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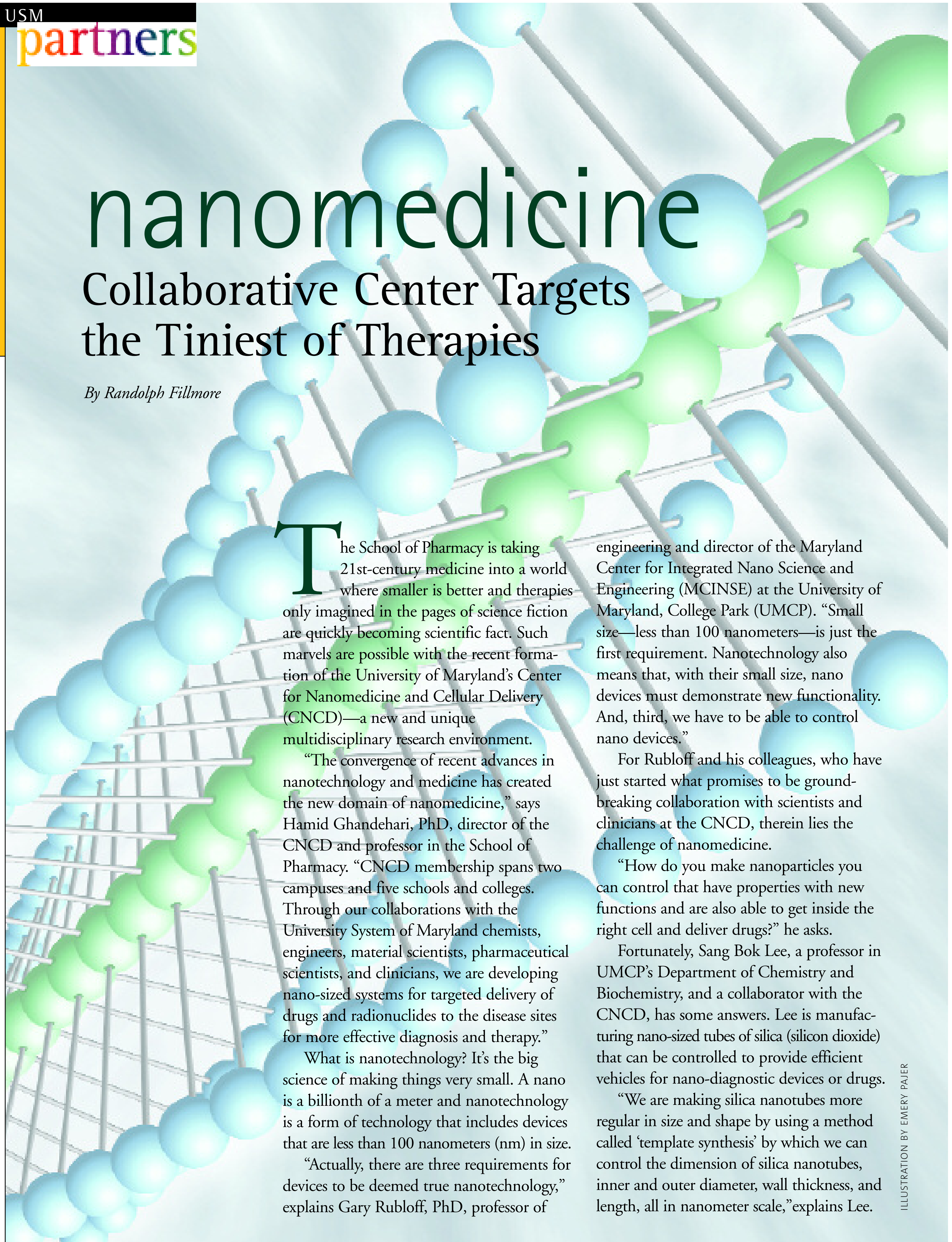

nanomedicine

Collaborative Center Targets the Tiniest of Therapies

By Randolph Fillmore

The School of Pharmacy is taking 21st-century medicine into a world where smaller is better and therapies only imagined in the pages of science fiction are quickly becoming scientific fact. Such marvels are possible with the recent formation of the University of Maryland's Center for Nanomedicine and Cellular Delivery (CNCD)—a new and unique multidisciplinary research environment.

