NCI Alliance for Nanotechnology in Cancer

BULLETIN

An NCI Alliance for Nanotechnology in Cancer publication to connect participants, partners, affiliates, and colleagues

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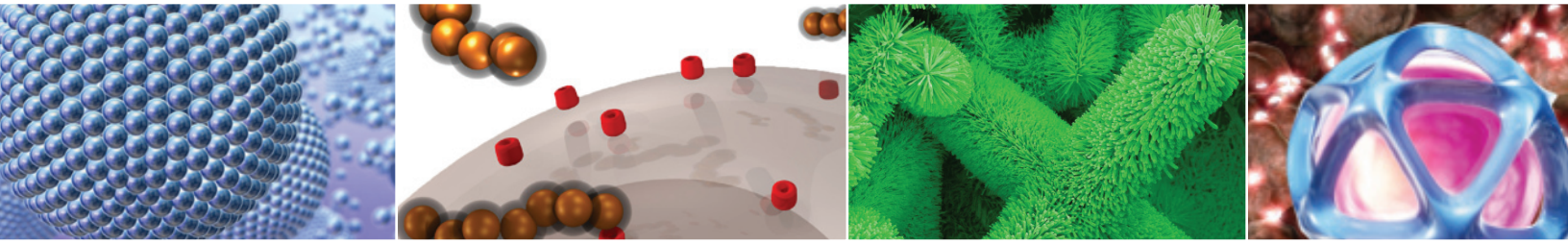

IN THIS ISSUE

Building Team Science

NANO MOTHER SHIPS DESIGNED TO DETECT AND TREAT CANCER

By Michael J. Sailor[1], Ji-Ho Park[1], Sangeeta N. Bhatia[2], Geoffrey von Maltzahn[2], and Erkki Ruoslahti[1]

Collaborating Centers:

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A key nanotechnology objective is to build molecular devices that surpass the function of single molecules. Ultimately these enhanced nanodevices would provide modern medicine with integrated therapeutic and diagnostic function within a single *in vivo* delivery device.

Until recently, multi-functional hybrid nanosystems have been studied *in vitro*, but there have been specific obstacles in moving to animal studies. The poor stability of nanodevices led to toxicity issues and poor targeting. The natural clearing process of the animal's circulation system limited the nanodevice circulation time and subsequent effectiveness. The recent development of "nano mother ships" that detect and treat cancer cells in a specific manner utilizes unique hybrid nanodevices. Conceptually the hull is composed of modified lipids and cancer related targeting molecules which provide a stable vehicle for accurate delivery of a multifunctional payload. The payload provides one or more unique methods of imaging the tumor (e.g. quantum dots and magnetic iron oxide particles) and a toxic drug designed to destroy the tumor *in vivo* with minimal effect on the patient (Figure 1, Drawing on Right).

A multidisciplinary, multi-CCNE team with varying specialties came together through the support and nurturing of the NCI Alliance to address these obstacles. Led by UCSD Prof. Michael J. Sailor, the team comprises of Ji Ho Park, UCSD, Prof. Sangeeta N. Bhatia and Geoffrey von Maltzahn, MIT, and Prof. Erkki Ruoslahti

of The Burnham Institute at UCSB. The NCI Alliance emphasizes collaborations focused on developing and applying nanotechnology and nanoscience solutions to the diagnosis and treatment of cancer. A purpose well represented in this team's focus on engineering multifunctional nanoparticles which exploit biological processes to guide the targeting, self-assembly, and remote function of these materials to treat tumors in mouse models of cancer. Specifically, the development of these unique long circulating "nano mother ships" of micellar hybrid nanoparticles (MHN). These MHN are composed of magnetic particles (MN) and quantum dots (QD) for dual mode imaging (magnetic resonance and fluorescence) and an anti-cancer drug doxorubicin (DOX) within a single polyethylene glycol (PEG)-phospholipid micelle. Their recent publication in *Angewandte Chemie*[1] provides the first demonstration of a single nanodevice that utilizes multi-mode imaging and targeted drug delivery to tumor tissue both *in vitro* and *in vivo*. These unique MHN conjugated to a targeting peptide dock and merge contents into a specific cell utilizing the cells endosomal system to eventually allow the DOX to reach the nucleus. Each MHN carries multiple iron oxide nanoparticles to enhance Magnetic Resonance Imaging (MRI) brightness in locating the tumor in body and QD for near infrared (NIR) fluorescence detection to enhance tumor visualization.

