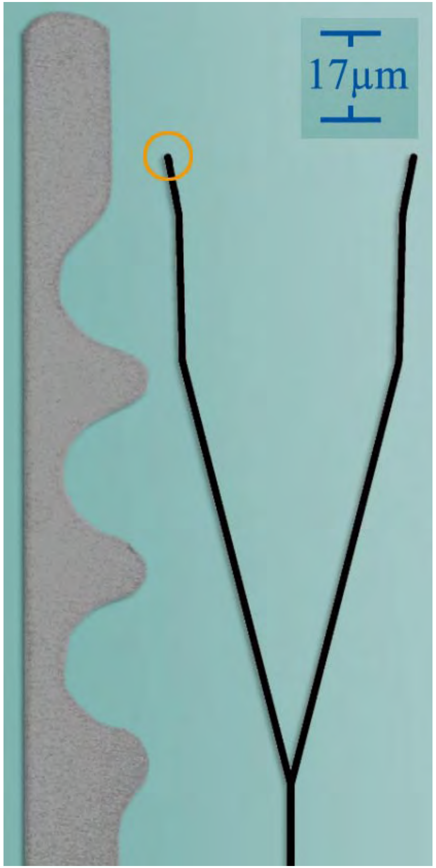

Microsurgical Tools for Self-Healing Incisions

Working with colleagues in the Penn State Milton S. Hershey Medical Center and the Department of Materials Science and Engineering, Professor **Mary Frecker** is designing a new generation of microsurgical instruments to help overcome the limitations in today's design and manufacture of minimally invasive surgical tools. "There is a need for multifunctional instruments that are an order of magnitude smaller than current instruments. We're talking about a tiny scissors-forceps that can be used, for example, in surgery on the retina. With an instrument that size, you can do sutureless surgery, self-healing incisions."

In minimally invasive surgery, surgeons use a host of instruments which are continually inserted and removed. During each instrument exchange, there is a risk of inadvertent tissue damage that may cause the patient to bleed internally. In addition, frequent instrument exchanges tend to disrupt the surgeon's concentration.

To create small enough instruments for use in flexible endoscopy, around .5 mm in diameter, Frecker worked with materials scientist **James Adair,** who developed a method of gel casting pure zirconium nanoparticles that can be cast in a mold and sintered on a chip. After the instruments are hardened, they are sealed and coated with gold palladium using sputter coating techniques. The result is sub 100 micron surgical tools with small feature size and sharp edges.

Mary Frecker, Ph.D., Department of Mechanical and Nuclear Engineering. James Adair, Ph.D., Department of Materials Science and Engineering. Randy Haluck, MD, director of the Minimally Invasive Surgery Program at Penn State Milton S. Hershey Medical Center.

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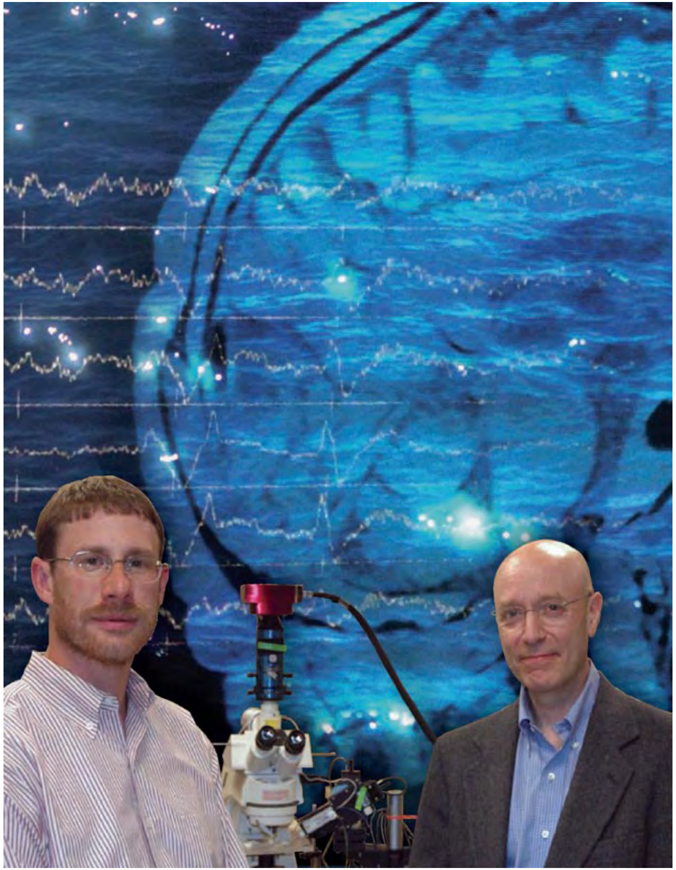

