

nano

a tiny force changing drug delivery—comes to the School of Pharmacy | By Randolph Fillmore

What is smaller than 100 nanometers (a nanometer is one billionth of a meter), able to leap biological cell walls in a single bound, carry therapeutics and diagnostic agents, and yet be biodegradable or nontoxic?

It's your friendly carbon or silica nanotube, polymer construction, liposomal carrier, or other nanosized device yet in development. These super small devices and their big potential to change the drug delivery landscape were the focus of the Third International Nanomedicine and Drug Delivery Symposium. It was held in Baltimore Sept. 26-27 and hosted by the newly launched Center for Nanomedicine and Cellular Delivery (CNCD).

The symposium attracted researchers from around the world to discuss issues in nanomedicine—the brave new world of “smaller-is-better” medicine—represented by the convergence of nanotechnology, biology, and medicine.

“The focus of the symposium was on recent advances in nanomedicine with an emphasis on the delivery of bioactive agents for therapeutic and diagnostic purposes using polymeric biomaterials,” said Associate Professor in the Department of Pharmaceutical Sciences Hamid Ghandehari, PhD. As director of the School of Pharmacy's newest center that celebrated its grand opening on Sept. 20, he heads a new and unique multidisciplinary research environ-

ment. “We received 61 abstracts from researchers in 10 countries and had 150 pre-registered attendees.”

Founded by Ghandehari and Natalie Eddington, PhD, chair of the Department of Pharmaceutical Sciences, and co-directed by Peter Swaan, PhD, associate professor in the Department of Pharmaceutical Sciences, the CNCD spans two University System of Maryland campuses, and five schools and colleges as 23 chemists, engineers, material scientists, pharmaceutical scientists, and clinicians work together to develop nanosized systems for targeted delivery of drugs or radionuclides to disease sites for more effective therapies or diagnoses.

“Our goal is to create a multidisciplinary research environment to provide expertise and foster collaborations for the design, development, and translation into clinic of nanosystems for therapeutic and diagnostic purposes,” Ghandehari told attendees. “To minimize therapeutic side effects or background for imaging diagnostics, we want to localize therapeutic and diagnostic entities at the target site.”

Although the emphasis is on new nanotechnologies with multiple delivery

capabilities, patient-centered efforts are what drive the new center. Those efforts also served as a focus for the international forum.

“We want to use nanomedicine to improve the health of patients with acute and chronic illnesses,” Eddington told attendees after they were welcomed to the University of Maryland School of Pharmacy by Dean David Knapp, PhD. Knapp encouraged attendees to continue their efforts to bring the results of laboratory research into economic development and eventually to the patient's bedside.

Presentations included those on the structure and construction of nano-sized drug delivering vehicles (including liposomal delivery systems and more recently developed delivery systems of silica and gold); improving drug delivery to disease sites; measuring efficacy and effectiveness of drug or diagnostic delivery; the variety of targeted cells and cell organelles and their impact on drug pharmacology; and the types of therapies and diagnostics that can potentially be carried by nano-sized delivery systems.

Delivering the symposium keynote address, Francis Szoka, Jr., PhD, professor of biopharmaceutical science at the University of California, San Francisco, spoke about the potential for the success of gene transfer and gene therapy offered by advances in nanomedicine.

“Gene therapy has been on a roller-coaster,” said Szoka, referring to the unfortunate 1999 death of Jesse Gelsinger,

a volunteer in a gene therapy clinical trial. “Early euphoria about gene therapy dipped to depression, but gene therapy is not dead.”

Briefly discussing nonviral vectors, Szoka suggested that there was a need to provide enough DNA for gene transfer, that gene transfer must be transient, and that the gene product needed to have known pharmacology.

“The technology is developed, but the challenge is to find out how best to use it and for what types of diseases,” he explained. “Gene therapy's story can be improved when we can raise the level of expression, and this requires better nano delivery systems.”

Efforts to develop better and more effective delivery systems struck a chord throughout the symposium as researchers agreed and debated, agreed to disagree, and agreed not to agree on a number of issues at the heart of the new science. For example, lively discussions about the benefits of liposomal carriers versus carriers made of new materials, such as porous gold nanoparticles and silica nanotubes, shaped one facet of the symposium.

“They were healthy discussions,” said Ghandehari.

Some researchers raised questions about the biodegradability and potential toxic effects of the new nanoparticles and nanotubes as compared to established nontoxic liposomal nano-sized delivery systems which, said Teresa Allen, PhD, of the Department of Pharmacology at the University of Alberta, are more flexible and can attach to or penetrate cell walls. Liposomes also have a long, proven clinical safety and efficacy track record as drug transport systems.

