

Meeting Report

## Third international nanomedicine and drug delivery symposium

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The University of Maryland–Baltimore’s (UMB’s) Center for Nanomedicine and Cellular Delivery (CNCD) ([www.pharmacy.umaryland.edu/nanomedicine](http://www.pharmacy.umaryland.edu/nanomedicine)), located in the School of Pharmacy, hosted the Third International Nanomedicine and Drug Delivery Symposium on September 26–27, 2005. Organized collectively by Hamid Ghandehari (UMB), Alexander Kabanov (University of Nebraska Medical Center, Omaha, Nebraska), and Kalle Levon (Polytechnic University, Brooklyn, NY), the National Institutes of Health (NIH)–funded symposium attracted more than 150 multidisciplinary researchers from 10 countries who discussed issues in nanomedicine 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 Hamid Ghandehari, director of the new center that celebrated its grand opening September 20, formally initiating a new and unique multidisciplinary research environment based in the School of Pharmacy.

Founded in March 2005, the CNCD spans two University of Maryland campuses, as well as 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.

Dean of the UMB School of Pharmacy David Knapp and Chair of the Department of Pharmaceutical Sciences Natalie Eddington welcomed the attendees and encouraged them to continue bringing research from the laboratory into economic development and eventually to the bedsides of patients. Presentations included research on nanobiomaterials engineering and characterization, subcellular fate and function of nanoconstructs, drug and gene delivery, bioimaging, diagnostics and radiotherapy, targeted delivery of anti-cancer agents, and a panel discussion on global perspectives on nanomedicine.

Delivering the symposium keynote address, Francis Szoka, Jr., professor of biopharmaceutical sciences at the University of California San Francisco, spoke on gene delivery and the potential success of gene transfer and gene therapy.

“For a long time, gene therapy has been a glimmer in the eye of people who do molecular medicine, but it 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 and gene transfer is a reality.”

Briefly discussing viral vectors and nonviral vectors, and whether nonviral vectors could carry enough DNA to accomplish therapy, Szoka suggested that there is a clear need to provide sufficient DNA for gene transfer, that gene transfer must be transient, and that the gene product must have a known pharmacology.

He pointed to the great number of continuing gene therapy trials with viral and nonviral vectors. “The technology is developed, but the challenge is to find out how best to use it and for what types of diseases,” he explained.

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“[The] gene therapy story can be improved when we can raise the level of expression, and this requires better nanodelivery systems.”

Martyn Davies, director of the Laboratory of Biophysics and Surface Analysis at the School of Pharmacy at the University of Nottingham, England, discussed the study of surface structure as a way to better understand the performance and function of biomedical health care devices. He focused on the role of scanning probe microscopy in such analyses and the range of techniques to view surface morphology and study surface interactions, especially surface and drug interactions with DNA, and the mechanical properties of DNA.

Kristi Kiick, Department of Materials Science and Engineering at the University of Delaware (Newark, DE), discussed the application of glycopolymers targeted to multivalent toxins and discussed recombinant methods available in producing polymeric constructs useful in nanomedicine applications. “Our interest is to design artificial sequences that would afford us a chemically neutral background that could be functionalized collectively to present biological ligands commensurate with receptor spaces on surface targets,” explained Kiick. “Ultimately, our goals are not only to understand the macromolecular structure-function relationships that govern the biological responses of materials, but also to produce macromolecules with uniquely optimized properties for applications in biology and medicine.”

Kiick noted that the polymer research community has made important contributions in the last 10 years to the critical area of building scaffolds. “We are trying to combine polymeric strategies with control over biological methods using recombinant techniques to control the presentation of saccharides on scaffolds,” she said.

Tamara Minko, Department of Pharmaceuticals at Rutgers, the State University of New Jersey, discussed cellular hypoxia and the serious tissue damage that can result from it. “Cellular hypoxia complicates the treatment of edema, anemia, myocardial infarction, and hemorrhage,” said Minko, who also discussed liposomal drug delivery and the release inside the cell of doxorubicin, a drug with potential for tumor suppression if not for the problem of entry into the solid tumor where there are no blood vessels.

