2011
NCI Alliance for Nanotechnology in Cancer Annual Bulletin

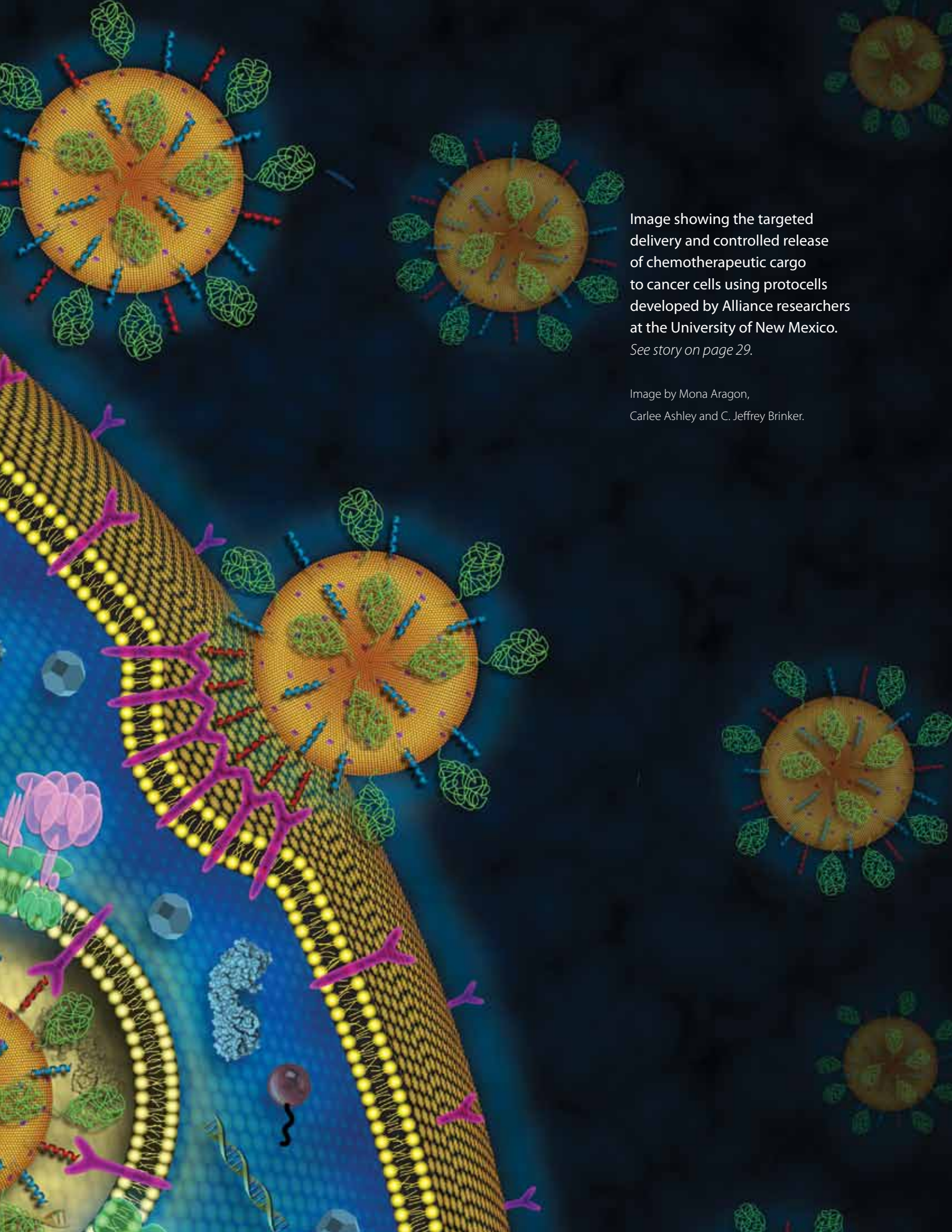

Image showing the targeted delivery and controlled release of chemotherapeutic cargo to cancer cells using protocells developed by Alliance researchers at the University of New Mexico.
See story on page 29.

Image by Mona Aragon, Carlee Ashley and C. Jeffrey Brinker.

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INTRODUCTION

THE NATIONAL CANCER INSTITUTE (NCI) ALLIANCE FOR NANOTECHNOLOGY IN CANCER (Alliance) links physical scientists, engineers, and technologists working at the nanoscale with cancer biologists and oncologists specializing in the diagnosis, prevention, and treatment of cancer. This multidisciplinary program and its infrastructure are specifically designed to rapidly advance new nanotechnology discoveries and transform them into cancer-relevant clinical applications. The Alliance supports fundamental research in nanotechnology and oncology, standardization of nanomaterial characterization methods and translation of new technologies and methods from university laboratories to the clinical environment. The Alliance is also engaged in training the next generation of researchers in cancer nanotechnology.

The research mission of the Alliance is to generate new materials and devices to detect, treat and monitor cancer. Alliance research ranges from a cooperative nanoparticle system that enables *in vivo* communication between nanoparticles in a tumor and circulating nanoparticles for recruitment of contrast enhancement agents and drugs to the tumor site, to synthesis of lipid and polymer based nanocarriers for frontline anticancer agents for improved therapeutic efficacy and reduced toxicity, to a magnetic nanosensor array for multiplexed detection of proteins in serum using magnetic nanoparticles. Alliance supported research currently in clinical trials includes nanoparticle formulations of therapeutic siRNA and chemotherapy drugs and a biobarcode device for the ultrasensitive detection of a cancer biomarker. The first generation of graduate students and post-doctoral researchers supported by the Alliance is now transitioning into faculty positions, where they will continue to expand the scope and reach of cancer nanotechnology research.

The second phase of the Alliance was launched in September 2010 with the award of five year, multi-institutional awards to support research in cancer prevention, diagnosis and treatment. These awards are joined in a national network of research centers, individual projects and training centers. The Alliance is currently comprised of nine Centers for Cancer Nanotechnology Excellence (CCNEs), twelve smaller Cancer Nanotechnology Platform Partnerships (CNPPs), six Cancer Nanotechnology Training Centers (CNTCs), seven Pathway to Independence Awards in Cancer Nanotechnology (K99/R00s) and the Nanotechnology Characterization Laboratory (NCL). The Alliance network fosters a collaborative environment in which members can pull together their resources to bridge the usual gap between physical and biomedical sciences, and then transform the approach to cancer diagnosis and treatment. The Alliance is committed to continue to build a community of multi-disciplinary researchers dedicated to using nanotechnology to advance the fight against cancer.

The CCNEs form the research foundation and core infrastructure of the Alliance. They focus on integrated nanotechnology solutions with practical clinical applications, pursue the aggressive development of these solutions to the pre-clinical stage and provide a path to clinical translation of their new technology. The multi-disciplinary CCNE teams are the main venue for the discovery and tool development toward the application of nanotechnology to clinical oncology.

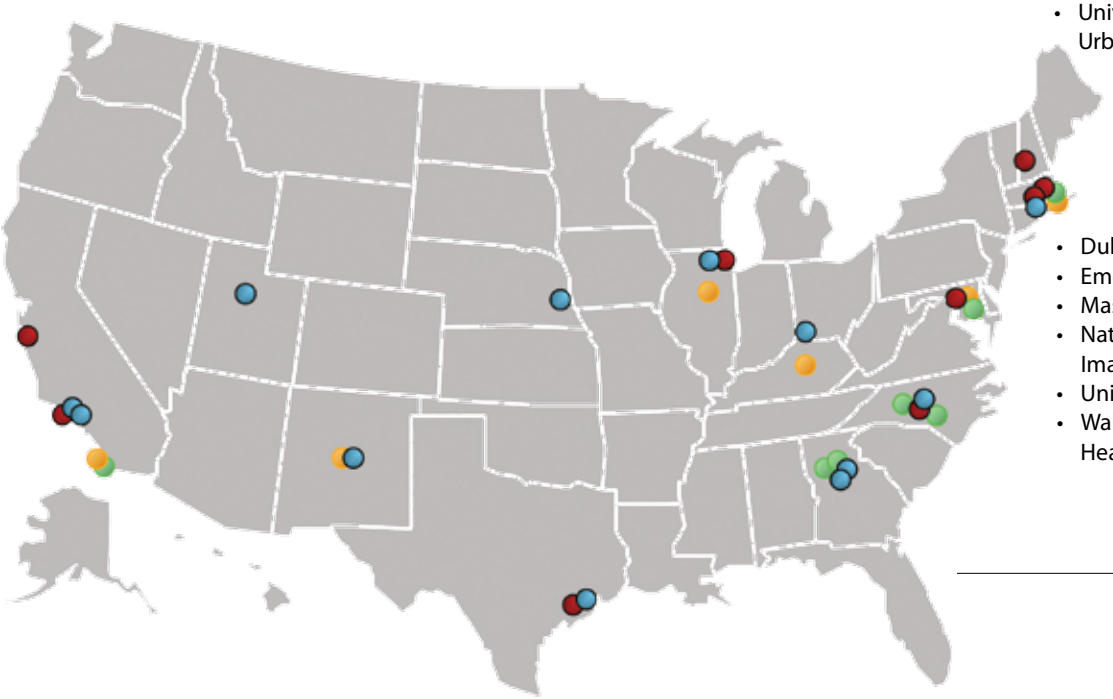
The CNPPs pursue smaller and more focused nanotechnology projects. CNPPs are designed to enable multi-disciplinary team research and transformative discoveries in basic and pre-clinical cancer research. The proposed individual, circumscribed research projects address major barriers and fundamental questions in cancer biology, diagnosis, prevention and treatment of the disease using innovative nanotechnology solutions.

The CNTCs were established to educate and train researchers from diverse fields in the use of nanotechnology-based approaches. They are designed to establish innovative research education programs supporting the development of a multidisciplinary nanotechnology workforce capable of pursuing cancer

research through mentored laboratory-based training as well as participation in dedicated research projects. CNTCs target graduate students and post-doctoral researchers with backgrounds in medicine, biology, and other health sciences as well as in the physical sciences, chemistry, and engineering.

The primary purpose of the Pathway to Independence Award Program is to increase and maintain a strong pool of new, talented investigators focused on research in cancer nanotechnology. The program is designed to facilitate a timely transition from a mentored postdoctoral research position to a stable independent research position with independent research support at an earlier stage than is currently the norm.

Finally, the NCL is an intramural laboratory established by the Alliance to perform standardized characterizations of nanoscale materials developed by researchers from academia, government, and industry and to serve as a national resource and knowledge base for cancer researchers working with nanoparticles and nanoscale materials. The NCL operates under a three-way agreement among the NCI, the National Institute of Standards and Technology (NIST), and the U.S. Food and Drug Administration (FDA). The NCL has developed an assay cascade that serves as the standard protocol for physicochemical, preclinical toxicological and pharmacological characterization of nanoscale materials and devices. NCL also supports efficacy testing of submitted materials. The NCL is speeding the development of nanotechnology-based products for cancer patients, reducing potential risks, and encouraging private-sector investment in cancer nanotechnology.



Centers of Cancer Nanotechnology Excellence

- California Institute of Technology
- Dartmouth College
- Johns Hopkins University
- MIT and Harvard University
- Northeastern University
- Northwestern University
- Stanford University
- The University of Texas Health Science Center
- University of North Carolina

Cancer Nanotechnology Platform Partnerships

- Cedars-Sinai Medical Center
- Children's Hospital Los Angeles
- Emory University (2 Platforms)
- Northeastern University
- Northwestern University
- Rice University
- University of Cincinnati
- University of Nebraska Medical Center
- University of New Mexico
- University of North Carolina
- University of Utah

Cancer Nanotechnology Training Centers

- Boston University
- Johns Hopkins University
- University of California, San Diego
- University of Illinois Urbana-Champaign
- University of Kentucky
- University of New Mexico

Pathway to Independence Awards in Cancer Nanotechnology Research

- Duke University
- Emory University (2 Awards)
- Massachusetts General Hospital
- National Institute of Biomedical Imaging and Bioengineering
- University of California, San Diego
- Wake Forest University Health Sciences

Training in the Alliance: Cancer Nanotechnology Training Centers

BY DOROTHY FARRELL AND MARY SPIRO

LAURA MILLER, UIUC

MARY SPIRO, JHU

Top: M-CNTC trainee Li Tang teaches visitors about gold nanoparticles at the UIUC Engineering Open House.

Bottom: Jude Phillip trains at the Johns Hopkins University CNTC.

To train new scientists and engineers to combat the spread of cancer, the National Cancer Institute's Alliance for Nanotechnology in Cancer recently established the Cancer Nanotechnology Training Center (CNTC) program. The CNTCs have initiated innovative research programs aimed at training graduate students and post-doctoral researchers from diverse scientific and clinical backgrounds. Six CNTCs have been launched across the nation, and each approaches training in its own unique way, drawing from the resources and strengths in place at its home institution.

For example, Johns Hopkins Institute for NanoBioTechnology (INBT) established a pre-doctoral (PhD) training program in Nanotechnology for Cancer Medicine that, together with the institute's successful Nanotechnology for Cancer Medicine postdoctoral fellowship already in existence, comprises the Johns Hopkins Cancer Nanotechnology Training Center (CNTC).

"We are seeking to train people who can develop new nanoscale materials and nanoparticles that will address biological functions related to the growth and spread of cancer at a mechanistic level," said CNTC principle investigator Denis Wirtz, PhD, who also directs the Johns

Hopkins Physical Sciences-Oncology Center and is associate director of INBT.

Anirban Maitra, MD, professor of pathology and oncology at the Johns Hopkins School of Medicine and co-PI of the Hopkins CNTC, said research focuses on identification and preclinical validation of the most cancer-specific nanotechnology based therapies, drawing upon the wealth of knowledge on the cancer genome emerging from CNTC participant scientists such as Kenneth Kinzler, PhD, and Bert Vogelstein, MD, both of Johns Hopkins School of Medicine. "The Johns Hopkins CNTC is uniquely poised to leverage this information for developing molecularly targeted nanotechnology-based tools for cancer therapy," Maitra said.