"The convergence of recent advances in nanotechnology and medicine has created the new domain of nanomedicine," says Hamid Ghandehari, PhD, director of the CNCD and professor in the School of Pharmacy. "CNCD membership spans two campuses and five schools and colleges. Through our collaborations with the University System of Maryland chemists, engineers, material scientists, pharmaceutical scientists, and clinicians, we are developing nano-sized systems for targeted delivery of drugs and radionuclides to the disease sites for more effective diagnosis and therapy."

What is nanotechnology? It's the big science of making things very small. A nano is a billionth of a meter and nanotechnology is a form of technology that includes devices that are less than 100 nanometers (nm) in size.

"Actually, there are three requirements for devices to be deemed true nanotechnology," explains Gary Rubloff, PhD, professor of engineering and director of the Maryland Center for Integrated Nano Science and Engineering (MCINSE) at the University of Maryland, College Park (UMCP). "Small size—less than 100 nanometers—is just the first requirement. Nanotechnology also means that, with their small size, nano devices must demonstrate new functionality. And, third, we have to be able to control nano devices."

For Rubloff and his colleagues, who have just started what promises to be groundbreaking collaboration with scientists and clinicians at the CNCD, therein lies the challenge of nanomedicine.

"How do you make nanoparticles you can control that have properties with new functions and are also able to get inside the right cell and deliver drugs?" he asks.

Fortunately, Sang Bok Lee, a professor in UMCP's Department of Chemistry and Biochemistry, and a collaborator with the CNCD, has some answers. Lee is manufacturing nano-sized tubes of silica (silicon dioxide) that can be controlled to provide efficient vehicles for nano-diagnostic devices or drugs.

"We are making silica nanotubes more regular in size and shape by using a method called 'template synthesis' by which we can control the dimension of silica nanotubes, inner and outer diameter, wall thickness, and length, all in nanometer scale," explains Lee.

ILLUSTRATION BY EMERY PAJER

Another beauty of Lee's silica nanotubes is that they are able to carry various attachments—drugs, antibodies, diagnostic devices, or all three. These functions can be incorporated differently between the surfaces—inside and outside of the tubes.

Lee is also enhancing the performance of his silica nanotubes by manufacturing them with magnetic properties. "Magnetic nanotubes (MNTs) have ideal characteristics for drug delivery," says Lee. "Our process involves layering the inner surface of the silica tubes with magnetite (a natural magnet). Drugs are carried inside the nanotube. The outer surface of the nanotube holds targeting moieties—specific segments of a molecule—that can recognize targeted cells. The magnetic properties allow for magnetic resonance imaging capabilities, so the nanoparticles become traceable. The magnetic properties may also help keep the nanoparticles at specific places inside the body, allowing more time for the particles to interact with the targeted cells."

However, using nanostructures to get a therapeutic moiety, a diagnostic device, or a radiological tracking system to a disease site may be just half of the problem. Getting the nano-packaged and nano-delivered drug inside the cell requires other kinds of expertise.

"That's where we come in," says Ghandehari. "Drug delivery scientists are not unlike UPS (United Parcel Service) drivers. Like the UPS driver, we don't necessarily understand very well what's in the package, but we know how to get it where it is needed."

It's no accident that the Center for Nanomedicine and Cellular Delivery resides in the School of Pharmacy—drug delivery scientists are always trying to figure out how to get a drug to the place in the body where it is most needed. While drug delivery scientists at universities throughout the world are exploring the nanotechnology and nanomedicine frontier, the University of Maryland is fortunate, if not unique, says Ghandehari, in assembling a diverse and highly collaborative group of professionals with a focus on nanomedicine. He knows that the path from the bioengineer's bench to the patient's bedside is a long one. He adds that the best nanodevices, coupled with the clearly identified needs of clinicians, leave out one important aspect: The drug must reach its target site with maximum benefit to the patient.

"Targeting a drug to a specific site has enormous advantages for patients, especially those with cancer," says Ghandehari. "Conventional chemotherapy attacks not only tumor cells but others, such as hair cells or white blood cells. If we can target a therapy directly to the tumor, attaching a moiety such as a specific antibody, or a gene that expresses a protein at the target site, toxicity can be minimized. The patient will suffer fewer side effects."

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New, more efficient nanocarriers can play a role in defeating the growing problem encountered with drug-resistant diseases, says Ghandehari. The ideal nanocarrier would not only localize the drug to specific cells, but also move it past the surface of the cells where it might be ineffective due to resistance.

There are other barriers near the end of the nanodevice journey that must be overcome. For example: How can the nano-sized carriers and devices cross what is called the blood-brain barrier—a tight seal of cells that protects the brain? Will it get past the cell wall? If it gets past the cell membrane, can the therapeutic cargo be released into the target site inside the cell such as the nucleus?