Nanosystems biology with applications to *in vitro* and *in vivo* diagnostics was the topic discussed by James R. Heath, professor of molecular and medical pharmacology at the University of California–Los Angeles. According to Heath, “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 disease by pathway and create a window into the biology of disease without having to do invasive procedures?” He discussed his group’s research efforts in the identification of relatively large panels of organ-specific secreted biomarkers that can serve for *in vitro* diagnostics.

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

Patrick Stayton, Department of Bioengineering, the University of Washington (Seattle, Washington), spoke about the necessity for polymeric biomolecular machines to change their structural and functional properties in response to environmental signals so as to enter the cytoplasm of targeted cells more effectively. “Getting into the cell involves better stability, better transport, and better targeting. To accomplish this, we can take lessons from nature at all levels,” said Stayton while indicating pH-sensitive polymers containing pyridyl disulfide acrylate comonomers developed in his group’s laboratory.

Martin C. Woodle, chief scientific officer at Intradigm Corporation (Rockville, Maryland), spoke on inhibiting genes to a high degree of selectivity. To be successful, said Woodle, we need to understand medical needs and issues, delivery system aspects, and the chemistry elements within the systems. Addressing cancer treatment issues, Woodle discussed Intradigm’s approach of PEGylated liposome-based short interfering RNA delivery systems containing targeting moieties to tumor angiogenesis.

Sang Bok Lee, Department of Chemistry and Biochemistry, University of Maryland–College Park, discussed his work in synthesizing magnetic silica nanotubes for drug delivery. “We can create different sizes and shapes of nanotubes using various materials,” said Lee. “The template method provides for creating inner and outer surfaces that can easily be modified to carry groups of differentiated functional moieties.” Lee said that the silica nanotubes have well-defined dimensions and have the potential to be targeted and carry drugs and imaging agents. “By combining the attractive tubular structure with magnetic property, the magnetic nanotube (MNT) can be an ideal candidate for the multifunctional nanomaterial toward biomedical applications, such as targeting drug delivery with magnetic resonance imaging capability,” said Lee.

Sonke Svenson, of Dendritic Nanotechnologies (Mount Pleasant, MI), discussed encapsulation into and release of cisplatin and indomethacin from poly(amidoamine) (PAMAM) STARBURST dendrimers. He noted that the encapsulation was successful in dendrimers with amino (NH<sub>2</sub>), hydroxyl (OH), and carboxylate (COO<sup>-</sup>) surfaces with NH<sub>2</sub>>OH>COO<sup>-</sup>. He discussed two examples using encapsulated cisplatin. “The dendrimers deliver five times as much drug to tumors and less to the liver,” said Svenson. “Tumors were reduced by 40%.” He concluded by saying that the dendrimers could be “used in oral drug delivery and enhanced transdermal drug delivery.”

Philip Deshong, Department of Chemistry and Biochemistry, University of Maryland–College Park, discussed exploiting nanomaterials for drug delivery and introduced the idea of a “molecular toolbox” that included solid, porous, hollow, and composite (both surface and embedded)

nanomaterials with novel optical and magnetic properties. “We can control the size, channels, and porosity,” said Deshong. “and we can attach targeting moieties, including sugars and proteins.” He suggested that potential applications include vaccine development, drug delivery, and hyperthermal therapy.

Alexei Bogdanov, Jr., University of Massachusetts (Worcester, Massachusetts) Medical School, discussed *in vivo* imaging techniques and the power of new noninvasive imaging with its strict requirement that nanoimaging agents and probes be biocompatible, biodegradable, and completely amenable to elimination. Bogdanov characterized these three requirements as sufficiently important to preclude consideration by the Food and Drug Administration (FDA) for approval of any newcomer that fails to demonstrate its potential for complete elimination.