At the Boston University Cross-Disciplinary Training in Nanotechnology for Cancer (XTNC), PIs Bennett B. Goldberg, PhD and Douglas Faller, MD, PhD, will train pre- and post-doctoral students in projects developing nanotechnology approaches for the detection and diagnosis of cancer. The XTNC emphasizes outreach to the scientific community through workshops and seminars, including "Workshop on Biomolecular Microarrays: Technology, Techniques, Design and Analysis" held in August 2011 and the short course "An Introduction to Cancer Care for Engineers and Physical Scientists," directed by Dr. Jennifer Rosen, MD, in May 2011.

The research focus of the Integrative Cancer Nanoscience and Microsystems Training Center at the University of New Mexico, directed by Janet M. Oliver, PhD, and Abhaya Datye, PhD, is on the development of novel nanoprobes for *in vivo* imaging, *in vitro* cancer detection and drug delivery applications. The CNTC is closely affiliated with the CNPP at the University of New Mexico and the University of New Mexico Cancer Center.

The Midwest Cancer Nanotechnology Training Center (M-CNTC), is located at the University of Illinois Urbana-Champaign. PIs Rashid Bashir, PhD, and Ann Nardulli, PhD, have clinical partners at the University of Illinois, Chicago, the Mayo Clinic, the Indiana University School of Medicine, and Washington University at St. Louis. The M-CNTC will act as a hub for cancer nanotechnology training in the Midwest, with a scientific focus on *ex vivo* diagnostic nanotechnology, *in vivo* imaging, therapeutics and mechanobiology.

The University of Kentucky Cancer Nanotechnology Training Center, under the direction of Bradley D. Anderson, PhD, and B. Mark Evers, MD, will focus training in early detection and diagnosis in lung, colon and ovarian cancer and the treatment of gastrointestinal tumors, lung cancer and gliomas. The UK-CNTC emphasizes educational outreach and improved recruitment of young people to the cancer nanotechnology field. UK-CNTC trainees participate in this outreach to K-12 students through campus activities like Engineering Day.

The UCSD Cancer Nanotechnology Training Center, led by Robert F. Mattrey, MD, and Andrew Kummel, PhD, provides training in cancer nanotechnology to pre-doctoral students, post-doctoral researchers and physicians with tailored tracks for physical scientists/engineers and biological/life scientists and a well-developed plan for minority recruitment and retention.

The NCI Alliance for Nanotechnology in Cancer asserts that solutions to intractable problems of cancer diagnosis and treatment require close collaboration between experts from the biological and physical sciences, engineering and clinical disciplines. Each of the aforementioned CNTCs is rapidly growing, attracting talented students and fellows to participate in this novel mode of doctoral and post-doctoral training. ◆

Dr. Mirkin Goes to Washington

BY GEORGE HINKAL

On July 14, a bipartisan group of six U.S. senators called to order a hearing. This had nothing to do with economic turmoil or steroids in baseball. Rather, the U.S. Senate Subcommittee on Commerce, Science and Transportation requested leading U.S. researchers to serve on a panel to testify on the topic "National Nanotechnology Investment: Manufacturing, Commercialization and Job Creation," to consider the reauthorization of the National Nanotechnology Initiative (NNI). The NNI is an interagency effort of 25 federal agencies that informs and influences the federal budget and planning processes through its

RICK REINHARD

Alliance PI Chad Mirkin (at far left) testifying at a Senate subcommittee hearing on "National Nanotechnology Investment: Manufacturing, Commercialization and Job Creation."

member agencies and through the National Science and Technology Council (NSTC). The NNI advocates policies that will maintain the United States at the forefront of nanotechnological innovation and commercialization. Since its founding in 2000, the NNI has been a catalyst for steering federal funding toward innovative applications of nanotechnology research, development, and policy. Key to enacting these policies are the NNI Signature Initiatives, which seek to focus resources on critical challenges and R&D gaps across national agencies.

The first witness of the distinguished panel to testify was professor Chad Mirkin, principal investigator of the Northwestern University Nanomaterials for Cancer Diagnostics and Therapeutics Center for Cancer Nanotechnology Excellence. Beyond his role as an internationally renowned scientist, Mirkin also serves on the President's Council of Advisors on Science and Technology and contributes to the World Technology Evaluation Center. As a leader in these science policy groups, Mirkin has been central to several key nanotechnology guidance reports including the "Report to the President and Congress on the Third Assessment of the National Nanotechnology Initiative" and "Nanotechnology Research Directions for Societal Needs in 2020." These two documents establish an introspective overview of nanotechnology in the United States as compared to the rest of the world, identify the success and pitfalls over the last decade, and propose directions for development to maintain "U.S. dominance in the decade ahead" scientifically and commercially while being attentive to sustainability and environmental health and safety concerns.

In his testimony, Mirkin highlighted his institute's successes in translating tens of millions of federal research dollars into hundreds of millions of dollars in leveraged venture capital investment and the creation of hundreds of new high-tech jobs with the three nanotechnology companies he founded. This thematic example set the tone for his repeated emphasis on the importance of maintaining funding for basic nanotechnology research while doubling funding for nanomanufacturing and commercialization over the next five years. Tying this to a senatorial question regarding the legacy of U.S. basic research being the catalyst of many international translational efforts, Mirkin noted, "If the United States does not act now and aggressively pursue the development of nanoscience and nanotechnology, we will lose our position as the global leader in this transformative field."

Other panelists echoed the current and future economic impact of nanotechnology for the energy and healthcare fields, including specific discussion of the work of Alliance investigators Jennifer West and Naomi Halas of Rice University, whose engineered nanoparticles absorb light to locally heat and "destroy nearby tumors." This work has garnered venture funding and entered clinical trials. These topics prompted the members of the Senate Subcommittee to reiterate their fascination by and support for the panel's efforts. The senators consistently demonstrated a working knowledge of the field with pointed questions of how nanotechnology could be used to cross biological barriers and specifically target tumors.

Remarkably, although many of the senators expressed interest in health-related applications of nanotechnology, they did not mention such efforts being done by their constituents. Senator Kay Bailey Hutchison (R-TX) highlighted the Texas Consortium for Nanomaterials for Aerospace Commerce and Technology that has been working on ways to power mobile devices. Senator Kelly Ayotte (R-NH) described two companies in New Hampshire, Nanocomp Technologies and Moore

Nanotechnology Systems, that respectively specialize in carbon nanotube synthesis and precision manufacture of advanced optics. While these institutions reflect the ongoing concern regarding economic development resulting from nanotechnology, it may also reflect an opportunity for scientific involvement in the policy arena. Recently, NCI director Dr. Harold Varmus has reiterated this sentiment encouraging scientists to inform the Legislature of the work being done in their state.

Reaching beyond individual technological achievements, the Senate Subcommittee often focused on points of broader political concern. There was a shared sentiment between the Subcommittees and the panelists that nanotechnology presents opportunities to address Science-Technology-Engineering-Mathematics (STEM) education. By integrating nanotechnology themes into K-12 and undergraduate curricula, senators and scientists agree that there can be a better appreciation of the "old disciplines (when taught) in the context of nanotechnology" such that students can "feel a part of the next 100 years not the last 200 years." Of particular interest to the subcommittee was how the government could best facilitate public-private partnerships to leverage funding and accelerate commercialization. In response to this Mirkin returned to his successful model at Northwestern University: build a structure to achieve a "critical mass" of interactions, technology, investment ability, along with business and research talent. These centers create an "international presence (that are) the best places in the world to do this." One facilitative measure mentioned that met with many positive comments from the panel was a bill proposed by Senator Mark Pryor (R-AR), S.256 The American Opportunity Act, which would provide a 25% tax credit to angel investors who target early stage technology companies. When asked whether the existence of so many funding agencies could make it confusing for scientists to find funding for their projects Mirkin noted how large center-based research groups, in particular the NCI CCNEs, are successful models of interagency funding and project successes. However, he also pointedly discussed how many agency funding efforts have lost their focus over the last decade such that the advancing of the NNI "Signature Initiatives (will be) important in getting the agencies to figure out what it is we're to go after, what bets we want to make, to create a theme of excellence in a few areas and develop them extremely well."

Also serving on the panel were Charles Romine, the acting Associate Director of Laboratory programs at NIST, Diandra Leslie-Pelecky, the Director of the West Virginia Nano Initiative, Thomas O'Neal, Executive Director of the University of Central Florida Business Incubation Program, and George McLendon, Howard R. Hughes Provost of Rice University. This U.S. Senate Subcommittee is composed of Chairman John Rockefeller IV (D-WV), Ranking Member Kay Bailey Hutchison (R-TX), Bill Nelson (D-FL), John Boozman (R-AR), Mark Pryor (D-AR), and Kelly Ayotte (R-NH).

If you would like to watch the entire hearing, please visit *http://commerce.senate.gov/public* and search for National Nanotechnology Investment hearing. ◆

PRINT Technology Moves into Clinical Trials

JOSEPH DESIMONE, PH.D.; MARY E. NAPIER, PH.D.; STEPHANIE E. A. GRATTON; AND STUART S. WILLIAMS

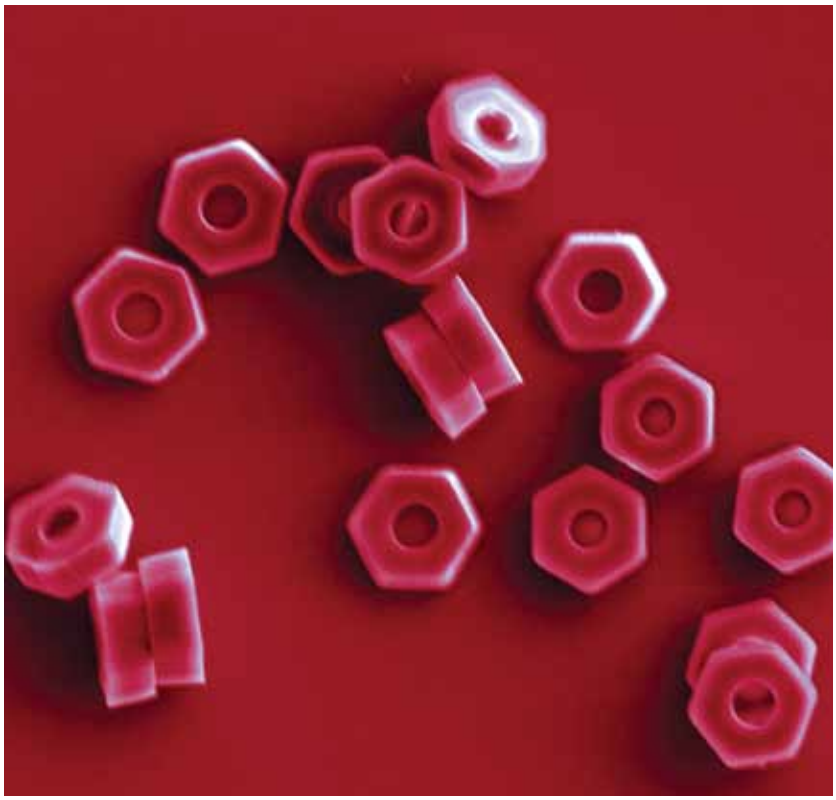


Image illustrating one of the unique shapes and sizes available using PRINT technology.

In 2004 Professor Joseph M. DeSimone founded Liquidia Technologies, Inc. to commercialize the PRINT® (Particle Replication In Non-wetting Templates) technology developed in his laboratory at the University of North Carolina at Chapel Hill. PRINT enables the fabrication of particles with unprecedented precision, uniformity, and control over size, shape, chemical composition, modulus, and surface chemistry. Currently, Liquidia's major focus is on optimizing its manufacturing processes and driving the PRINT technology forward in the area of vaccines. In 2010 Liquidia achieved success in converting PRINT into a GMP compliant process, and recently, the company advanced the development of 80x80x320 nm PLGA-based particles (LIQ001) through GLP toxicology and into Phase 1 clinical studies. GLP safety studies of the product in combination with Fluzone®, a seasonal trivalent influenza vaccine, were completed with no adverse health effects observed. A Phase 1/2a clinical trial of LIQ001+Fluzone involving both young and elderly healthy adults was also recently completed.

Strain specific immune responses generated in pre-clinical studies with

PRINT particles and adsorbed trivalent influenza vaccine suggest that a mixture of the particles and the protein antigen could enhance the immune responses to a variety of vaccines. In addition, the LIQ001 design allows the flexibility to incorporate adjuvants into the particle design. Co-delivery of antigen and adjuvants could allow the tailoring of the immune response for appropriate prevention or treatment of disease. Liquidia's demonstration of PRINT's potential in this light has led to a new partnership, announced in February 2011, with the PATH Malaria Vaccine Initiative (MVI) to explore the use of PRINT to design the next generation of malaria vaccines.

Even more significantly, in March 2011 PRINT's versatility and promise resulted in Liquidia's receipt of the Bill and Melinda Gates Foundation's first-ever equity investment in a for-profit biotech company, totaling $10 million. The investment in Liquidia is the Gates Foundation's first in a for-profit biotech firm, and grew out of a meeting between Bill Gates and DeSimone at an investor's meeting last year. DeSimone explained the PRINT technology, which creates particles using lithographic techniques adapted from those used by the semiconductor industry, during a conversation with Gates. The PRINT template design process enables high volume production of vaccines based on antigens, polysaccharides or nucleic acids, giving Liquidia the flexibility to develop vaccines of different types for distinct targets, a crucial capability for tackling the complex and varied global health landscape. Not only does this investment bolster Liquidia's ability to advance the PRINT technology and its applications in medicine, but it also sets a unique precedent for partnerships among philanthropies, other investors, and for-profit companies with shared goals to tackle pressing global health issues. Overall, Liquidia has raised over $60 million in venture financing and currently employs roughly 60 people in Research Triangle Park, NC.