According to Natalie Eddington, PhD, chair of the School of Pharmacy's Department of Pharmaceutical Sciences and a member of CNCD, exploiting natural physiology and transport systems already in the body can help accomplish the targeting goal.

"In my lab, we are investigating how the cell membrane can be manipulated, or how we might open the tight junctions between cells, or modify protein structures to enhance transport," she explains.

For Eddington, a specialist in pharmacokinetics—the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body—getting big molecules into the system has never been an easy task. The pre-nano pharmaceutical world has grappled with it for years.

Moving therapies across the blood-brain barrier has remained an especially difficult task. However, suggests Eddington, by exploiting natural processes, such as being able to use the natural receptors in the body, or by modulating the barriers to make them more flexible, the nano-transported therapy can better get to where it is needed.

Peter Swaan, PhD, co-director of the CNCD and vice chair of the School of Pharmacy's Department of Pharmaceutical Sciences, also works on transport issues, and, like Ghandehari and Eddington, is concerned not only with delivery, but also with bioavailability and the biocompatibility of drugs delivered by nanodevices. He emphasizes that nano drug delivery is so new that many questions need to be answered before nanomedicine can move from the laboratory to animal studies and then to phase I clinical trials.

"The Food and Drug Administration (FDA) has approved only a few compounds for use in nanomedicine," points out Swaan. "Biocompatibility is a real issue as nanomedicine particles must be proven safe and nontoxic. Particles with delivery capabilities are just in the experimental stage, so how they will be processed by the body is a compelling question."

This question also brings up the intriguing reality that, according to the FDA, the old drug, placed in a new carrier, becomes a new drug. Thus, new patenting and licensing possibilities are also on the horizon for successful nanomedicine constructs. Consequently, the University's Office of Research and Development (ORD) is keeping a close watch on the groundbreaking work at the CNCD for future patenting and licensing opportunities.

"Patenting and licensing is a long and expensive process," says James Hughes, MBA, ORD vice president. "We pursue commercialization of approximately 30 discoveries each year out of the 110 that we receive. With the assistance of the faculty who serve on our Scientific Review Committee, we evaluate each discovery's patentability, its scientific merit, and finally, the most difficult test, its marketability."

Everyone involved is confident that many useful and marketable new products will emerge from the Center for Nanomedicine and Cellular Delivery after more of the biological barriers are overcome.

For example, Swaan and his colleagues are investigating how microfabricated porous silicon particles can enhance the delivery of insulin across the permeable barrier in the intestine, the barrier so difficult for large molecules to cross.

"The holy grail for treating Type 1 diabetes would be to develop something patients can take orally rather than by injection," says Swaan. "We are working to increase intestinal absorption of water soluble drugs. In our transport studies, porous silicon particles offer an attractive possibility. We found that transport efficiency can be improved tenfold when insulin is delivered by porous silicon particles."

Ghandehari concedes that the bridge from the science lab to the patient's bedside is a long one. But he is confident, based on extensive and important collaborations formed during its first year, that the CNCD is on the right track.

"Our mission is to design, develop and evaluate nano-structures for the delivery of therapeutic and diagnostic agents," he says. "To realize this goal, we are going to help transfer promising delivery systems to the clinic. We are also going to build on our collaborations, recruit new experts and provide multidisciplinary training in nanomedicine."

Ghandehari cites federal initiatives, such as the National Nanotechnology Initiative and the National Institutes of Health (NIH) Roadmap Initiative, and their funding opportunities, as essential to the task.

"The University of Maryland is in a unique position to capitalize on the ongoing research into the development of novel nanoconstructs for use in medicine," he says. "Researchers at the schools of pharmacy and medicine are, likewise, in a unique position to understand nanomedicine from the perspective of interactions with cellular barriers and translate that knowledge and research to the bedside."

The federal agencies with a stake in nanotechnology and nanomedicine include the NIH, FDA, U.S. Department of Defense, National Science Foundation, and the University of Maryland constituent centers and schools—UMB, UMCP, University of Maryland Biotechnology Institute, and others.

"Simply put, our focus is on looking at how nano carriers will interact with cells," concludes Ghandehari. "At the CNCD, we are concerned with transport across barriers such as the GI [gastrointestinal] tract and the blood-brain barrier. We are also focused on biorecognition by target and non-target cell surface receptors—their internalization and subcellular transport and their effect on gene expression."