In reviewing the development of delivery systems made of new materials, Sang Bok Lee, PhD, of the University of Maryland, College Park, listed the variety of attachments that magnetic silica nanotubes could carry—including drugs and diagnostic devices placed inside and outside of the tubes. Lee explained how the tubes can be capped at each end in such a

way as to have the therapeutic agent released only when it reaches its target.

Patrick Stayton, PhD, of the Department of Bioengineering at the University of Washington, spoke about the necessity for biomolecular machines to change their structural and functional properties in response to environmental signals inside cellular compartments in order to more effectively move genes into the cytoplasm of the target cells.

“Getting into the cell involves better

Kopecek cautioned that “many drugs may act differently at the sub-cellular level” than at the cellular level and that drugs introduced into the cytoplasm, mitochondria, or nucleus by targeted delivery systems may behave differently, depending on the final target area.

Nano systems biology and applications for *in vitro* and *in vivo* diagnostics was the topic addressed by James R. Heath, PhD, professor of molecular and medical pharmacology at UCLA. According to Heath,



Hamid Ghandehari (left), director of the CNCD, welcomes Reza Sadaie, founder and CEO of NovoMed Pharmaceuticals, Inc., to the September symposium.

stability, better transport, and better targeting. To accomplish this, we can take lessons from nature at all levels,” said Stayton, pointing to various membrane-destabilizing methods that might let drugs into the targeted cell.

Speaking on the advantages of polymer-bound drugs, Jindrich Kopecek, PhD, professor of pharmaceutical chemistry and bioengineering at the University of Utah, suggested that future conjugates will have double-targeting capabilities. To accomplish this, Kopecek suggested that we need biocompatible devices that will circulate longer and utilize new target strategies to accompany new mechanisms that involve sub-cellular targeting—in other words, scientists can develop polymer nanocarriers to go places that liposomal delivery systems may not be able to go.

the “picture of cancer is evolving into different and distinct diseases” with the implication that “therapeutics and diagnostics will become increasingly coupled.” Heath asked if, in the future, we can “stratify diseases by pathway and create a window into the biology of disease without having to do invasive procedures. *In vivo* imaging probes, with high affinity and the ability to image metastasis, could be a reality, he said.

“In 10 years it will be possible to look into the serum, measure proteins, get a picture of the evolving health picture and be proactive with therapy based on that picture,” he said.

The symposium ended with the panel discussion: “Nanomedicine: A Global Perspective.” Panelists included Ruth Duncan, PhD, the Centre for Polymer



Pictured at the recent opening of the Center for Nanomedicine and Cellular Delivery (left to right): University President David J. Ramsay, Dean David A. Knapp, Natalie Eddington, Hamid Ghandehari, and Department of Business and Economics Development Secretary Aris Melissaratos.

Therapeutics, Cardiff University; Kazunori Kataoka, PhD, Department of Materials Engineering, University of Tokyo; Alexander Kabanov, PhD, the Center for Drug Delivery and Nanomedicine, University of Nebraska; and Mansoor Khan, PhD, of the U.S. Food and Drug Administration (FDA). Each speaker offered personal insight into the state of nanomedicine and research in Europe, the U.S. and Asia.

Duncan noted that caution is the byword in Europe, where a nanomedicine policy position was recently hammered out by European scientists. She suggested that attendees should “look for the science amidst the hype.”

According to Duncan, European scientists, while looking forward to potential benefits as well as risks, worry about pharmacology issues and want assurances that they will see health care benefits at the end of the pipeline.

Offering a perspective on Asian research and development, Kataoka said that Asian nations and scientists are realizing that they need a “road map” and that scientists and government agencies who don’t normally communicate “now realize they have to.”

“New initiatives are focusing on interdisciplinary fields,” said Kataoka.

Speaking from a U.S. perspective, Kabanov noted the progress in establishing nanomedicine centers at the University of Nebraska and the University of Maryland, Baltimore. He noted that the National Institutes of Health and other

government agencies have been proactive after an initial response that sought to “disconnect” nanomedicine from cellular drug delivery.

“This led to objections from a number of scientists, including myself,” Kabanov said. “After some soul searching at the national level, this situation has stabilized.”

He also noted that the big pharmaceutical companies have, at present, “missed the boat” in terms of biotechnology drug development, allowing smaller biotechnology companies to take the lead.