Engineering the Brain

One American in six is affected by a neurological illness each year. Neural engineering relies on materials science as well as computation and electrical engineering to attempt to restore brain functions. In the Penn State Center for Neural Engineering, researchers are studying the brain's electrical system in the hope of controlling the malfunctions of disease such as epilepsy and Parkinson's.

Pediatric neurosurgeon, **Steven Schiff** (right), and experimental physicist, **Bruce Gluckman** (left), are the director and associate director respectively of the Center, which is designed to act as a bridge between the clinical researchers at the Penn State Hershey College of Medicine and the engineering and materials disciplines at the University Park campus.

In the Brain-Machine Interface Lab, students learn to control the movements of objects using the electrical signals generated by their brain captured by electrodes connected to a computer. A second lab is devoted to animal brain slice research in which low frequency electrical fields are applied to neurons to modulate their response. In a third lab, Gluckman builds small implantable electronic circuits to record the firing of single neurons under low frequency.

Using the tools of nanotechnology and microengineering available at Penn State, Schiff and Gluckman hope to speed the progress of neural engineering by developing a better model of the brain. Their research has potential to help the 50 million Americans affected by neurological illnesses, ranging from Alzheimer's to serious depression to stroke.

Bruce Gluckman, Ph.D., is associate professor of engineering science and mechanics. Steven Schiff, M.D., Ph.D., is Brush Chair professor of engineering.

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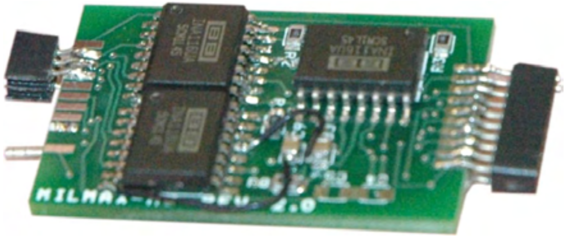

A Materials Answer to Deadly Blood Clots

Penn State professor and researcher **Chris Siedlecki** works at the interface where the surface of devices meets the human body, and in particular where artificial materials contact the blood supply. In his laboratories for materials fabrication and characterization and biology at the Penn State Milton S. Hershey College of Medicine, he pursues the understanding of the cascade of events that occurs when proteins in the blood meet a foreign object, such as a vascular stent or heart assist device, in the circulatory system.

Blood thinning drugs used to control clotting, such as heparin and warfarin, carry serious risks. It is hard to control the amount of drug that will keep a patient from clotting without making the blood too thin. Too much of the drug can cause dangerous bleeding in critical locations, including the brain. Bleeding complications are found in as many as 20 percent to 50 percent of patients receiving some forms of blood contacting devices, such as artificial hearts.

Siedlecki and his colleagues have developed an approach that minimizes the binding force that attaches blood platelets to the surface of the implanted device. At the Penn State Nanofabrication Facility at University Park, the researchers used a soft lithography replication molding technique to create patterns of pillars 700 nm wide, roughly 1/2 to 1/4 the size of the platelets, and 700 nm apart. The tiny pillars limit the contact area between platelets and the material to only about 25 to 30 percent of what it would be in a smooth material. The 700-nm spacing showed a significant decrease in adhesion of platelets at low shear. With further refinements of the material, platelet adhesion was reduced by almost 10-fold, equivalent to the best results that can be achieved chemically.

For the significant number of people who cannot tolerate the anticoagulant drug regimen required for current device implants, a materials solution to blood clotting will come as an important development. Penn State has filed a U.S. patent application on the sub-micron texturing technique.