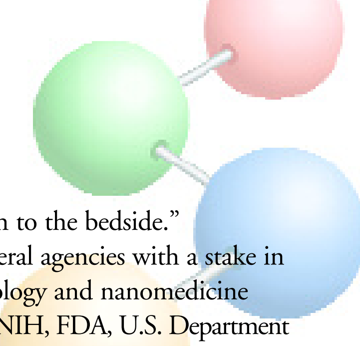
At College Park, Rubloff and his colleagues, along with Lee, describe their "unlimited" enthusiasm for the collaboration with CNCD. Still in its nascent stages, it is an enterprise they already find rewarding.

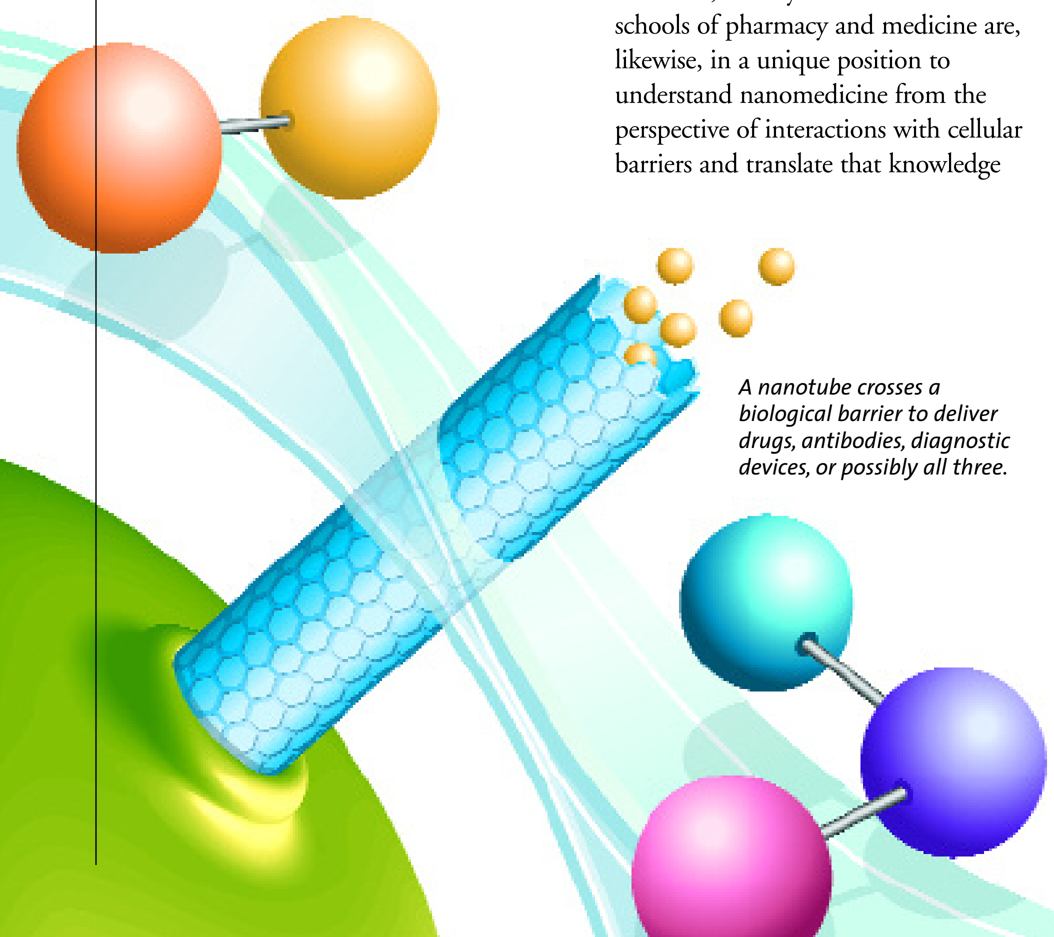
"It's real synergy," says Rubloff with a smile. "The CNCD provides a focus for our efforts. It is hard to find a nano problem that does not need collaboration, and collaboration means developing a broad appreciation for everyone's part."

Ghandehari and Swaan concur. For them, true collaboration means, in real terms, moving the thinking process out of individual "silos" and sharing ideas and problems face-to-face with a wide range of experts. "There is a huge need to establish focal points of multidisciplinary research for the development of functional nanosystems for use in medicine," says Ghandehari. "The CNCD is providing the right environment for maximizing our expertise and nurturing fruitful collaborations."