Liquidia and DeSimone's lab at UNC maintain a strong working partnership in order to further the development of the PRINT technology. In addition to providing molds to researchers in DeSimone's lab to facilitate particle making, Liquidia has helped the UNC team to design and install a single pass, semi-automated, roll-to-roll PRINT machine which came on line in spring 2011. Already, this has significantly enhanced the scale up of PRINT particles for UNC studies. Further, since this line is based on Liquidia's existing roll-to-roll lines, new PRINT-related developments at UNC sponsored through the Carolina CCNE will be more easily transitioned to Liquidia going forward. ◆

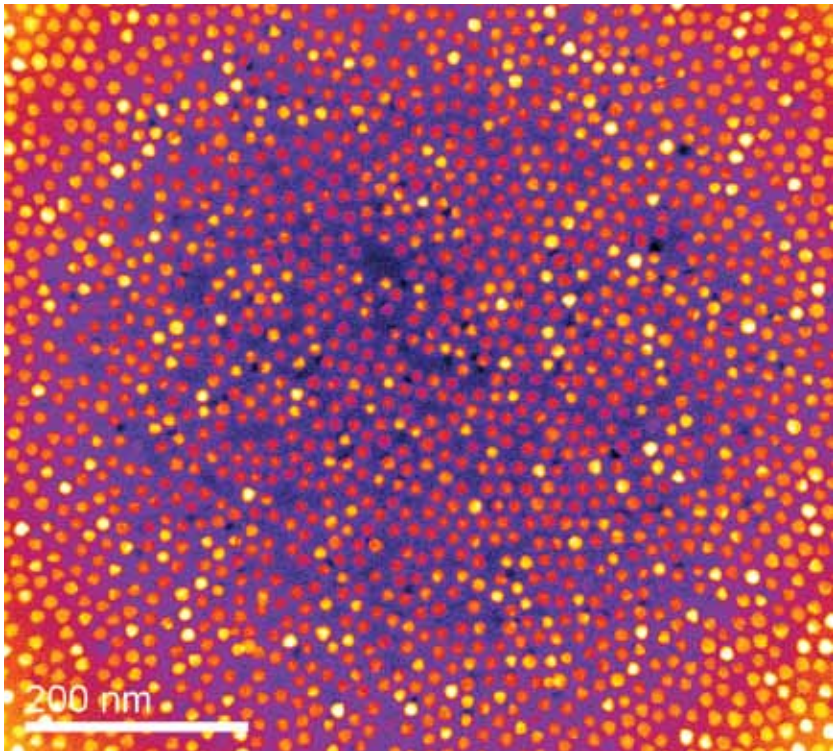
News and Notes

A new Nanomedicine Research Center for Translational has been established at the Department of Neurosurgery at Cedars-Sinai Medical Center. **Julia Ljubimova**, PI of the CNPP "Nanobioconjugate Based on Polymalic Acid for Brain Tumor Treatment," has been named director of the new center.

Vladimir Torchilin and **Mansoor Amiji** of the Center for Translational Cancer Nanomedicine (CTCN) at Northeastern University and **Timothy P. Coleman**, CEO of the CTCN's industrial partner Nemucore Medical Innovations Inc. (NMI), attended a meeting at Fox Chase Cancer Center (FCCC) on July 13, 2011 to discuss clinical development of nanomedicine for recurrent cancer. After opening remarks from **Jonathan Chernoff** of FCCC and a talk from Coleman on the role of NMI in cGMP scale up of nanomedicine production, FCCC members **G. P. Adams**, **A. J. Olsznaski** and **Z. Yang** presented their experience with developmental therapeutics and Phase I clinical trials, as well as ongoing research on the use of brain stem cells for the treatment of glioblastoma. Torchilin then highlighted the promises of liposome based drug delivery systems and drug nanocolloids using layer-by-layer (LBL) technology and Amiji shared some recent accomplishments in the field of multi-drug resistant cancer treatment using nanoemulsion and polymeric drug delivery systems. The meeting concluded with a discussion of potential collaborating projects and a poster session showcasing recent developments in cancer therapeutics.

Jeremy Edwards, a mentor in the University of New Mexico CNTC, received one of ten NIH "Revolutionary Genome Sequencing Technologies – The $1000 Genome" grants. The three year $2.8 million award will support development of microfluidics-based fast, inexpensive whole genome sequencing technology.

The **Northwestern University CCNE** was awarded a $2.1 million Lever Award from the Chicago Biomedical Consortium to build infrastructure that enables the investigation of nanomaterials in new collaborations that would otherwise be beyond the capacity of NU-CCNE. This includes the establishment of three "foundries" and support for the necessary technical personnel who are dedicated applications specialists who will assist with model development in collaborators' labs.



ANDREW SMITH, HONG YI, SHUMING NIE

Researchers at the UNC CCNE led by **Otto Zhou** have successfully designed and manufactured a prototype stationary digital breast Tomosynthesis scanner by combining the strength of their unique carbon nanotube based x-ray source array technology with Hologic's advanced detection system. The UNC prototype is aimed at improving early detection of breast tumors by overcoming limitations of current digital tomosynthesis scanners, such as long scanning time, patient and x-ray source motion blurring and low sensitivity for micro-calcification.

Zhou's group has also created a compact Microbeam Radiation Therapy (MRT) system using carbon nanotube field emission technology (the first new way to create X-rays in 100 years). MRT irradiates cancerous tissues while producing minimal injury to healthy tissue and will open new possibilities in treating currently incurable or hard to treat malignancies. It has previously been generated only by using huge synchrotron facilities, which are available only in a few places around the world. The UNC technology was selected as Therapy Best in Physics in the 2011 American Association of Physicists in Medicine (AAPM) meeting and will be featured in the *AAPM Hot Topic* by the meeting press.

Hui Mao, co-PI with **Lily Yang** of the CNPP "Theranostic Nanoparticles for Targeted Treatment of Pancreatic Cancer" located at Emory University, has developed a new ultrashort echo time MR imaging approach that allows sensitive detection of magnetic iron oxide nanoparticles using T_1-weighted positive or bright contrast enhancement. The paper describing this work, "T_1-weighted Ultrashort Echo Time Method for Positive Contrast Imaging of Magnetic Nanoparticles and Cancer Cells Bound with the Targeted Nanoparticles," was published in the *Journal of Magnetic Resonance Imaging*, 2011; 33:194-202.

The cover of the January 2011 issue of *Nature Biotechnology* featured work from the lab of **Steven Quake** of the Stanford CCNE-T. The paper, "Whole-genome Molecular Haplo-Typing of Single Cells," describes a microfluidic device capable of isolating each of the sister chromatids from single cells, allowing whole-genome haplotyping by sequencing and arrays. This capability is important, because the two copies of each chromosome in a diploid organism may contain different patterns of genetic variants.

Shan Wang, co-PI of the Stanford CCNE-T, published a paper in *Nature Nanotechnology*, "Quantification of Protein Interactions and Solution Transport Using High-Den-

sity GMR Sensor Arrays," that was highlighted by the Stanford Report and covered widely in trade journals. In this work, magnetic nanosensors were used to measure the binding kinetics of various proteins with high spatial and temporal resolution. The ability to monitor these reactions on a dense sensor array (over 100,000 sensors per cm^2) has great potential in both proteomic analysis and drug development.

Mauro Ferrari and **David Gorenstein**, co-PIs of the Texas Center for Cancer Nanomedicine (TCCN), published their paper "Thioaptamer Conjugated Liposomes for Tumor Vasculature Targeting" in *Oncotarget*. The system described in the work can be expanded to test combinations of thioaptamer and liposome for targeted delivery of therapeutics and imaging agents to multiple cancer types.

Anil Sood and **Gabriel Lopez-Berestein**, fellow co-PIs at the TCCN, published a paper titled "Targeted Delivery of Small Interfering RNA Using Reconstituted High-Density Lipoprotein Nanoparticles" in the April issue of *Neoplasia*. The paper describes work done at the TCCN on the highly efficient delivery of siRNA based on receptor mediated scavenging of the HDL nanoparticles, which are biocompatible.

Ralph Weissleder, co-PI of the MIT-Harvard CCNE, published a paper, "Micro-NMR for Rapid Molecular Analysis of Human Tumor Samples," in *Science Translational Medicine* describing a handheld NMR device used to analyze fine needle biopsies from patients suspected of having malignant abdominal tumors. The device diagnosed cancer with 96 percent accuracy in less than one hour, compared to three days for traditional histopathology.

Wenbin Lin, PI of the CNPP "Nanoscale Metal-Organic Frameworks for Imaging and Therapy of Pancreatic Cancer" has developed a contrast agent for identifying tumor cells *in vitro*, based on phosphorescent ruthenium complex incorporated into nanoparticles of a metal–organic coordination polymer, which allows an extraordinarily high level of dye loading. The work was published in the April 2011 issue of *Angewandte Chemie* International Edition, in an article titled "Phosphorescent Nanoscale Coordination Polymers as Contrast Agents for Optical Imaging."

Julia Ljubimova's group has demonstrated that nanoparticles made from the slime mold polymer polymalic acid can successfully target brain and breast tumors and are safely tolerated in animal studies. The initial work, published in the October 2010 issue of the *Proceedings of the National Academy of Sciences* in the article "Inhibition of Brain Tumor Growth by Intravenous Poly (β-L-malic acid) Nanobioconjugate with pH-dependent Drug Release," detailed the delivery of antisense oligonucleotides to block production of laminin-411, a protein that promotes the growth of tumor vasculature in glioblastoma. The polymer backbone contained molecules to help the nanoparticles cross the blood-brain and brain-tumor barriers, along with an endosomal escape unit to assure drug delivery to the cell cytoplasm. The polymalic acid nanoparticles were also used to deliver the targeted therapeutic Herceptin to breast tumors, along with an antisense oligonucleotide that greatly reduces a breast cancer cell's production of the *HER2/neu* protein. The article detailing that work, "Polymalic Acid-Based Nanobiopolymer Provides Efficient Systemic Breast Cancer Treatment by Inhibiting both Her2/neu Receptor Synthesis and Activity," was published in the February 2011 issue of *Cancer Research.*

Plant-derived polyphenols such as curcumin hold promise as a therapeutic agent in the treatment of chronic liver diseases, but poor aqueous solubility results in equally poor bioavailability.

Researchers in the laboratory of **Anirban Maitra**, professor of pathology at the Johns Hopkins

School of Medicine and affiliated with the Johns Hopkins CCNE have developed a polymeric nanoparticle formulation of curcumin called NanoCurc™ that overcomes this pitfall. NanoCurc™ results in sustained intrahepatic curcumin levels that can be found in both hepatocytes and non-parenchymal cells, as well as markedly inhibited carbon tetrachloride-induced liver injury, production of pro-inflammatory cytokines and fibrosis. It also enhances antioxidant levels in the liver and inhibits pro-fibrogenic transcripts associated with activated myofibroblasts. The team also showed that NanoCurc™ directly induces stellate cell apoptosis *in vitro*. These results suggest that NanoCurc™ might be an effective therapy for patients with chronic liver disease. The article describing this work, "A Polymeric Nanoparticle Formulation of Curcumin (NanoCurc™) Ameliorates CCl(4)-induced Hepatic Injury and Fibrosis Through Reduction of Pro-Inflammatory Cytokines and Stellate Cell Activation," appeared in the June 20, 2011 issue of the journal *Laboratory Investigation*.

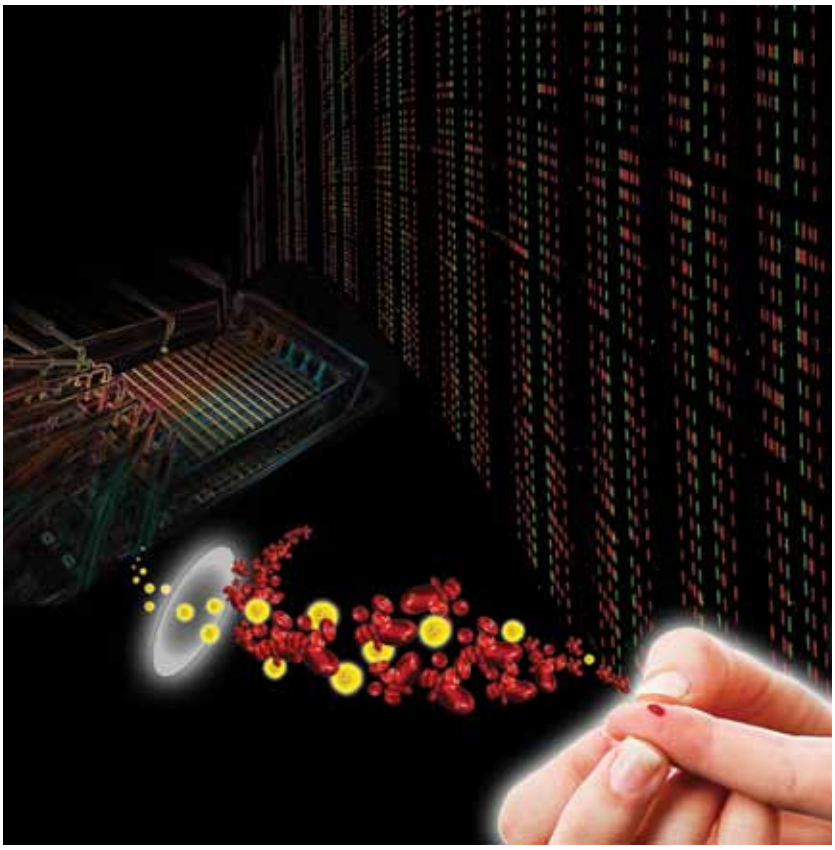
The Anirban Maitra group also has published "Restitution of Tumor Suppressor microRNAs Using a Systemic Nanovector Inhibits Pancreatic Cancer Growth in Mice" in the May 27, 2011 issue *Molecular Cancer Therapy*. The article details a promising lipid-based nanoparticle (nanovector) they have developed for systemic delivery of miRNA expression vectors to cancer cells. The aim of the delivery system is to restore misexpressed microRNAs common in human cancer, especially pancreatic cancer, that are downregulated, specifically tumor suppressor miRNAs. The plasmid DNA-complexed nanovector, approximately 100nM in diameter, showed no apparent histopathological or biochemical toxicity with intravenous injection. Two miRNA candidates known to be downregulated in the majority of pancreatic cancers were selected for nanovector delivery: miR-34a (a component of the p53 transcriptional network that regulates cancer stem cell survival); and the miR-143/145 cluster, which together repress the expression of KRAS2, and its downstream effector Ras-responsive element binding protein-1. Systemic intravenous delivery with either miR-34a or miR-143/145 nanovectors inhibited the growth of MiaPaCa-2 subcutaneous xenografts. The effects were even more pronounced in the orthotopic (intra-pancreatic) setting, when compared to a "mock" nanovector delivering an empty plasmid. Tumor growth inhibition was accompanied by increased cell death and decreased proliferation. miRNA restitution was confirmed in treated xenografts by significant upregulation of the corresponding miRNA, and significant decreases in specific miRNA targets.