In discussing optical imaging, Bogdanov said that “optical imaging has several challenges.” Among those is the depth to which one can “see,” methods for quantifying measurements, and procedures for clinical implementation of advances. He demonstrated that amplification effects based on enzyme-mediated relaxivity changes in paramagnetic chelates are highly feasible *in vitro* and *in vivo*. “The application of these approaches for *in vivo* imaging enables widening the repertoire of potential molecular targets that could be detected with an aid of noninvasive imaging modalities.”

Bruce R. Line, professor of radiology at the UMB, spoke on angiogenesis targeting of radionuclides to solid tumors. “Tumor angiogenesis is common to all solid tumors,” said Line, who tested a copolymer-multivalent conjugate (HPMA-RGD4C) to determine if it showed better targeting than a peptide alone (RGE4C) and if alpha and beta radiotherapy could be delivered by a nanohybrid in sufficient quantity to arrest tumor growth. Results showed that tumor neovasculature could be specifically targeted using the multivalent peptide polymer conjugates of RGD4C.

Mostafa Sadoqi of the St. Johns University Biophotonics Laboratory (Queens, NY), discussed a study to develop a stable, biodegradable, biocompatible, nontoxic, targetable, and long circulating near-infrared fluorescent nanoparticulate system. “The goal is to use the system for drug delivery, controlled drug release, and tumor-targeting applications as well as imaging and noninvasive therapy,” explained Sadoqi. [Two different kinds of poly(dl-lactic-co-glycolic acid)-poly(ethylene glycol) (PLGA-PEG) nanoparticles were engineered by entrapping near-infrared fluorescent and light-activated cell destruction (photosensitizing) agent indocyanine green (ICG), was assessed for effect of the nanoparticles.]

“Compared with the free ICG aqueous solution, the ICG-loaded nanoparticles enhanced stability, intracellular uptake, [and] blood circulation time, and showed potential for photodynamic therapy,” explained Sadoqi.

Speaking on the advantages of polymer-bound drugs, Jindrich Kopecek, distinguished professor of pharmaceutical

chemistry and bioengineering at the University of Utah (Salt Lake City, Utah), reviewed the history of macromolecular therapy and suggested that new targeting strategies are needed. He suggested that in the future, conjugates will have double-targeting capabilities and be required to target subcellular organelles, utilizing the multivalency effect to enhance binding. “To achieve targeted delivery to the subcellular organelles, more understanding in two main areas is needed,” Kopecek said. “First, differences in the mechanism of action of free vs. polymer-bound drugs have to be determined by gene and protein expression arrays, and second, reliable technologies enabling targeting of macromolecular therapeutics to a location different from endosomes have to be developed.”

Teresa Allen, Department of Pharmacology, University of Alberta (Edmonton, Alberta, Canada), said that nano-sized liposomal therapies, in use for decades, are simple, self-assembling, water soluble, flexible in size, and able to attach to or penetrate cell walls via antibodies. They have proven clinical safety and efficacy track records as drug transport systems. “We can improve the therapies offered by the liposomal delivery systems,” she told the attendees while offering data on slow-release experiments on mice showing that slow-release liposomal delivery systems modestly extended the lives of mice with B lymphoma.

Tatiana Bronich, College of Pharmacy and Center for Drug Delivery and Nanomedicine, the University of Nebraska (Omaha, Nebraska), discussed polymer micelles (spherical in shape with a porous core). She outlined their self-assembly abilities, their potential usefulness in gene and drug delivery, and their ability to perform as nanoreactors as well as do bioassays and imaging. She discussed work with incorporating cisplatin into micelle cores. “The cisplatin decreased the size of the micelles, and they were easily internalized by the cells,” she explained. “The carrier is nontoxic and allows for lower toxicity.”

Ashutosh Chilkoti, associate professor of bioengineering at Duke University (Durham, North Carolina), described targeting cancer therapeutics to solid tumors using heat; both heated polymers (to 40°C) and heated tissue were discussed as providing windows of opportunity for facilitated transport across all barriers. Chilkoti suggested that recombinant polymer technology provides the means to engineer the next generation of thermally sensitive nanocarriers.