Dr. Sailor and Ji Ho Park concentrated on developing and evaluating the multi-functional nanoparticles containing the magnetic iron oxide nanoparticles and quantum dots for stability and imaging efficacy in this study. Synthesis of the "nano mother ship" involved combining MN, and QD (both coated with hydrophobic chains) followed by encapsulation into micelle of PEG-modified phospholipid (60-70 nm in size, see Figure 1, inset TEM micrograph). They noted that as the ratio of MN:QD increases, the fluorescence spectra was found to decrease, though detection was observed at sub-nanomolar QD concentrations. The presence of both MN and QD in the hybrid micelles allows the detection of tumors in both fluorescence and MRI imaging systems. Thus providing dual mode imaging detection capabilities. The anti-cancer drug DOX was also incorporated during the encapsulation process to provide demonstration of targeted drug delivery.

Dr. Ruoslahti's research focuses on identifying unique tumor vasculature "zip codes" that can be used to identify homing peptides as targeting elements to deliver nanoparticles into tumors and other sites of disease. The targeting ligand F3 he identified specifically binds to endothelial cells in tumor blood vessels and was conjugated to the MHN[1]. This peptide has been shown to transport payloads into tumor vasculature *in vivo*. At MIT, Dr. Bhatia, physician and engineer, and von Maltzahn research the use of micro and nanotechnologies in tissues studies. They utilized their expertise in cell and animal imaging to evaluate the targeting, detection and delivery of the "nano mother ships" for *in vitro* and *in vivo* studies. They demonstrated an increase in

both NIR fluorescence and MRI contrast within cells incubated with these hybrid nanoparticles. The F3 ligand of the surface of the hybrid particles was observed to chaperone the DOX into cancer cells and utilize the endosomal pathway to facilitate the release of the drug into the nucleus. The inherent red fluorescence of the drug provided a means to visualize this delivery process (Figure 1, Left colorized cell culture image). Distinct fluorescence and MRI contrast was observed in nude mice bearing tumors, and treated with the "nano mother ships."

With any *in vivo* study, toxicity must be a consideration. The potentially toxic nature of QD (cadmium), was not observed in this encapsulated form. Additionally the efficacy of the DOX was increased. The cytotoxicity of the delivered DOX in the hybrid nanoparticles was significantly greater than equivalent levels of free or untargeted DOX containing hybrid particles. The circulation of the PEG coated MHN remained significantly longer in the blood circulation than previous formulations.

These long circulating MHN provided stable "nano mother ships" for target specific delivery to cells *in vitro* and *in vivo*. This form of dual mode imaging may one day allow diagnosticians the advantage of full body tumor localization (MRI) and optical imaging at higher resolution using NIR. Followed by secondary payload delivery of a therapeutic drug into specific cells. The enhanced efficacy may lead to smaller doses of drug, and reduced side effects of toxic cancer drugs by limiting the exposure to normal tissues.

The recent discovery that aggregates of polymer coated iron oxide nanoparticles, coined "nanoworms", can effectively evade the body's natural elimination process further reflects on the potential impact of these nanodevices for both diagnostics (enhanced and tumor specific detection) and therapeutics (target specific delivery effective killing drugs).[2] In addition to MRI and fluorescence imaging consider the possibility of future hybrid nanodevices which may allow a combination of photo-thermal therapy, and/or Raman imaging. This unique NCI Alliance provides a powerful example of what can be accomplished from a cross CCNE collaboration, the development and successful demonstration of a nanodevice with potential impact on cancer diagnostics and therapeutics.