Jeff Bulte, professor of radiology at Johns Hopkins School of Medicine and affiliated with the Johns Hopkins CCNE, published "Synthesis of Magnetic Resonance, X-ray– and Ultrasound-Visible Alginate Microcapsules for Immunoisolation and Noninvasive Imaging of Cellular Therapeutics" in the July 14, 2011 issue of *Nature Protocols*. The article details a 3-step process for creating dual layer microcapsules capable of encapsulation and immunoisolation of cellular therapeutics. The microcapsules are easily made visible for X-ray, ultrasound or magnetic resonance and could be used for non-invasive tracking of cell therapy in a clinical setting. The microcapsules can be rendered visible during the first step by adding contrast agents to the primary alginate layer. These contrast agents include superparamagnetic iron oxide for detection by magnetic resonance imaging (MRI), radiopaque agents barium or bismuth sulfate for detection by X-ray modalities; or perfluorocarbon emulsions for trimodal detection by MRI, X-ray and ultrasound imaging. The entire synthesis takes just two hours. ◆

Improving Health Assessments with a Single Cell

from the NSBCC at the California Institute of Technology

BY JOE ALPER



COURTESY OF NSBCC

A panel of proteins is measured from blood collected from patients using the microfluidic barcode chip developed by researchers at the NSBCC

There's a wealth of health information hiding in the human immune system. Accessing it, however, can be very challenging, as the many and complex roles that the immune system plays can mask the critical information that is relevant to addressing specific health issues. Now research led by scientists from the California Institute of Technology has shown that a new generation of microchips developed by the team can quickly and inexpensively assess immune function by examining biomarkers—proteins that can reflect the response of the immune system to disease—from single cells.

"The technology permits us for the first time to quantitatively measure the levels of many functional proteins from single, rare immune cells," says James Heath, the principal investigator of the Nanosystems Biology Cancer Center. "The functional proteins are the ones that are secreted by the cells, and they control biological processes such as cell replication and inflammation and, specific to our study, tumor killing."

In 2008 Heath led the development of a "barcode chip" that, using just a pinprick's worth of blood, could measure the concentrations of dozens of proteins, including those that herald the presence of diseases like cancer and heart disease. This latest single-cell barcode chip

(SCBC) device builds upon the success of that initial design, which is currently being utilized in diagnostic medical testing of certain cancer patients.

The researchers tested the chip by measuring a cancer patient's response to a type of cell-based immunotherapy designed to target and kill tumor cells. The only way to know if the therapy is doing its job is to measure many proteins at the same time from the individual cells that were targeting the tumor. The SCBC aced this test, generating readouts of a dozen secreted biomarkers—each of which represented a distinct cell function—and taking those readings from about a thousand single cells simultaneously.

The team was able to conduct a proof-of-concept study by looking at samples from a melanoma patient participating in the immunotherapy trials and comparing those results to similar samples from three healthy subjects. According to the investigators, the technology is minimally invasive, cost-effective, and highly informative. The goal is to help physicians closely track the effectiveness of a therapy and to rapidly alter or switch that therapy for the maximum benefit of the patient.

The next step for the team will be to systematically apply the technology to clinical studies. The researchers have already begun to test the technology in additional patient populations and to combine the SCBC with existing assays in order to get a more comprehensive picture of a therapy's efficacy. In fact, the same study that showed the microchip's efficacy is already helping the researchers better evaluate the specific cancer immunotherapy trial from which the patient in the study was drawn.

"We are doing these same types of measurements on similar patients but at a significantly higher level of detail, and at many time points over the course of the cancer immunotherapy procedure," explained Heath. "It is helping us put together a 'movie' of the patient's immune system during the therapy, and it is providing us with some very surprising but also valuable insights into how the therapy works and how we might work with our UCLA colleagues to improve it."

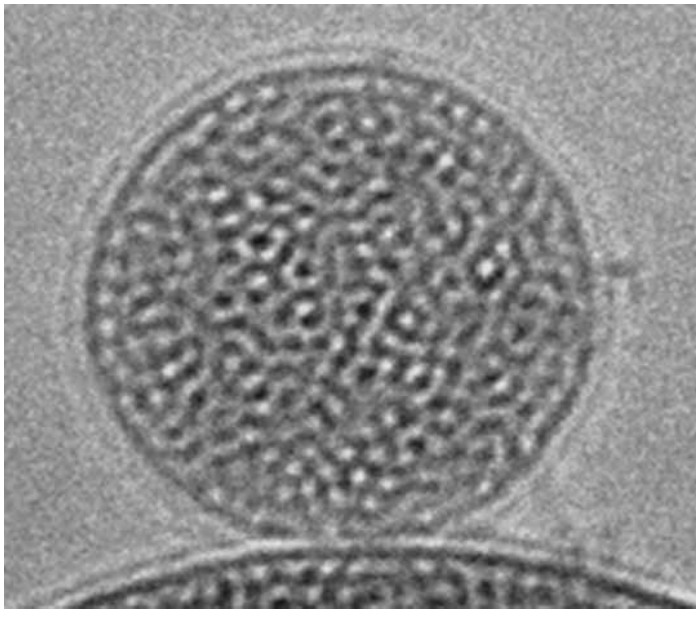
"Application of this technology provides an unprecedented understanding of the human immune system by allowing an efficient and multiplexed functional readout of immune responses using limiting numbers of lymphocytes," says Antoni Ribas, a colleague of Heath's who led the clinical trial portion of the study at UCLA's Jonsson Comprehensive Cancer Center.

This work was detailed in a paper titled, "A Clinical Microchip for Evaluation of Single Immune Cells Reveals High Functional Heterogeneity in Phenotypically Similar T Cells," in the June 2011 issue of *Nature Medicine*. ◆

Nanoparticles Deliver Drug Cocktails to Tumor

from the University of New Mexico CNPP

BY JOE ALPER



COURTESY OF C. JEFFREY BRINKER

Cryogenic TEM image of a protocell, showing nanoporous core and supported lipid bilayer.

Melding nanotechnology and medical research, researchers from Sandia National Laboratories, the University of New Mexico, and the UNM Cancer Research and Treatment Center have produced an effective strategy that uses nanoparticles to treat tumors with a mélange of anticancer agents. This strategy relies on using silica nanoparticles honeycombed with cavities that can store large amounts and varieties of drugs loaded inside a lipid-based nanoparticle known as a liposome.

"The enormous capacity of the nanoporous core, with its high surface area, combined with the improved targeting of an encapsulating lipid bilayer, permits a single 'protocell' loaded with a drug cocktail to kill a drug-resistant cancer cell," says team leader Jeff Brinker, who is the co-principal investigator of the University of New Mexico Cancer Nanotechnology Platform Partnership. "That's a millionfold increase in efficiency over comparable methods employing liposomes alone — without nanoparticles — as drug carriers."

The nanoparticles and the surrounding cell-like membranes formed from liposomes create what the researchers call a protocell: the membrane seals in the deadly cargo and is modified with targeting molecules that bind specifically to re-

ceptors overexpressed on the cancer cell's surface. The nanoparticles provide stability to the supported membrane and release the therapeutic cargo within the cell.

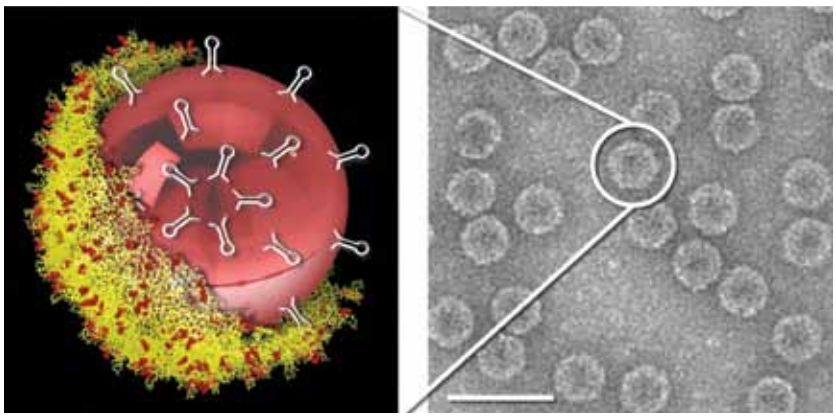
A current Food and Drug Administration-approved nanoparticle delivery strategy is to use liposomes themselves to contain and deliver the cargo. In a head-to-head comparison of targeted liposomes and protocells with identical membrane and peptide compositions, Brinker and colleagues report that the greater cargo capacity, stability, and targeting efficacy of protocells leads to a drug formulation that is much more effective at killing human liver cancer cells.

Another advantage to protocells over liposomes alone is that it is far easier to load drugs into the porous nanoparticles than it is with liposomes. Loading drugs into liposomes requires complex strategies that boost the cost of making those formulations. In contrast, loading the porous nanoparticles can be done by simply soaking the nanoparticles in a drug solution. The liposome then serves as a shield that restricts toxic chemotherapy drugs from leaking from the nanoparticle until the protocell binds to the cancer cell. This means that only low levels of anticancer agents, at most, escape into the blood stream or attack other cells.

The UNM researchers have also developed a parallel nano-platform using virus-like particles (VLPs) of bacteriophage MS2. These VLPs are protein capsids that are highly uniform in size and shape and capable of encapsulating large amounts of cargo in their interior. The ability of the VLPs to spontaneously self-assemble in the presence of nucleic acids further allows loading with siRNA or RNA labeled drugs or imaging agents. The ease of modifying the VLP surface through either chemical conjugation or genetic engineering of the protein envelope makes the VLPs ideal candidates for targeted delivery of therapeutics to cancerous tissue.

The researchers tested the suitability of VLPs for targeted cancer therapy by modifying the VLP surface with a peptide that targets human hepatocellular carcinoma (HCC). The peptide modified VLPS were then loaded with siRNA, a cocktail of chemotherapy drugs or a protein toxin and delivered to both HCC and control cells. The VLPs were able to kill the HCC cells or knock down target gene expression with high efficiency, while leaving control cells relatively untouched, indicating that the peptide targeting scheme is effective.

The protocell work was published in the May 2011 issue of *Nature Materials*, in an article titled "The Targeted Delivery of Multi-Component Cargos to Cancer Cells by Nanoporous Particle-Supported Lipid Bilayers." The VLP work was published in *ACS Nano*, volume 5 number 7, in an article titled "Cell-Specific Delivery of Diverse Cargos by Bacteriophage MS2 Virus-Like Particles." ◆



COURTESTY OF C. JEFFREY BRINKER

TEM image and schematic of virus like particles. The TEM image is of siRNA loaded VLPs. The scale bar is 50 nm.

Nanoparticles Working in Harmony

from the MIT-Harvard CCNE

BY JOE ALPER

For decades, researchers have been working to develop nanoparticles that deliver cancer drugs directly to tumors, minimizing the toxic side effects of chemotherapy. However, even with the best of these nanoparticles, only about one percent of the drug typically reaches its intended target. Now, a team of researchers from MIT, the Sanford-Burnham Medical Research Institute, and the University of California at San Diego (UCSD) has designed a new type of delivery system in which a first wave of nanoparticles hones in on the tumor, then calls in a much larger second wave that dispenses the cancer drug. This communication between nanoparticles, enabled by the body's own biochemistry, boosted drug delivery to tumors by more than 40-fold in a mouse study.

This new strategy could enhance the effectiveness of many drugs for cancer and other diseases, say the investigators. This multi-institutional team was led by MIT's Sangeeta Bhatia, who is also a member of the MIT-Harvard Center of Cancer Nanotechnology Excellence. Michael Sailor of UCSD and Erkki Ruoslahti of the Sanford Burnham Institute, both senior members of the Alliance for Nanotechnology in Cancer, also participated in this study.

Bhatia and her collaborators

drew their inspiration from complex biological systems in which many components work together to achieve a common goal. For example, the immune system works through highly orchestrated cooperation between many different types of cells. In this case, the team's approach is based on the blood coagulation cascade—a series of reactions that starts when the body detects injury to a blood vessel. Proteins in the blood known as clotting factors interact in a complex chain of steps to form strands of fibrin, which help seal the injury site and prevent blood loss.

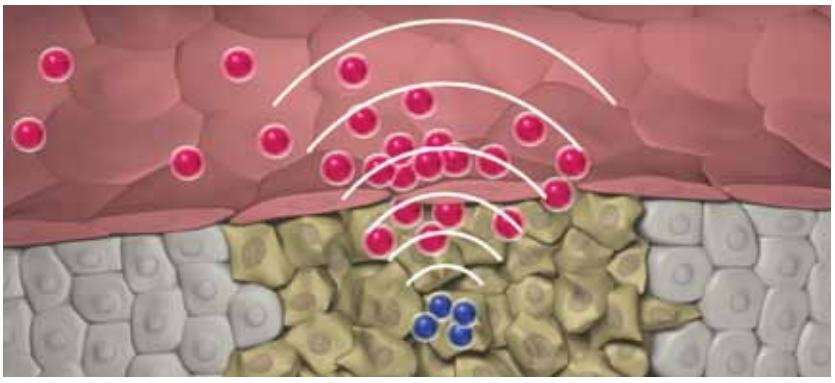
To harness the communication power of that cascade, the researchers needed two types of nanoparticles—signaling and receiving. Signaling particles, which make up the first wave, exit the bloodstream and arrive at the tumor site via tiny holes in the leaky blood vessels that typically surround tumors (this is the same way that most targeted nanoparticles reach their destination). Once at the tumor, this first wave of particles provokes the body into believing that an injury has occurred at a tumor site, either by emitting heat or by binding to a protein that sets off the coagulation cascade. Gold nanorods activated by external stimulation with a near infrared laser were used to induce coagulation by heating, and an engineered, tumor-targeted version of a human protein was used to test biological induction of coagulation signaling.