Christopher A. Siedlecki, is associate professor of surgery and bioengineering, Alan J. Snyder is professor of surgery and bioengineering.

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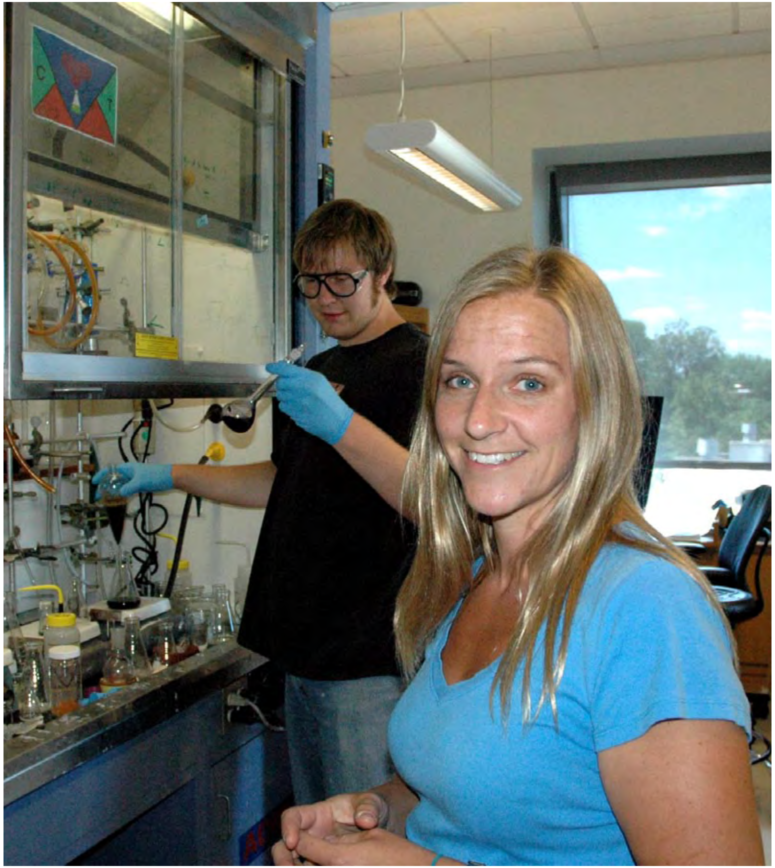

Creating Systems that Mimic Nature

"Ultimately, we want to mimic biology's ability to do things," says **Mary Beth Williams**, associate professor of chemistry.

Her hard materials group focuses on making chemically functional magnetic structures and controlling their motion in solution. These magnetic nanomaterials are less than 20nm in diameter, some potentially small enough to cross the blood/brain barrier, which opens huge areas of application in drug delivery and magnetic resonance imaging (MRI) contrast agents.

Much of this group's efforts go into creating a library of nanoparticles and developing ways of attaching chemical functionalities to the outside of the particle. With this knowledge, it will be possible to attach a particular drug to the particle in predictable ways. In addition to drug delivery, these functionalized particles could be used for separations—attaching to a particular type of molecule in a solution, for instance, to perform bioanalysis—and in high density magnetic storage.

Williams is working with neurosurgeon **Jim Connor** at the Penn State Milton S. Hershey Medical Center to put proteins on particles that target neuroblastomas. His group is using MRI to better image brain tumors with their particles. Her hard materials group has been building models of microfluidic chips and using magnetic fields to control where the particles go. With the hard nanomaterials—functional magnetic particles—Williams sees a real near-term role in bioanalysis, bioseparation, and biomedicine.

Mary Beth Williams, Ph.D., is assocate professor of chemistry, James R. Connor, Ph.D., is university distinguished professor of neurosurgery.

To learn more visit www.mri.psu.edu/research/

Treating Chronic Disease with Ultrasound

Penn State is attacking diabetes on a number of fronts – in the doctor's office, the lab, in what are called lifestyle or behavioral modifications, and, not least, through engineering and technological approaches. Today, diabetes cannot be cured, but it can be controlled. For many diabetics this means careful monitoring of their blood glucose level with painful finger pricks to test for blood sugar and needle injections of insulin as often as four times a day. This combination of finger pricks and injections makes maintenance of their disease a major compliance issue for diabetics.