In September 2005, the Center for Nanomedicine and Cellular Delivery hosted the Third International Nanomedicine and Drug Delivery Symposium, which was attended by an international array of nanomedicine researchers.

www.pharmacy.umaryland.edu/nanomedicine





A nanotube crosses a biological barrier to deliver drugs, antibodies, diagnostic devices, or possibly all three.

ILLUSTRATION BY EMERY PAIER

Collaborators in the Center for Nanomedicine and Cellular Delivery

Natalie Eddington, PhD, professor and chair, Department of Pharmaceutical Sciences, School of Pharmacy

Area of expertise: transport systems and biodistribution

Eddington's research interests include drug delivery across biological membranes, modulation of drug transporters, and investigations on using tight junctions at the blood-brain barrier to enhance drug delivery to the central nervous system (CNS) for the treatment of CNS-related diseases.

Hamid Ghandehari, PhD, director, Center for Nanomedicine and Cellular Delivery; associate professor, Department of Pharmaceutical Sciences, School of Pharmacy

Area of expertise: drug delivery and biomaterials

Ghandehari's research involves developing novel polymeric biomaterials in the nanoscale for targeted delivery of bioactive agents (drugs, genes, radionuclides, imaging agents, etc.) to specific sites in the body. *www.pharmacy.umaryland.edu/faculty/hghandeh*

Sang Bok Lee, PhD, assistant professor, Department of Chemistry and Biochemistry, University of Maryland, College Park

Area of expertise: nanotube synthesis

Lee synthesizes nanomaterials and nanostructures of silica and iron oxide, including fabrication of magnetic nanotubes, for targeted drug delivery and release. The magnetic properties allow for magnetic resonance imaging (MRI) capabilities. *www.chem.umd.edu/faculty/boklee/index.html*

Bruce Line, MD, director, Department of Nuclear Medicine; professor of diagnostic radiology, School of Medicine

Area of expertise: nuclear medicine

Line is developing new approaches to treating solid tumors. He recently developed a novel approach using polymeric nanohybrids to deliver radionuclides directly into tumors to destroy the blood vessels that feed cancer cells.

Gary Rubloff, PhD, professor, Department of Materials Science and Engineering, and the Institute for Systems Research; director, Maryland Center for Integrated Nano Science and Engineering, A. James Clark School of Engineering, University of Maryland, College Park

Area of expertise: semiconductor and materials processing

Rubloff specializes in semiconductor research, including the development of semiconductor materials and processes, characterization, real-time process sensing, equipment design, simulation, and control. His recent efforts involve developing new approaches relevant to semiconductors, and pursuing new areas of bioengineering and nanotechnology. *https://www.isr.umd.edu/gwrubloff/GWR/gwr.php*

John J. Sauk, DDS, MS, associate dean, Department of Diagnostic Sciences and Pathology, Dental School; professor of pathology, School of Medicine and the University of Maryland Marlene and Stewart Greenebaum Cancer Center

Area of expertise: targeted drug delivery

Sauk develops novel targeting moieties that recognize cancer cells (e.g., head and neck squamous carcinoma). When attached to nanocarriers, these devices can target drugs to tumors.

Edward A. Sausville, MD, PhD, professor and associate director, Greenebaum Cancer Center

Area of expertise: translational cancer research

Sausville works to bridge the gap between basic research and preclinical and clinical translation of novel nanomedicines. *www.umm.edu/doctors/edward_a_sausville.html*

Peter Swaan, PhD, associate professor and vice chair, Department of Pharmaceutical Sciences, School of Pharmacy; co-director, Center for Nanomedicine and Cellular Delivery

Area of expertise: transport systems and biodistribution

Swaan's research aims to improve oral bioavailability of pharmacologically active compounds under development, with attention to several transport routes (bile acid and peptide carrier systems), to better understand systems at the molecular level of transport mechanisms. *http://www.pharmacy.umaryland.edu/faculty/pswaan*

Michael Zachariah, PhD, professor of mechanical engineering and chemistry, University of Maryland, College Park; director, Center for NanoEnergetics Research

Area of expertise: nanoparticle design

Zachariah's research interests include nanoparticle science; manufacturing and measurement; microcombustion; energetic materials and reacting flows; fundamentals of gas-phase chemical kinetics; measurement and theory ab-initio computational chemistry; and classical molecular dynamics. *www.chem.umd.edu/faculty/zachariah/index.html*