Receiving particles are coated with proteins that bind to fibrin, which attracts them to the site of blood clotting. Those second-wave particles can carry a drug payload, which they release once they reach the tumor, or have some ability to locate tumors, so the system can be used for therapeutic or diagnostic applications. Two types of clot-targeted receiving nanoparticles were investigated in this work, a model therapeutic module and a model imaging agent. The therapeutic module consisted of liposomes loaded with the chemotherapy drug doxorubicin. The imaging agent was magnetofluorescent iron oxide nanoworms, previously developed by the team for use in magnetic resonance imaging applications.

In a study of mice, one system of communicating nanoparticle systems delivered 40 times more of the widely used anticancer agent doxorubicin than did non-communicating nanoparticles. The researchers also saw a correspondingly amplified therapeutic effect on the tumors of mice treated with communicating nanoparticles.

To pave the path for potential clinical trials and regulatory approval, Dr. Bhatia and her colleagues are now exploring ways to replace components of these cooperative nanosystems with drugs already being tested in patients. For example, drugs that induce coagulation at tumor sites could replace the signaling particles tested in this study.

This work, which is detailed in a paper titled, "Nanoparticles That Communicate *In Vivo* to Amplify Tumour Targeting," was published in the July 2011 issue of *Nature Materials*. ◆



GARY CARLSON

This image shows a schematic of the in vivo communication system. Signaling particles lodged in the tumor recruit receiving particles circulating in the bloodstream.

RNA Nanoparticles Deliver

from the University of Cincinnati CNPP, currently University of Kentucky

BY JOE ALPER

For years, RNA has seemed an elusive tool in nanotechnology research. Although easily manipulated in the laboratory, RNA is susceptible to quick destruction in the body when confronted with a commonly found enzyme. "The enzyme RNase cuts RNA randomly into small pieces, very efficiently and within minutes," explains Peixuan Guo of the University of Cincinnati. But by replacing a chemical group in the macromolecule, Guo says he and fellow researchers have found a way to bypass RNase and create stable three-dimensional configurations of RNA, greatly expanding the possibilities for RNA in nanotechnology.

In their work, Guo and his colleagues focused on the ribose rings that, together with alternating phosphate groups, form the backbone of RNA. By changing one section of the ribose ring, Guo and his team altered the structure of the molecule, making it unable to bind with RNase and able to resist degradation. "RNase interaction with RNA requires a match of structural conformation," he explained. "When RNA conformation has changed, the RNase cannot recognize RNA and the binding becomes an issue." While previous researchers have shown this alteration makes RNA stable in a double helix, Guo says that they did not study its potential to affect the folding of RNA into a

three-dimensional structure necessary for nanotechnology.

After creating the RNA nanoparticle, Guo and his colleagues successfully used it to power the DNA packaging nanomotor of bacteriophage phi29, a virus that infects bacteria. "We found that the modified RNA can fold into its 3-D structure appropriately, and can carry out its biological functions after modification," says Guo. "Our results demonstrate that it is practical to produce RNase-resistant, biologically active, and stable RNA for application in nanotechnology."

Because stable RNA molecules can be used to assemble a variety of nanostructures, Guo says, they are an ideal tool to deliver targeted therapies to cancerous or viral-infected cells. "RNA nanoparticles can be fabricated with a level of simplicity characteristic of DNA while possessing versatile structure and catalytic function similar to that of proteins. With this RNA modification, hopefully we can open new avenues of study in RNA nanotechnology."

Guo's group has also tested the safety of RNA constructs in the delivery of therapeutics to targeted cells. This work, explained Guo, represents "two very important milestones in RNA nanotherapy. One problem in RNA therapy is the requirement for the generation of relatively large quantities of RNA. In this research, we focused on solving the most challenging problem of industry-scale production of large RNA molecules by a bipartite approach, finding that pRNA [packaging RNA] can be assembled from two pieces of smaller RNA modules." Guo discovered pRNA in a bacterial virus in 1987 and later demonstrated that this unique form of RNA can self-assemble into nanoparticles.

Guo and colleagues detail multiple approaches for the construction of a functional pRNA molecule containing small interfering RNA (siRNA). siRNA has already been shown to be an efficient tool for silencing genes in cells, but previous attempts have produced chemically modified siRNA that last only 15-45 minutes in the body and often induce undesired immune responses.

"The pRNA particles we constructed to harbor siRNA have a half-life of between five and 10 hours in animal models, are non-toxic, and produce no immune response," said Guo. "The tenfold increase of circulation time in the body is important in drug development and paves the way towards clinical trials of RNA nanoparticles as therapeutic drugs."

Guo says the size of the constructed pRNA molecule is crucial for the effective delivery of therapeutics to diseased tissues. "RNA nanoparticles must be within the range of 15 to 50 nanometers," he said, "large enough to be retained by the body and not enter cells randomly, causing toxicity, but small enough to enter the targeted cells with the aid of cell surface receptors."

Guo also said that to his knowledge, this is the first naked RNA nanoparticle to have been comprehensively examined pharmacologically *in vivo* and demonstrated to be safe, as well as deliver itself to tumor tissues by a specific targeting mechanism. "It suggests that the pRNA nanoparticles without a coating have all the preferred pharmacological features to serve as an efficient nanodelivery platform for broad medical applications," he noted.

This RNA construct work is detailed in a paper titled, "Fabrication of Stable and RNasae-Resistant RNA Nanoparticles Active in Gearing the Nanomotors for Viral DNA Packaging Engineering of Self-Assembled Nanoparticle Platform for Precisely Controlled Combination Drug Therapy," published in the January 2011 issue of *ACS Nano*. The therapeutic delivery work is detailed in two papers titled, "Assembly of Therapeutic pRNA-siRNA Nanoparticles Using Bipartite Approach" and "Pharmacological Characterization of Chemically Synthesized Monomeric phi29 pRNA Nanoparticles for Systemic Delivery," published in the journal *Molecular Therapy* in July 2011. ◆

Nanomedicine: One Step Closer to Reality

from the Stanford University CCNE-T

BY JOE ALPER

A class of engineered nanoparticles—gold-centered spheres smaller than viruses—has been shown safe when administered by two alternative routes in a mouse study led by investigators at the Stanford University Medical School. This marks the first step up the ladder of toxicology studies that, within a year and a half, could yield to human trials of the tiny agents for detection of colorectal and possibly other cancers.

"These nanoparticles' lack of toxicity in mice is a good sign that they'll behave well in humans," said Dr. Sanjiv Sam Gambhir, co-principal investigator of the Stanford University CCNE-T and leader of this study. "Early detection of any cancer, including colorectal cancer, markedly improves survival," said Dr. Gambhir. For example, the widespread use of colonoscopy has significantly lowered colon-cancer mortality rates, he said. "But colonoscopy relies on the human eye. So this screening tool, while extremely useful, still misses many cancer lesions such as those that are too tiny, obscure, or flat to be noticed."

A promising way to catch cancer lesions early is to employ molecular reporters that are attracted to malignant sites. One method in use involves fluorescent dyes coupled with antibodies that recognize and bind to surface features of cancer cells. But that approach has its drawbacks, said Dr. Gambhir. The body's own tissues also fluoresce slightly complicating attempts to pinpoint tumor sites. Plus, the restricted range of colors at which antibody-affixed dyes fluoresce limits the number of different tumor-associated features that can be simultaneously identified. Some versions of this approach have also proved toxic to cells.

The new study is the first-ever successful demonstration of the safety of a new class of agents gold nanoparticles that have been coated with materials designed to be detected with very high sensitivity, then encased in see-through silica shells and bound to polyethylene glycol molecules to make them more biologically friendly. Molecules that hone in on cancer cells can be affixed to them. The resulting nanoparticles measure a mere 100 nanometers in diameter.

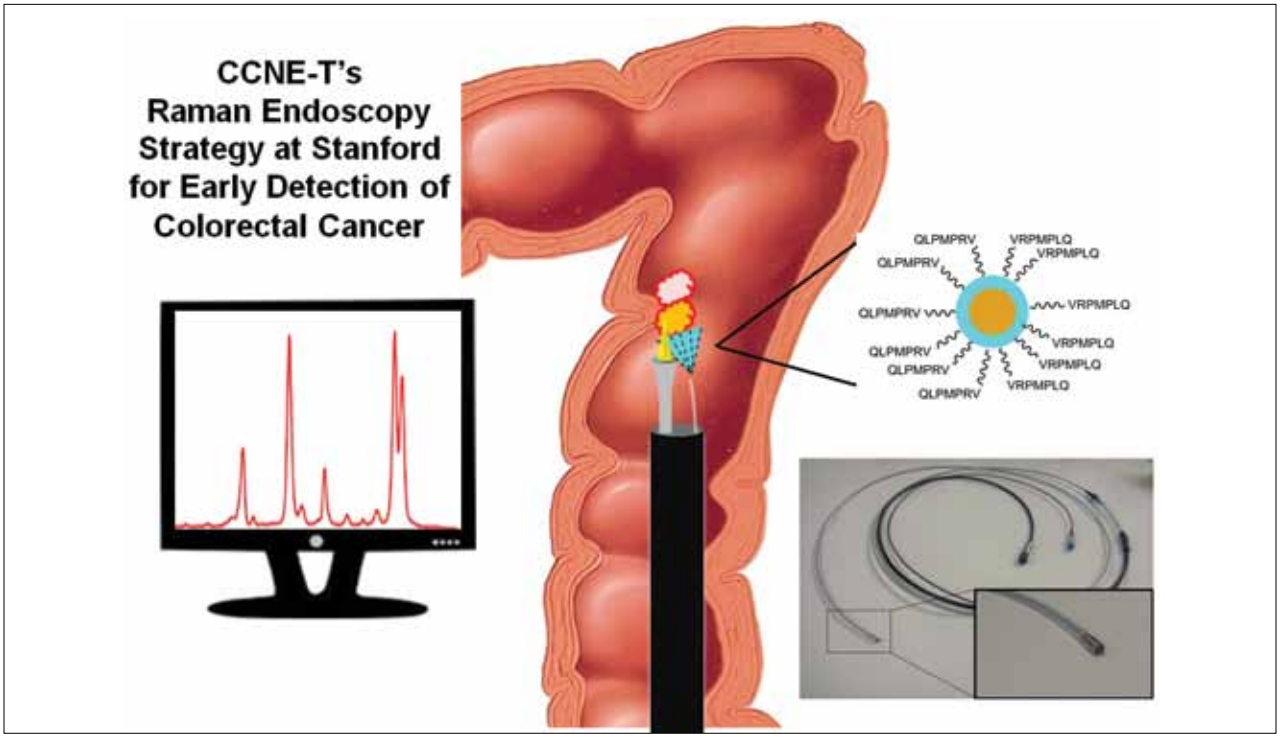
The materials surrounding the nanoparticles gold centers have special, if subtle, optical properties. Typically, light bounces off a material's surface at the same wavelength it had when it hit the surface. But in each of the specialized materials, about one ten-millionth of the incoming light bounces back in a pattern of discrete wavelengths characteristic of that material. The underlying gold cores have been

roughened in a manner that greatly amplifies this so-called "Raman effect," allowing the simultaneous detection of many different imaging materials by a sensitive instrument called a Raman microscope.

Nanoparticles of this type were originally used in currency inks to make them difficult to counterfeit. But Dr. Gambhir's laboratory, in collaboration with Oxonica Materials, has adapted them for biological use. "Photoimaging with these nanoparticles holds the promise of very early disease detection, even before any gross anatomical changes show up, without physically removing any tissue from the patient," said Dr. Gambhir. But until now, there has been no proof these particles won't be toxic. The potential effects of anything so small it can be taken up by cells can't be taken for granted.

To see if this concern could be put to rest, the investigators administered the nanoparticles to two groups of mice, each consisting of 30 male and 30 female animals, and assessed toxicity in a variety of ways. In each case, the dose was 1,000 times as large as would be required to get a clear signal from the nanoparticles.

The first group of 60 mice received the nanoparticles rectally. The researchers followed up with a series of measurements at five different time points ranging from five minutes to two weeks. They monitored the test animals' blood pressure, electrocardiograms and white-blood-cell counts. They examined several tissues for increases in the expression of antioxidant enzymes or pro-inflammatory signaling proteins, which would suggest physi-



STANFORD CCNE-T

Image and schematic of endoscope and gold nanoparticle Raman tags developed at the Stanford University CCNE-T for early detection of colorectal cancer.

ological stress on the animals' cells. They stained tissues with dyes that flag dying cells.

These inspections yielded virtually no signs of stress to any tissues, and none at all by two weeks after the time of administration. Importantly, the team inspected tissues via electron microscopy to find out where the gold-containing particles had lodged themselves. They found no gold anywhere outside the bowel, indicating that the nanoparticles remained confined to that organ and thus, when rectally administered, posed no threat of systemic toxicity. Furthermore, the nanoparticles were quickly excreted. "That lowers the bar for testing of these agents by the Food and Drug Administration for use in detecting colorectal cancers, because it addresses worries about systemic toxicity," Dr. Gambhir explained.

However, even if the nanoparticles had moved beyond the bowel, it seems they would have caused no systemic problems. On administering the nanoparticles intravenously to the second group of 60 mice, the investigators once again found scant signs of inflammation or other evidence of toxicity, and virtually none by two weeks after administration. Scavenger cells resident in organs such as the liver and spleen rapidly sequestered the intravenously administered nanoparticles.

This opens the door to human tests of intravenous injections of these nanoparticles to search for tumors throughout the body. "We can attach molecules targeting breast, lung or prostate cancer to these spheres," Dr. Gambhir said. In the study, the researchers did test nanoparticles conjugated to one such targeting molecule. Again, no toxic effects were observed. Dr. Gambhir's group is now filing for FDA approval to proceed to clinical studies of the nanoparticles for the diagnosis of colorectal cancer.