FDA administrator Khan encouraged attendees to think about the practicality of the products they are developing and keep in mind what will help lead to FDA approval, mentioning that many of the products have already performed well in animal models. He cautioned that less than 10 percent of investigational new drugs survive phase III clinical trials, and that of those survivors only one in three drugs or devices recover their expenses once in the market.

Combination products, such as many of those discussed, will have different approval paths than drugs, he predicted, noting that the FDA was dependent on statutory classifications and will look at primary modes of action.

CNCD Director Ghandehari called the September symposium a success. “This NIH-funded conference was an excellent venue to learn more about the burgeoning area of nanomedicine with focus on drug delivery.”



Casey Jakubowski, Matt Casciano, and Katie Dincher reach Lake Michigan.

Students Biking Across America for Leukemia

Raising money for the Leukemia and Lymphoma Society (LLS), three School of Pharmacy PharmD students completed an 18-day, 1,000-mile bike trip to Chicago. Setting out right after finals, Matt Casciano and Katie Dincher (both Class of 2008), met up with Casey Jakubowski, PharmD '05, in Cumberland, Md. There they spent the night as guests of the Area Health Education Center of Western Maryland. With donations totaling \$1,000 from students and faculty, Vanessa Casciano (Matt’s cousin) raised \$45,000 for the society, and was named Chicago’s LLS Woman of the Year.

The trip didn’t begin auspiciously. A cold rain accompanied their first few days and the hills of Western Maryland sorely tested their physical and mental resolve. A prowling bear at midnight outside their tent in West Virginia, snakes, a lost bull wandering on a trail and many barking dogs contributed to making this a trip they won’t soon forget!

For the initial portion of the journey, the three followed the America Discovery Trail and then created their own route from Cincinnati, Ohio, through Indiana to Chicago. “It was a huge physical task,” says Dincher, “but everyone we met along the way was so friendly and helpful, especially when they learned of our goal. The idea for the trip came from Matt and he was also the most experienced cyclist.”

The trio discovered they could have used more training than they were able to manage in the spring. Averaging 70 miles a day, however, they reached their destination, the Navy Pier in Chicago, five days ahead of schedule. There they were warmly welcomed at a dinner sponsored by the LLS, affording them the chance to meet with those involved in the fundraising campaign. “The trip itself was probably one of the happiest times of my life and I would definitely do it again, if given the chance,” says Matt Casciano.

Laurels

Brian Hose, Class of 2006, was appointed chair of the Maryland Pharmacy Coalition (MPC) in July. “It is a singular distinction for a student pharmacist to lead this coalition of pharmacy organizations,” says Cynthia Boyle, PharmD '96, the outgoing chair. Hose has served on the coalition since the Student Government Association became a member of the group in spring 2004. The coalition works to unite various state pharmacy organizations into a combined voice for pharmacy legislation, and toward the promotion of the profession during American Pharmacy Month, Maryland Pharmacy Legislative Day, and other events throughout the year. “I am looking forward to having an active role in promoting the advancement of our profession through MPC in my final year at the School of Pharmacy and afterward,” says Hose.

Melody Maglinao, a fourth-year PharmD student, was chosen to participate in the Academy of Managed Care Pharmacy/Pfizer Summer Internship Program. Maglinao was one of many contenders chosen for this unique experience. The internship program is designed to introduce participants to managed care pharmacy. The interns must develop a project that results in a professional poster presentation at the Academy’s Fall Educational Conference.

Stuart Cantor, a third-year PhD student in the Department of Pharmaceutical Sciences, had his poster selected as one of “Five Best” at the annual Graduate Research Association of Students in Pharmacy (GRASP) conference at Arnold & Marie Schwartz College of Pharmacy of Long Island University in June.

Kim Raines, a PhD student in the Department of Pharmaceutical Sciences, received the Procter & Gamble Graduate Student Travel Award.

Lisa Durham, a PhD student in the Department of Pharmaceutical Sciences, completed a summer internship with the U.S. Food and Drug Administration.

Ahmed Othman, a PhD student in the Department of Pharmaceutical Sciences, completed a summer internship in pharmacokinetics at GlaxoSmithKline.

Matt Metcalf, a PhD student in the Department of Pharmaceutical Sciences, was awarded a National Research Service Award by the National Institute on Drug Abuse.

Sudipta Ganguly, a PhD student in the Department of Pharmaceutical Sciences, presented a poster at the Respiratory Drug Delivery Europe Symposium held in Paris in May. The symposium attracted more than 300 international participants.

Web site for CNCD is:

www.pharmacy.umaryland.edu/nanomedicine.