Hayat Onyuksel, University of Illinois–Chicago, discussed drug-loaded “mixed micelles” as attractive drug carriers. “The efficiency of chemotherapy is hampered by dose-limiting side effects,” said Onyuksel. “This is due largely to the nonspecificity of the drugs. We developed drug-loaded PEGylated phospholipid micelles with vasoactive intestinal peptide for increasing therapeutic effectiveness in cancer chemotherapy and rheumatoid arthritis with lower drug toxicity.”

The symposium ended with a panel discussion titled “Nanomedicine: A Global Perspective.” Panelists included

Ruth Duncan, the Centre for Polymer Therapeutics, Cardiff University (United Kingdom); Kazunori Kataoka, Department of Materials Engineering, University of Tokyo (Japan); Alexander Kabanov, the Center for Drug Delivery and Nanomedicine, University of Nebraska (and one of the organizers of the conference); and Mansoor Khan, of the US FDA. It was moderated by symposium organizers Hamid Ghandehari and Kalle Levon. Each panel speaker offered personal insight into the state of nanomedicine discussion and research in Europe, the United States, and Asia.

Caution is the byword in Europe, where a nanomedicine policy position was recently hammered out by European scientists, said Duncan, who suggested that attendees “look for the science amidst the hype.” According to Duncan, European scientists, while looking forward at potential benefits and risks, worry about pharmacology issues and want assurance that they will see health care benefits at the end of the nanomedicine pipeline. “When a field suddenly becomes fashionable, it is important to keep perspective and, most importantly, distinguish the science fact from science fiction. Although not widely appreciated, progress in the development of nanosized hybrid therapeutics and nanosized drug delivery systems over the past decade has been remarkable,” Duncan said. “Will nanorobots be routinely used to diagnose, locate, and then successfully treat disease, as and when needed? Why not? The notion may seem fantastic, and there are many technical and safety issues to address, but it is noteworthy that many of the drug delivery technologies in everyday use today were dismissed as impractical 30 years ago, being then viewed as science fiction.”

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. “Notably, drug delivery systems and gene delivery has been recognized as the key technology in the field of ‘cell therapy,’ which has recently been decided by Nanotechnology Committee of Japan Ministry of Education, Culture, Sports, Science, and Technology as the guiding concept in nanomedicine research.”

Offering a US perspective, Kabanov described the National Nanotechnology Initiative and that the NIH have

been proactive in funding Centers of Excellence that encompass both drug delivery and nanomedicine research. He also noted progress in establishing nanomedicine centers at the University of Nebraska and the University of Maryland. He cited a recent Lux Research report suggesting that the big pharmaceutical companies may be, at present, “missing the boat” in terms of use of nanotechnology for drug development, allowing smaller nanotechnology companies to take the lead. He encouraged the scientists to “get out of the box” and cross barriers between disciplines “to ensure that nanomedicine is not only a futuristic field, but also a realistic one, with the near-term prospective to improve human health.”

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 demonstrated well in animal models. He cautioned that fewer than 10% 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 on the market.

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

In addition to the invited talks, there were 41 poster presentations from young investigators, with several fellowships made possible by the NIH grant and other sponsors of the conference. “These symposium series were first pioneered by Kabanov and Kataoka in 2003 in Nebraska, followed by capable organization by Kalle Levon of the second symposium at Polytechnic University in New York City in 2004. The increasing number of scientists, especially students and young investigators who participated in the Third Symposium bodes well for the future of this burgeoning area of research,” concluded Ghandehari.

Attendees were invited to the Fourth International Nanomedicine and Drug Delivery Symposium to be held October 8–10 at the University of Nebraska–Omaha Medical Center (<http://cddn.unmc.edu>). For more information about the Third symposium visit: [www.pharmacy.umaryland.edu/nanomedicine](http://www.pharmacy.umaryland.edu/nanomedicine) or contact: [nanomedicine@rx.umaryland.edu](mailto:nanomedicine@rx.umaryland.edu).