Dr. Gambhir and his colleagues performed a related set of experiments using radioactively labeled gold nanoparticles to track the accumulation of nanoparticle imaging agents inside mice. After labeling the nanoparticles with a radioactive isotope of copper, the investigators used micro-positron emission tomography (micro-PET) to image the nanoparticles' location in the body. When the nanoparticles were injected intravenously, they accumulated in a variety of organs, with almost 10 percent of the dose of nanoparticles ending up in the liver. In contrast, when the nanoparticles were injected rectally into the colon, less than 1/10th of 1 percent of the nanoparticles accumulated outside of the large intestine even as far as two weeks after injection. In the colon, the nanoparticles could be visualized using an endoscope modified to detect Raman signals.

The above work was detailed in two papers, "The Fate and Toxicity of Raman-Active Silica-Gold Nanoparticles in Mice," published in the April 20, 2011 issue of *Science Translational Medicine*, and "Preclinical Evaluation of Raman Nanoparticle Biodistribution for their Potential Use in Clinical Endoscopy Imaging," published in the August 8, 2011 issue of *Small*. ◆

Quantum Dots: DNA Methylation Detector

from Johns Hopkins University CCNE

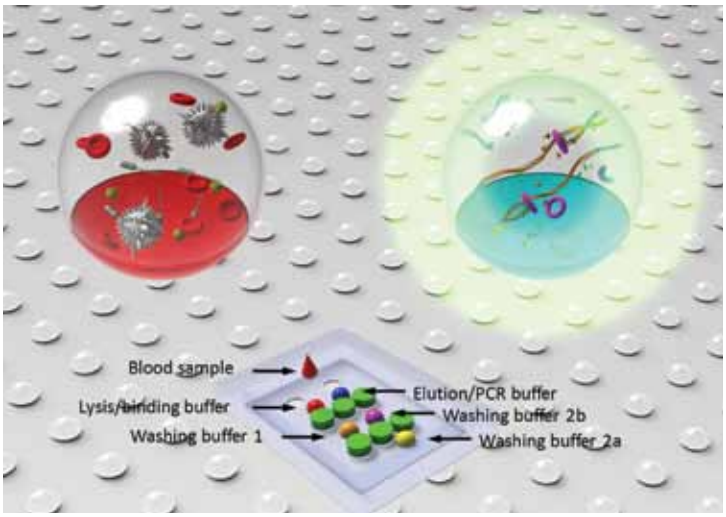
BY MARY SPIRO

Tza-Huei "Jeff" Wang, associate professor of mechanical engineering in the Whiting School of Engineering leads a research project within the Johns Hopkins Center of Cancer Nanotechnology Excellence that seeks methods to screen bodily fluids such as blood or urine for epigenetic cancer indicators. Working with Stephen Baylin, the Virginia and Daniel K. Ludwig Professor of Cancer Research in the Johns Hopkins School of Medicine; and James Herman, a professor of cancer biology in the School of Medicine, Wang's project uses semiconductor nanocrystals, also known as quantum dots, as well as silica superparamagnetic particles to detect DNA methylation.

DNA methylation, in which a chemical group is added to the backbone of the code's double helix, is a cancer specific biomarker that can be identified with nanotechnology based tools.

"Recent advances in technologies have significantly enhanced the way in which diseases are studied and have opened new avenues for diagnosis and treatments," Wang said. "We now have tools to observe biological phenomena at the single molecular level, to sequence the entire genome and to understand the molecular basis of diseases. In addition, the rapid development in nanotechnology has allowed us to design sensors engineered at the nanoscale from molecular probes and nanostructures as the basis for next-generation biosensors to achieve even higher sensitivity and more pervasive application."

Nanoparticles, such as quantum dots, possess "well defined shapes, sizes, and compositions as well as a high surface to volume ratio," Wang said. That means a nanosensor using quantum dots can be more efficient in binding molecules associated with epigenetic markers and therefore, is better



YI ZHANG, JHU

This work describes a droplet microfluidic, sample-to-answer platform for genetic detection of diseases, such as cancer and infectious diseases, using crude biological samples including blood. The platform exploited the dual functionality of silica superparamagnetic particles (SSP) for solid phase extraction of DNA and magnetic manipulation of droplets. This enabled the full integration of the entire sample preparation and genetic analysis process in droplets, including the steps of cell lysis, DNA binding, washing, elution, amplification and detection. The microfluidic device was self contained, with all reagents stored in droplets, thereby eliminating the need for fluidic coupling to external reagent reservoirs.

able to detect very low volumes of these indicators in bodily fluids.

"There is tremendous need for early detection of cancer…a need to find circulating tumor cells in the blood," said Baylin, and creative nanotechnology science may be the tool that allows for this early detection. Baylin compared DNA to a computer's hard drive, while the epigenome would be more like a computer's software, he said, giving instructions on how and when to use that genetic information.

"Detecting these molecules and knowing their biology and their methylation offers us another hope," Baylin said, "because we have drugs now that can change a methylated DNA back to its non-methylated state." Furthermore, Baylin noted that different types of colon cancers, for example, methylate differently. "This can tell you not only the stage but where the cancer is located in the gastro-intestinal tract," he said.

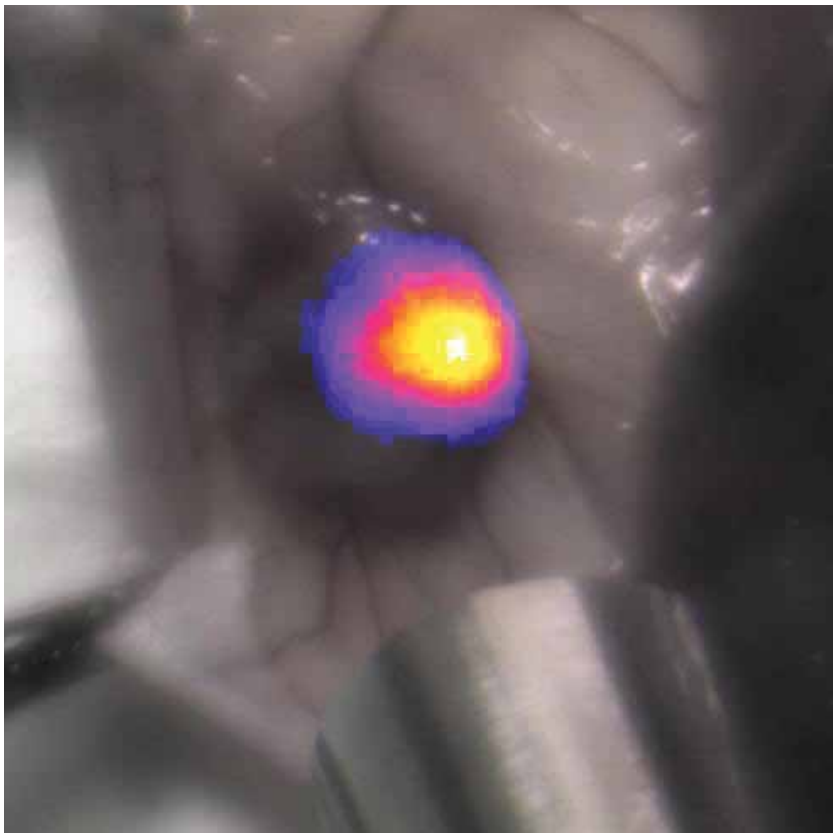
Quantum dots, which range from a few nanometers up to a couple hundred nanometers in diameter, work by capturing molecular targets and, something like a light switch, transducing the molecular binding events into fluorescent signals, in a process called fluorescence resonance energy transfer (FRET), Wang explained. "Quantum dots make excellent FRET donors that overcome pitfalls associated with conventional molecular FRET," he said.

Because quantum dots of different sizes absorb different wavelengths of light, measurable fluorescence is emitted even at the single molecule level of detection. QD-based DNA nanosensors easily filter out background "noise" to perceive circulating biomarkers including single point mutations to the genetic code and DNA methylation in clinical samples.

"The quantum dot assays and other nanomaterials enabled assays possess ultrahigh sensitivity that address the challenge in rare markers in bodily fluids such as blood, present a promising solution for non-invasive disease screening and monitoring in the near future," Wang said.

An article describing the use of superparamagnetic particles in a microfluidic device for the detection of biomarkers entitled "A Surface Topography Assisted Droplet Manipulation Platform for Biomarker Detection and Pathogen Identification" was published in the February 7, 2011 journal *Lab on a Chip*. The complete list of authors included Yi Zhang, Seungkyung Park, Kelvin Liu, Jennifer Tsuan, Samuel Yang and Tza-Huei "Jeff" Wang, all from Johns Hopkins University. ◆

K99/R00 Pathway to Independence Awards in Cancer Nanotechnology



COURTESY OF AARON MOHS

Detection of tumor margins using dextran-based nanoparticles that encapsulate the near infrared fluorescent dye, ICG, for use in intraoperative image-guidance.

Jin Xie, PI of the K99/R00 Award "Nanoplatform-based Combinational Therapy Against Breast Cancer," has joined the faculty of the University of Georgia in Athens, Georgia as an assistant professor in the Department of Chemistry. He will also have an appointment in the Bioimaging Research Center, a state-of-the-art facility providing support for researchers across biomedical disciplines, and access to the Nanoscale Science and Engineering Center at the University. Xie completed the K99 phase of his research at the National Institute of Biomedical Imaging and Bioengineering under the mentorship of Xiaoyuan Chen.

Xie's primary research interest is in the development of engineered nanoparticles for simultaneous imaging and treatment of cancer, work which encompasses development of polymer, nanocrystalline and protein-based materials. The Alliance supported K99/R00 award is for the development of human serum albumin coated iron oxide nanoparticles to deliver multiple, complementary drugs to breast tumors. The multiple drug formulation targets three critical problems in treating breast cancer—drug delivery, drug resistance and cancer stem cells. Careful engineering of

the nanoparticle-coating interface leads to favorable pharmacokinetics and enhanced nanoparticle accumulation in tumors. This increases the delivered dose of encapsulated therapeutics, including cytotoxic agents, drug resistance inhibitors and anti-cancer stem cell agents. The complementary cancer cell killing mechanisms of the three classes of drug should result in greater therapeutic efficacy than either class delivered alone. Xie will also investigate potential magnetic resonance image (MRI) enhancement resulting from the high loading of superparamagnetic nanoparticles in the tumor. The MRI contrast properties of the nanoparticles will be used to track drug loading and therapeutic response in the tumors.

Jin Xie

Aaron Mohs

Aaron Mohs, PI of the K99/R00 award, "Nanotechnology for Minimally Invasive Detection and Resection of Cancer," has accepted a position as assistant professor in the Department of Biomedical Engineering , Virginia Tech – Wake Forest University School of Biomedical Engineering and Sciences. He will hold joint appointments in the Wake Forest Institute for Regenerative Medicine and Department of Cancer Biology and will be a member of the Comprehensive Cancer Center of Wake Forest University. Mohs completed his post-doctoral training at Emory University under the mentorship of Shuming Nie, and additionally trained with co-mentor Sunil Singhal of the University of Pennsylvania.

Mohs' K99/R00 award supports development of a handheld optical system along with image contrast enhancement agents for imaging tumor margins and small, distributed masses intraoperatively. The system will enable surgeons to more accurately identify cancerous tissue during resection, reducing the likelihood that malignant tissue is left behind and improving patient outcomes. The contrast agent is a fluorescent dye entrapped in a self-assembled polymer nanoparticle. Confinement in the nanoparticle quenches the dye fluorescence; release of the dye in the tumor activates the fluorescence. Mohs and his collaborators will also develop an endoscope with an integrated excitation (provided by a near infrared laser diode) and collection unit, to enable intraoperative imaging in deep tissue. In his new faculty position, Mohs plans to test the intraoperative imaging system in spontaneous canine cancers, and to expand the system to include localized therapy. ◆

ERNIE BRANSON

Members of the NCI Alliance for Nanotechnology in Cancer gather at the program's Kick Off Meeting in November 2010.

Jin Wang, a post-doctoral associate in the laboratory of Joseph DeSimone, PI of the Carolina CCNE, has joined the faculty of the Baylor College of Medicine as a Cancer Prevention Research Institute of Texas (CPRIT) Scholar in Cancer Research. Wang will be an assistant professor in the Department of Pharmacology, a member of the Dan L. Duncan Cancer Center and an adjunct faculty member in the Department of Bioengineering at Rice University.

Jered Haun, a post-doctoral associate in the laboratory of PI Ralph Weissleder of the MIT-Harvard CCNE, joined the faculty of the Department of Biomedical Engineering at the Henry Samueli School of Engineering at the University of California, Irvine as an assistant professor.

Neal Deveraj, another post-doctoral associate in the Weissleder lab, is now an assistant professor of Chemistry and Biochemistry at the University of California, San Diego.

Inoue Satoshi of the Cedars Sinai Medical Center CNPP is now an assistant professor in the Department of Neurosurgery at Cedars Sinai Medical Center.

Jose Portilla and **Rameshwar Patil** have joined the staff of Cedars Sinai Medical Center as project scientists, where they are members of the CNPP. **Hui Ding** is now a research scientist at Cedars Sinai.

Murali Venkatesan, a trainee at the Midwest (M)-CNTC in the Department of Electrical and Computer

Engineering at the University of Illinois Urbana-Champaign (UIUC), completed his PhD, with M-CNTC PI Prof. **Rashid Bashir**, and will continue as a post doc partially supported by the M-CNTC.

Stephen A. Boppart, adviser to two M-CNTC trainees at UIUC, has been recognized with a Bliss Professorship.

Andrew Goodwin, PI of the K99/R00 award "Enzyme-Responsive Nanoemulsions as Tumor-Specific Ultrasound Contrast Agents" at the University of California, San Diego, received a Breast Cancer Postdoctoral Fellowship Award from the U.S. Department of Defense to develop microbubbles for use as ultrasound contrast agents for sentinel lymph node identification prior to surgery to remove a breast tumor. Goodwin also received an AACR Scholar-in-Training Award, supporting travel to present a poster at the first AACR Nano in Cancer meeting in Orlando in January 2011.