One answer is being researched in the Therapeutic Ultrasound Applications Laboratory of **Nadine Barrie Smith**. Using a Penn State patented ultrasound technology, Smith has developed a device that she believes is capable of delivering therapeutically effective doses of insulin, and other medications, through the skin barrier without needles. The skin is a formidable barrier to the relatively large molecules in most therapeutic drugs. Low frequency ultrasound creates microbubbles in the skin that disrupt the lipid bilayer of the cell walls, allowing water channels to form that can carry the drug through the stratum corneum, the skin's toughest layer.

"The major drawback in exploiting ultrasound for transdermal drug delivery so far has been the size and lack of mobility of the commercial ultrasound devices," says Smith. The powerful ultrasound transducers developed by Robert Newnham at Penn State are small; an array of 9 transducers measures only about 2 ¼ inches on a side and weighs less than an ounce. An electric current activates a piezoelectric ceramic that produces the ultrasound wave that drives the drug through the skin The process takes about five minutes. In the future, a diabetic might be able to wear a patch against the skin that delivers a drug, like a nicotine patch.

Nadine Barrie Smith, Ph.D., is associate professor in the Department of Bioengineering.

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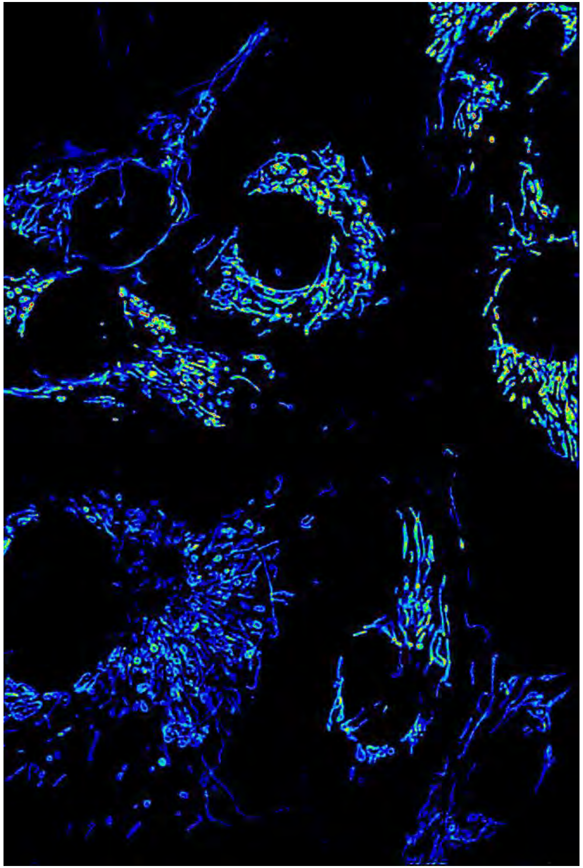

Tracking and Treating Cancer Using Nanoparticles

Medical researchers are looking at any number of new methods to get drugs to specific locations in the body. Some methods are efficient but less safe, while others are safe but often fail to deliver. Now a nontoxic nanoparticle developed by researchers at Penn State University is proving to be an all-around effective delivery system for both therapeutic drugs and the fluorescent dyes that can track their delivery.

An interdisciplinary group of materials scientists, chemists, bioengineers, physicists, and pharmacologists have shown that calcium phosphate particles ranging in size from 20 to 50 nanometers will successfully enter cells and dissolve harmlessly, releasing their cargo of drugs or dye.

The calcium phosphate nanoparticles were developed in the lab of **Jim Adair**, professor of materials science and engineering. The nanoparticles have several benefits other drug delivery systems do not. Unlike quantum dots, which are composed of toxic metals, calcium phosphate is a safe, naturally occurring mineral that already is present in substantial amounts in the bloodstream. "What distinguishes our method are smaller particles (for uptake into cells), no agglomeration (particles are dispersed evenly in solution), and that we put drugs or dyes inside the particle where they are protected, rather than on the surface. For reasons we don't yet understand, fluorescent dyes encapsulated within our nanoparticles are four times brighter than free dyes," says **Thomas Morgan**, a graduate student in the Adair group.