Austin (Yin Kyai) Hsiao, a trainee at the M-CNTC in the Department of Bioengineering at UIUC, earned an Honorable Mention in the National Science Foundation Graduate Research Fellowship and an Honorable Mention in the Ford Foundation Predoctoral Fellowship. Austin also won a Poster Award in the 2011 Bioengineering Day Poster Competition.

M-CNTC trainee **Ross DeVolder** of the Department of Chemical and Biomolecular Engineering won a Best Poster Award in the 2011 Center for Nanoscale Science and Technology Annual Workshop. Ross' research focuses on "Tissue-Engineered Cancer Construct for Studies of Nanobiomaterial Transport."

Terence Ta, a trainee at the Boston University (BU) Cross-Disciplinary Training Program in Nanotechnology for Cancer (XTNC) was awarded the student award for best nanoscience poster at the 2011 BU Science and Engineering Day. His work was titled: "Cationic Nanoemulsion for Targeting siRNA Delivery to Tumors."

Kelvin Liu completed his PhD in biomedical engineering at Johns Hopkins University. Liu was a trainee in the laboratory of **Jeff Wang**, a project leader with the Johns Hopkins CCNE. Liu was named the 2011 Siebel Scholar. The Siebel Scholars program was established by the Siebel Foundation in 2000 to recognize the most talented students at the world's leading graduate schools of business, computer science, and bioengineering.

Bridget Wildt completed her PhD with Johns Hopkins CCNE co-director **Peter Searson** in the Department of Materials Science and Engineering at Johns Hopkins University. Wildt is now a post-doctoral fellow at the Food and Drug Administration.

Also from the Searson Group at Johns Hopkins University, **Kyan Hyi Li** completed his PhD in Materials Science and Engineering. He is now a senior scientist at the Korea Institute of Science and Technology in Seoul.

Janice Lin completed her PhD in Materials Science and Engineering with the Searson Group at Johns Hopkins University and has taken a position as a senior engineer in the Technology Leadership Development Program at Becton Dickinson in Sandy, Utah.

Several CCNE affiliated trainees at Johns Hopkins were honored for their poster presentations at the 5th Annual Johns Hopkins Institute for NanoBioTechnology symposium. Cancer nanotechnology was the theme of this year's symposium. This year's winning poster titles and authors were: 1st, Tumor-Specific Imaging through Progression Elevated Gene-3 Promoter-Driven Gene 60 Expression by **Hyo-eun "Carrie" Bhang**, **Kathleen L. Gabrielson**, **John Laterra**, **Paul B. Fisher** and **Martin G. Pomper** (Pomper is co-PI for the Hopkins CCNE) and 3rd, Quantum Dot Enabled Ultrahigh Resolution Analysis for Copy Number Variation 36 Detection and DNA Methylation Quantification by **Yi Zhang** and **Tza-Huei Wang**. Honorable mentions were received by Restitution of

Tumor Suppressor microRNAs Using a Systemic Nanovector Inhibits Pancreatic Cancer Growth in Mice by **Dipanikar Pramanik**, **Nathaniel R. Campbell**, **Collins Karikari**, **Raghu Chivukula**, **Oliver A. Kent**, **Joshua T. Mendell**, and **Anirban Maitra** (co-director of the Hopkins CNTC) and Brain Penetrating Nanoparticles by **Graeme F. Woodworth**, **Elizabeth A. Nance** and **Justin Hanes** (Hanes is a project leader with the Hopkins CCNE).

Hyo-eun "Carrie" Bhang of **Martin Pomper**'s Lab (Hopkins CCNE co-PI) received The Paul Ehrlich Research Award.

Martin G. Pomper was named the inaugural William R. Brody Professor of Radiology at the Johns Hopkins School of Medicine. Pomper, designated as the Radiologist Physician Scientist who excels in translational innovation in imaging in the footsteps of its namesake and former Johns Hopkins University president William R. Brody, will be officially installed on the afternoon of October 6, 2011.

Chad Mirkin, PI of the Nanomaterials for Cancer Diagnostics and Therapeutics at Northwestern University, was elected to the Institute of Medicine. Mirkin is one of only ten people to be elected to all three National Academies. Mirkin also testified at a Senate Subcommittee on Science and Space hearing, "National Nanotechnology Investment: Manufacturing, Commercialization and Job Creation." (See related story on page 8.) According to Thomson Reuters, Chad Mirkin is the most cited chemist in the world.

Michael Cima, Project Leader in the MIT-Harvard CCNE, was elected to the National Academy of Engineering. Cima was recognized for his innovations in rapid prototyping, high-temperature superconductors and biomedical device technology.

Robert Langer, PI of the MIT-Harvard CCNE, received the 2012 Priestly Medal by the American Chemical Society, the National Academy of Engineering's Founders Award, the Warren Alpert Foundation Prize, the Boston Museum of Science Walker Prize, Dartmouth College's Robert Fletcher Award, the IEEE Engineering in Medicine and Biology Society's EMBS Academic Career Achievement Award and the Society of Cosmetic Chemists' Frontier of Science Award. Langer also was elected as an International Fellow of the Royal Academy of Engineering (UK), a Founding POLY Fellow of the American Chemical Society's Division of Polymer Chemistry and a Fellow of the Controlled Release Society.

Mauro Ferrari, President and CEO of the Methodist Hospital Research Institute in Houston and co-PI of the Texas Center for Cancer Nanomedicine, received the 2011 Controlled Release Society Founders' Award. He joins fellow Alliance PIs Drs. Robert Langer and Vladimir Torchilin as recipients of this award.

Diane Lidke, an affiliate of the University of New Mexico CNTC, received the 2011 Margaret Oakley Dayhoff Award from the Biophysical Society for her innovative work integrating the disciplines of biophysics, bioimaging and quantitative biology.

Taekjib Ha, an affiliate of the M-CNTC and UIUC professor, was awarded the 2011 Ho-Am Prize in Science by the Ho-Am Foundation of Korea. The Ho-Am Prizes are widely regarded as the Korean equivalent of the Nobel Prize. He was recognized for his pioneering application of fluorescence resonance energy transfer techniques to reveal the behavior and physical characteristics of single biomolecules. Alliance member **Luke Lee** of the Stanford CCNE-T was the 2010 winner of the Ho-Am prize.

Steve Quake of the Stanford CCNE-T is the 2011 Promega Biotechnology Research Award Laureate.

The Radcliffe Institute named **Teri Odom**, Core Director at the Northwestern University CCNE, a Hryn Fellow for Advanced Study at Harvard University.

Thomas Meade, Project Leader in the Northwestern CCNE, was awarded the Society of Molecular Imaging Annual Exceptional Achievement Award (2010) and was elected a fellow of the American Chemical Society.

Vinayak Dravid, an investigator in the Northwestern CCNE, was elected a member of the American Academy of Arts and Sciences and of the American Physical Society.

Janet Oliver, PI of the New Mexico Cancer Nanotechnology Training Center, was elected a member of the American Academy of Arts and Sciences.

Sangeeta Bhatia, Project Leader in the MIT-Harvard CCNE, was selected as a Biomedical Engineering Society Class of 2011 Fellow. Fellow status is awarded to society members who demonstrate exceptional achievements and experience in the field of biomedical engineering and a record of membership and participation in the society.

Ian Baker, PI of the Dartmouth CCNE, was selected as a Materials Research Society (MRS) Fellow. Baker was recognized for exceptional contributions to the fundamental understanding of structure-property relationships in materials, particularly intermetallics, ice, and nanomaterials and for nearly 30 years of leadership in materials education and professional service.

James Heath, PI of the Nanosystems Biology Cancer Center at the California Institute of Technology, was also selected as an MRS Fellow. He was recognized for outstanding contributions to nanomaterials discovery, the elucidation of novel materials properties, and applications of this work to or in information technologies, energy conversion, and biotechnologies.

Hui Ding received the Excellence in Research Award by Cedars Sinai Medical Center.

Eggehard Holler was awarded the Faculty Team Player Award by Cedars Sinai Medical Center.

Larry Sklar, a mentor in the UNM CNTC and Regents' Professor and Distinguished Professor in the Department of Pathology at UNM's School of Medicine, has been recognized as the 2011 STC.UNM Innovation Fellow.

Alexander Stegh was awarded a 21st Century Science Initiative Award from the James S. McDonnell Foundation.

David Agus, investigator in the Center for Cancer Nanotechnology Excellence and Translation at Stanford University and professor of medicine at the University of Southern California (USC) and director of the USC Center for Applied Molecular Medicine, spoke at TEDMED 2010 about the necessity of viewing the body as a network when treating disease. Agus also spoke at TEDMED 2009 on "A new strategy in the war on cancer."

Times Higher Education ranked **Vladimir Torchilin**, PI of the Center for Translational Cancer Nanomedicine at Northeastern University, one of the world's most highly cited scientists.

Johns Hopkins CCNE investigator **Stephen Baylin**, MD, took part in the final games of the Major League Baseball's All-Star Game Fantasy Camp. Sponsored by MasterCard, the MLB All-Star Fantasy Camp provides a break from the world of cancer for a number of oncology researchers, physicians, patients, and family members involved in Stand Up To Cancer (SU2C), an initiative for which Major League Baseball is the founding donor. Baylin is deputy director of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University and leader of the Stand Up To Cancer Epigenetics "Dream Team." Baylin was also named among the 2010 Rock Stars of Science. ◆

OUTREACH BY THE ALLIANCE

The **University of Illinois at Urbana-Champaign**, home of the Midwest (M)-CNTC, hosted a Bio-Nanotechnology Summer Institute from July 25-August 5, 2011. A total of 47 undergraduates, graduates, postdocs, faculty, and research scholars from across the country and around the world participated this year. Experts from across the country, including **Sam Wickline** from the Washington University School of Medicine, **J. Zach Hilt** from the University of Kentucky, and **Muhammad Zaman** and **Bennett Goldberg** from Boston University, introduced participants to the basics of cancer biology and cell mechanics. Biological and engineering/physical science experimental methods were taught using a hands-on approach in the laboratory.

M-CNTC trainees participated in an Engineering Open House on March 11, 2011 (http://eoh.ec.uiuc.edu) and conducted visits with elementary children from two local schools, Barkstall and Next Generation. Through these outreach efforts, over 200 visitors and elementary school students were exposed to concepts and uses of nanotechnology in cancer (e.g., nanomedicine for cancer therapy, the use of gold nanoparticles as a sensor, red to blue color shift due to the aggregation of gold nanoparticles, etc.) through the use of a Jeopardy-style game and visual displays.

M-CNTC Trainees also participated in the Brain Fitness Fridays Summer Camp hosted by the Technology Entrepreneur Center at the University of Illinois at Urbana-Champaign.

The **University of New Mexico CNTC** hosted "The Art of Systems Biology and Nanoscience" exhibit, April 1-2, 2011, at the Santa Fe Complex. The exhibit explored some of the newest and most fascinating images from two emerging fields in science.

On June 2-3, 2011, the **UNM CNTC** co-hosted the Sandia/UNM Symposium on Nanoparticle Human Interactions. The symposium covered nanoparticle-human interactions at the nanoparticle, cellular, sub-cellular and systems (e.g., organ or tumor) levels. Topics discussed included detection and treatment of cancer and infectious and inflammatory human diseases, vaccine development, advanced imaging, and nanoparticle toxicology.

BRIAN STAUFFER, UIUC

Attendees at the BioNanotechnology Summer Institute held at UIUC July 25-August 5 2011.

On February 26, 2011, **Christin Hollis**, a predoctoral trainee at the **University of Kentucky CNTC**, hosted a CNTC booth at the UK Engineering Day. During the Engineering-day open house, attendees learned what engineers do and how they do it by participating in contests, winning prizes, watching experiments and demonstrations, and talking to engineers about their jobs. At her booth, Christin explained to students from the 1st to 12th grades and their parents the EPR (enhanced permeability and retention) effect and how nanotechnology, especially nanosized drug delivery, can be utilized for cancer therapy. Approximately 200 people stopped by the booth, and the response was very positive.

Markey Cancer Research Day is an annual, daylong event showcasing the work of cancer experts in all facets of cancer research at the University of Kentucky. CNTC trainees **Kyle Fugit** and **Christin Hollis** were among the 116 researchers who presented posters at this year's event on March 22, 2011.

The **Stanford University CCNE-T** is hosting a Monthly Nanobiotechnology Seminar Series, in which distinguished researchers are invited to speak on the Stanford campus. The seminars are recorded and webcast and are freely viewable for public use.

The staff of the **Stanford University CCNE-T** also helped produce a 7-part seminar series to detail the process of an Investigational New Drug (IND) application. This seminar is open to the public and is held on campus. The seminars were sponsored by the Stanford Cancer Center Clinical Trials Office and the Canary Center at Stanford for Cancer Early Detection, which is directed by CCNE PI **Sanjiv Sam Gambhir**.

The **Northwestern University CCNE** engages in outreach to the community throughout the year. Events for pre-college students include the annual All Scout Nano Day, which includes presentations, a poster competition, and laboratory tours, and a partnership with the Museum of Science and Industry, Chicago to present hands-on activities demonstrating nanotechnology concepts during NanoDays 2011. NanoDays is an annual, nationwide nano education and outreach event sponsored by the National Science Foundation's Nanoscale Informal Science and Education (NISE) Network. For the general public, the Center hosts Nanotechnology Town Hall Meetings. The latest event featured presentations by NU-CCNE researcher and Project 2 leader, Professor **Milan Mrksich**, and NU Assistant Director of Research Safety, **Markus Schaufele**.