The researchers include graduate students Thomas Morgan, chemistry, Erhan Altinoglu and Amra Tabakovic, materials science and engineering, and former group member, Sara Rouse, Ph.D., in materials; graduate students Hari Muddana and Tristan Tabouillot, bioengineering; graduate student Timothy Russin, physics; graduate student Sriram Shanmugavelandy, pharmacology; Peter Butler, associate professor of bioengineering; the late Peter Eklund, Distinguished Professor of Physics and Materials Science and Engineering; Jong Yun, associate professor of pharmacology; Mark Kester, professor of pharmacology; and Jim Adair, professor of materials science and engineering.

To learn more visit www.mri.psu.edu/research/

Modeling Deadly Viruses

As a post-doc at University of North Carolina, **Coray Colina** investigated a new way of understanding blood coagulation diseases based on the movement of proteins. Using molecular dynamics, she was able to show that a protein called Factor VIIa has to be in contact with another protein called Tissue Factor to stop VIIa's motion long enough for the clotting cascade to begin. The work gave her insight into how the motion of proteins can affect the active sites on proteins and viruses that new drugs are designed to attack, sometimes making the drugs lose their effectiveness.

Now at Penn State, she is doing similar work with biochemist **Craig Cameron** to understand the relationship between movement and function in an enzyme called polymerase, which helps viruses replicate and mutate. The Cameron lab has recently developed a model poliovirus to study how interfering with the speed and accuracy of replication in a virus can cause it to weaken dramatically.

Finding new vaccines to combat deadly viruses such as SARS or West Nile, or viruses that could be used as biological weapons, such as Ebola or smallpox, requires the production of an attenuated virus, a process involving slow, random mutations. With his model virus, professor Cameron hopes to create a universal strategy to speed up vaccine discovery and virus attenuation.

To help in that development, Colina models the polymerase process within the virus to gather information that is not available experimentally. Using x-rays of the frozen crystal structure of the virus, she can simulate the large proteins as they move. To test the validity of her simulation, she compares it to similar but smaller proteins that can be seen in motion using nuclear magnetic resonance imaging. Pulling the two techniques together, Colina can extrapolate the movement of the large proteins.

Coray Colina is associate professor of Materials Science and Engineering and co-director of the Center for the Study of Polymeric Systems. Craig Cameron is Paul Berg Professor of Biochemistry and Molecular Biology.

To learn more visit www.mri.psu.edu/research/

Following Breast Cancer into the Bone

Over the course of a lifetime, more than one in every eight women will be subjected to some form of breast cancer. A quarter of those cancers will metastasize, and a majority of those cancers (60 to 80 percent) will metastasize into the bone. Once in the bone, breast cancer is virtually incurable. Penn State researchers from bioengineering, materials science, and biology are studying the invasion of breast cancer cells into bone using a simple but highly effective device, called a bioreactor, invented by materials scientist **Erwin Vogler**, that for the first time grows highly complex bone tissue outside of the body.

Using the bioreactor, Vogler's student **Genevieve Brown** (senior, bioengineering) watches cancer cells attack bone at the molecular and cellular level in what is called single cell infiltration, in which a pioneer cancer cell degrades and penetrates bone tissue creating a path for other cancer cells to follow in line. This process greatly accelerates cancer colonization of bone. "The bioreactor is such a useful device, because it isolates the interactions that take place just when the cancer cells arrive in the bone," Brown explains. "It allows you to focus on just those first interactions between cancer and the bone."

Mature bone tissue grown in the bioreactor is complex enough to model actual clinical pathologies, unlike cells grown in petri dishes, but not as complex as opaque whole bone. The researchers have already discovered that cancer progresses slower in less mature bone tissue. Next they will attempt to see which drugs are effective at disrupting cancer's invasion of the bone.

Erwin Vogler is professor of materials science and engineering. Genevieve Brown's research is supported by the McNair Scholar's Program and the Pennsylvania Space Grant Consortium, for study of bone loss in microgravity.

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