A CNTC trainee from The Johns Hopkins University produced a science video news release related to his research as part of the **Johns Hopkins Institute for NanoBioTechnology**'s summer workshop, Science Communication for Scientists and Engineers. **Matthew Dallas**, a predoctoral fellow in the Department of Chemical and Biomolecular Engineering with professor and department chair **Konstantinos Konstantopoulos**, worked with fellow predocs **Shyam Khatau**, also in ChemBE, and C**raig Copeland** of the Department of Physics and Astronomy, to create a three-minute video describing his work on tracking the migration of tumor cells in the blood stream. Dallas' team presented their video at the INBT annual summer film festival on June 28, 2011, along with several other student groups. The video will be posted to YouTube and the Johns Hopkins CCNE website.

TRAINING IN THE ALLIANCE

On May 16-17, 2011, the **Boston University Cross-Disciplinary Training Program in Nanotechnology**

MARY SPIRO, JHU

Charli Dvoracek (center) of the JHU-CNTC helped lead a workshop on quantum dot fabrication.

for Cancer (XTNC) co-sponsored the workshop, "An Introduction to Cancer Care for Engineers and Physical Scientists," directed by **Jennifer Rosen**, MD FACS. The course was intended to provide a basis of knowledge for physical and engineering scientists to engage cancer researchers and clinicians. Topics covered included surgical oncology, chemotherapy and biologics, radiation oncology and specific tumor types.

The XTNC also co-sponsored a microarray workshop at Boston University from August 22-24, 2011. The goal of this workshop was for the students to understand the major issues in the design, instrumentation, techniques, and analysis of experiments using high throughput micro-array technology. The course covered various detection techniques as well as data collection and management using oligonucleotide arrays, statistical techniques for the identification of genes that have differential expression in different biological conditions, development of prognostic and diagnostic models for molecular classification, and the identification of new disease taxonomies based on their molecular profile. In addition to the BU trainees, student and postdocs from other Alliance institutions attended the workshop, including MIT, Harvard, and Northeastern University.

The laboratory of **Johns Hopkins CCNE** co-director **Peter Searson** hosted a workshop on the step-by-step fabrication of quantum dots during the Institute for NanoBio-Technology's annual research symposium. Predoctoral fellows **Charli Dvoracek**, **Justin Galloway** and **Jeaho Park** taught the two-hour workshop, presented in the style of a cooking show. Participants were allowed to take turns completing steps along the way. Students and staff from across the Johns Hopkins community and representatives

from local industry participated. Attendees provided positive feedback on the workshop, which will be held again in 2012.

The **Johns Hopkins CCNE** welcomed three undergraduates to its summer research internship program. **Justin Samorajski** worked in **Peter Searson's** laboratory analyzing the effect of electrical fields on cell motility within the confinement of microfluidic devices. Samorajski studies at the University of Dallas (Texas). Also in the Searson lab is Johns Hopkins University undergraduate **Scott Nussdorfer**. Nussdorfer is assisting PhD fellow **Charli Dvoracek** in the testing and analysis of various antigens' abilities to bind quantum dots to pancreatic cancer cells. His main responsibilities included passing the Panc-1 tumor cells to maintain their health and viability for experiments. He also helps analyze images of cells using the group's inverted microscope. Searson is a co-PI for the Hopkins CCNE. **Allatah Mekile**, from East Stroudsburg University in Pennsylvania, is studying DNA methylation for early cancer detection with CCNE project leader **Jeff Wang**, an associate professor of mechanical engineering at Hopkins. Mekile is working on optimizing the DNA isolation for the MOB (methylation on beads) protocol. MOB is an integrated assay that uses silica based paramagnetic beads for both DNA isolation and bisulfite conversion.

MEETINGS AND SYMPOSIA

Alexander Kabanov and **Tatiana Bronich**, PI and investigator at the University of Nebraska Medical Center (UNMC) CNPP, hosted the 8th International Nanomedicine and Drug Delivery Symposium (NanoDDS'10) in Omaha, Nebraska, October 3–5, 2010. Sessions included Nanomedicine in Cancer, Clinical Translation of Nanomedicines, Novel Nanoformulation Technologies and Nanomedicine Research Reports. Speakers included Alliance members **Leaf Huang** and **Joseph DeSimone** of the **Carolina-CCNE**, **Mark Davis** of Cal Tech, **Justin Hanes** of Johns Hopkins University, **Mostafa El-Sayed** of Emory University and **Robert Luxenhofer** of the Technische Universität Dresden, an investigator in the UNMC CNPP.

Peixuan Guo, PI of the **University of Cincinnati CNPP**, was chair of the 2010 International Conference of RNA Nanotechnology and Therapeutics, held in Cleveland, Ohio, October 23–25, 2010. Topics covered during the conference included Biophysical and Single Molecule Approaches in RNA Nanotechnology, RNA Structure for Nanoparticle Construction, RNA Computation and Modeling, RNA Nanoparticle Assembly, RNA Nanoparticles in Therapeutics and RNA Chemistry for Nanoparticle Synthesis, Conjugation, and Labeling.

Robert Sinclair, Core Director at the **Stanford CCNE-T**, **Rashid Bashir**, PI of the **M-CNTC**, **Wenbin Lin**, PI of the **UNC CNPP**, **Thomas Thundat** from Oak Ridge National Laboratory and **Larry Nagahara**, Director of the Office of the Physical Sciences-Oncology, NCI, organized the Symposium QQ: Nanofunctional Materials, Nanostructures, and Nanodevices for Biomedical Applications II at the Materials Research Society Fall 2010 Meeting, Boston, MA, held November 29–December 2, 2010.

CNPP PI **Julia Ljubimova** chaired the 2011 Nanomedicine and Drug Delivery Research Conference, hosted by the Department of Neurosurgery at Cedars Sinai Medical Center March 4–5, 2011. Speakers included Alliance PIs **Alexander Kabanov** of the **UNMC CNPP** and **Vladimir Torchilin** of the Center for Translational Cancer Nanomedicine at Northeastern University and NCL Director **Scott McNeil**.

On July 11–13, 2011, the Thayer School of Engineering and the Norris Cotton Cancer Center, Dartmouth College, home of the **Dartmouth CCNE**, hosted the Engineering in Medicine Conference: Redesigning Cancer Imaging and Therapy. Speakers included Alliance members **Martin Pomper**, co-PI of the **CCNE at Johns Hopkins University**, **Steven Rosen**, co-PI of the **Northwestern CCNE**, **Mostafa El-Sayed** and **Anna Wu** from the **Stanford CCNE-T**, as well as **Jose Conejo-Garcia** of the **Dartmouth CCNE**.

Students from the **Johns Hopkins CCNE** collaborated with members of the JHU Physical Sciences-Oncology Center to host a half-day symposium on March 23, 2011. The event showcased current research from nine students affiliated with its Physical Sciences-Oncology Center (PS-OC) and Center of Cancer Nanotechnology Excellence. Hopkins CCNE affiliated fellows who presented included **Jeaho Park** (Peter Searson Lab): "Quantum Dots for Targeting Cancer Biomarkers"; **Kelvin Liu**, PhD, (Jeff Wang Lab): "Decoding Circulating Nucleic Acids in Serum Using Microfluidic Single Molecule Spectroscopy"; **Craig Schneider** (Justin Hanes Lab): "Mucus-Penetrating Particles for the Treatment of Lung Cancer"; **Venugopal Chenna** (Anirban Maitra Lab): "Systemic Delivery of Polymeric Nanoparticle"; and **Yi Zhang** (Jeff Wang Lab): "A Quantum Dot Enabled Ultrahigh Resolution Analysis of Gene Copy Number Variation." **John Fini**, director of intellectual property for the Johns Hopkins Homewood campus schools, also gave a presentation on intellectual property and work of Johns Hopkins Technology Transfer. Plans are in the works for the cancer nanotechnology mini-symposiums to occur each spring and fall.

THE ALLIANCE AT AACR

The **NCI Alliance for Nanotechnology in Cancer** was a strong presence at the AACR 102nd Annual Meeting, held in April 2011 in Orlando, Florida. There were two Alliance associated educational sessions. Alliance Program Director **Piotr Grodzinski** chaired an education session, "Training the Next Generation of Cancer Nanotechnology Researchers," with speakers **Carolyn Anderson** from the University of Pittsburgh, **Andrew Kummel**, PI of the **University of California, San Diego CNTC**, **Jennifer Rosen** from the **XTNC** and **Gayle Woloschak**, PI of the Cancer Nanotechnology in Imaging and Radiotherapy training center at **Northwestern University**.

Mauro Ferrari, co-PI of the **Texas Center for Cancer Nanomedicine**, chaired a Methods Workshop "Practical Nanotechnologies." **Vincent Cryns**, Co-PI of the **Northwestern CNPP** was Chair and Invited Speaker for the "The Emerging Role of Nanotechnology in Cancer Therapy" Session. Ferrari also spoke in this session.

Stanford CCNE-T PI **Sanjiv Sam Gambhir** chaired a Major Symposium, "Recent Developments in Strategies for Early Cancer Detection." Gambhir and **Chad Mirkin**, PI of the **CCNE at Northwestern University**, both spoke during the symposium. Alliance PIs **James Heath**, of the **NSBCC at Cal Tech**, and **Lily Yang**, of the **Emory University CNPP**, were speakers at the Major Symposium "Nanotheranostics: Opportunities and Challenges for Clinical Translation." ◆

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Center Manager: Jason Sakamoto, Ph.D

Cancer Nanotechnology Platform Partnerships (CNPP)

Combinatorial-designed Nano-platforms to Overcome Tumor Resistance
Northeastern University
Principal Investigators: Mansoor Amiji, Ph.D., and Zhen-feng Duan, M.D., Ph.D.

High-Capacity Nanocarriers for Cancer Therapeutics
University of Nebraska Medical Center
Principal Investigator: Alexander Kabanov, Ph.D, D.Sc.

Magnetoresistive Sensor Platform for Parallel Cancer Marker Detection
University of Utah
Principal Investigators: Marc Porter, Ph.D., and Sean J. Mulvihill, M.D.

Nanobioconjugate Based on Polymalic Acid for Brain Tumor Treatment
Cedars-Sinai Medical Center
Principal Investigator: Julia Ljubimova, M.D., Ph.D.

Nanoscale Metal-Organic Frameworks for Imaging and Therapy of Pancreatic Cancer
University of North Carolina at Chapel Hill
Principal Investigators: Wenbin Lin, Ph.D., and Jen Jen Yeh, M.D.

Peptide-Directed Protocells and Virus-like Particles: New Nanoparticle Platforms for Targeted Cellular Delivery of Multicomponent Cargo
University of New Mexico
Principal Investigators: Cheryl Willman, M.D., and C. Jeffrey Brinker, Ph.D.

Preclinical Platform for Theranostic Nanoparticles in Pancreatic Cancer
Rice University
Principal Investigators: Naomi Halas, Ph.D., D.Sc., and Peter Nordlander, Ph.D.

RNA Nanotechnology in Cancer Therapy
University of Cincinnati
Principal Investigators: Peixuan Guo, Ph.D., John Rossi, Ph.D., and Henry Li, Ph.D.

Targeting SKY Kinase in B-Lineage ALL with CD-19 Specific C-61 Nanoparticles
Children's Hospital Los Angeles
Principal Investigator: Fatih Uckun, M.D., Ph.D.

Theranostic Nanoparticles for Targeted Treatment of Pancreatic Cancer
Emory University
Principal Investigators: Lily Yang, M.D., Ph.D., and Hui Mao, Ph.D.

Toxicity and Efficacy of Gold Nanoparticle Photothermal Therapy in Cancer
Emory University
Principal Investigators: Dong Shin, M.D., and Mostafa El-Sayed, Ph.D.

Tumor Targeted Nanobins for the Treatment of Metastatic Breast and Ovarian Cancer
Northwestern University
Principal Investigators: Thomas O'Halloran, Ph.D., and Vincent Cryns, M.D.

Centers for Cancer Nanotechnology Training

Boston University Cross-Disciplinary Training in Nanotechnology for Cancer
Boston University
Principal Investigators: Bennett B. Goldberg, Ph.D., and Douglas Faller, M.D., Ph.D.

Integrative Cancer Nanoscience and Microsystems Training Center
University of New Mexico
Principal Investigators: Janet M. Oliver, Ph.D., and Abhaya Datye, Ph.D.

Midwest Cancer Nanotechnology Training Center (M-CNTC)
University of Illinois Urbana-Champaign
Principal Investigators: Rashid Bashir, Ph.D., and Ann Nardulli, Ph.D.

The Johns Hopkins Cancer Nanotechnology Training Center
Johns Hopkins University
Principal Investigators: Denis Wirtz, Ph.D., and Anirban Maitra, M.D.

The University of Kentucky Cancer Nanotechnology Training Center
University of Kentucky
Principal Investigators: Bradley D. Anderson, Ph.D., and B. Mark Evers, M.D.

UCSD Cancer Nanotechnology Training Center
University of California San Diego
Principal Investigators: Robert F. Mattrey, M.D., and Andrew Kummel, Ph.D.

Pathway to Independence Awards in Cancer Nanotechnology

Enzyme-Responsive Nanoemulsions as Tumor-Specific Ultrasound Contrast Agents
University of California, San Diego
Principal Investigator: Andrew P. Goodwin, Ph.D.

Inhibition of Metastasis-Initiating Cells by Chimeric Polypeptide Nanoparticles
Duke University
Principal Investigator: Mingnan Chen, Ph.D.

Nanoplatform Based, Combinational Therapy Against Breast Cancer Stem Cells
National Institute of Biomedical Imaging and Bioengineering, NIH
Principal Investigator: Jin Xie, Ph.D.

Nanotechnology for Minimally Invasive Cancer Detection and Resection
Emory University
Principal Investigator: Aaron M. Mohs, Ph.D.

Next-Generation Quantum Dots for Molecular and Cellular Imaging of Cancer
Emory University
Principal Investigator: Andrew M. Smith, Ph.D.

Theranostic Nanomedicine for Breast Cancer Prevention and Image-Guided Therapy
Massachusetts General Hospital
Principal Investigator: Prakash R. Rai, Ph.D.

Tumor Targeting and Diagnostic Applications of Glycosylated Nanotubes
Wake Forest University Health Sciences
Principal Investigator: Ravi N. Singh, Ph.D.

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