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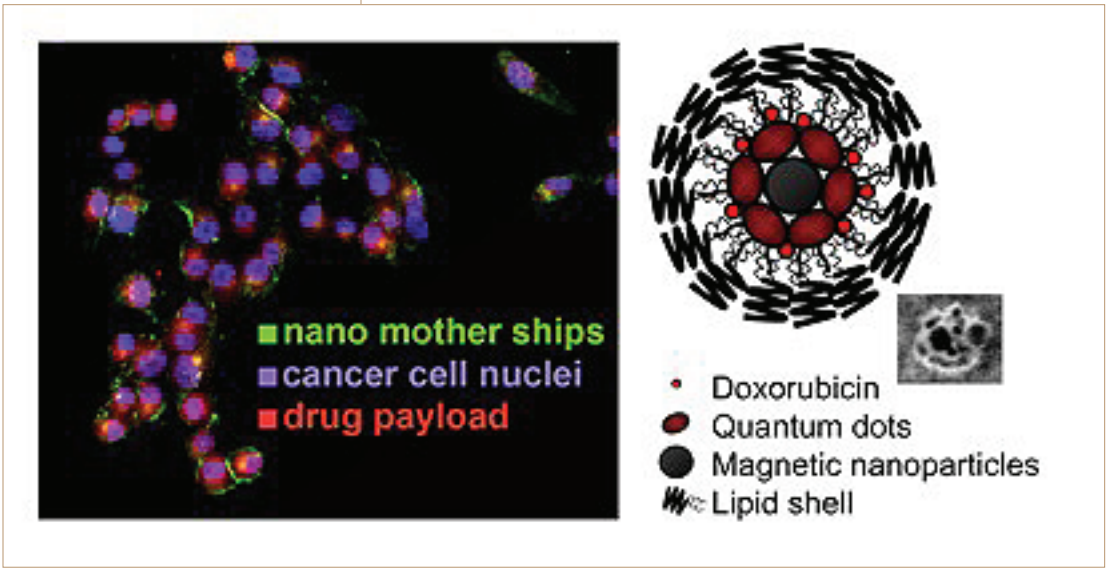
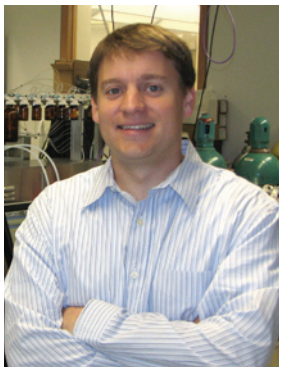


FIGURE 1. (Left) The image shows the mother ships in green, sticking to MDA-MB-435 human carcinoma cells, whose nuclei appear blue. The ships have just discharged their payload into the cancer cells: the anti-cancer drug doxorubicin (red in the image). (Right) Structural diagram of nano mother ship design (inset Transmission Electron Micrograph of MHN).

Young Investigator Highlight



C. Shad Thaxton, M.D., Ph.D.
NU-CCNE,
Evanston/Chicago, IL

INTERDISCIPLINARY TRAINING LEADING THE WAY TO EXCITING NEW DISCOVERIES

Ten years ago, Shad Thaxton knew that he wanted to pursue medicine as a career, what he never envisioned was the highly interdisciplinary road that this decision would ultimately lead him on.

In 2002, Shad read a series of articles in an issue of Scientific American dedicated to Nanotechnology. "As I read the articles, I appreciated the impact that nanotechnology was inevitably going to have on medicine and thought that the science was amazing," Shad explained. "When I got to the end of one of the articles, I found that the work that I had been reading about was being done by Professor Chad Mirkin at Northwestern University. " That day, Shad contacted Professor Mirkin and inquired about spending a year in the laboratory. After finishing his 3rd year of medical school, Shad prepared to enter the laboratory with funding from a Howard Hughes Medical Student Fellowship. "In order to hit the ground running, I scheduled the last of my 3rd year medical school rotations at Evanston Hospital so that I could spend time in the laboratory in the evenings to learn how to make DNA and conjugate gold nanoparticles." Ultimately, his one year commitment evolved into a PhD which he obtained in 2007.

As a graduate student, Shad co-invented the bio-barcode protein detection technology for the ultra-sensitive detection of protein analytes. Prostate specific antigen (PSA), a biomarker for prostate cancer, was the initial target of study. Depending upon the analyte and matrix complexity, the bio-barcode assay is between one and six orders of magnitude more sensitive than conventional immunoassays. In addition, near the end of his time in the Mirkin lab, Shad performed some of the initial experiments demonstrating the use of gold nanoparticles as intracellular gene regulating agents. "It is an amazing challenge and fascinating to me that one can fabricate a nanostructure, from the bottom-up, that can exquisitely interface with biological molecules and systems in order to cure disease," added Shad.

It is an amazing challenge and fascinating to me that one can fabricate a nanostructure, from the bottom-up, that can exquisitely interface with biological molecules and systems in order to cure disease.

Shad has been a member of the NU-CCNE Project on developing the Barcode Assays for the detection of ovarian and prostate cancer since 2005. He has been instrumental in bridging the efforts of the researchers in the Chemistry Department and the Department of Urology, and facilitating and coordinating the efforts of a multi-institutional and international research team in order to demonstrate in a pre-clinical trial the utility of ultra-sensitive monitoring of PSA in the serum of men treated for prostate cancer.

Completion of the pre-clinical study demonstrated that the bio-barcode assay is capable of monitoring the PSA levels in patients who have undergone treatment for prostate cancer at serum concentrations that were previously immeasurable. "This ability, provided by bringing new nanotechnology to bear on bio-molecular detection, may allow for the rapid detection of disease relapse, an objective measure of the response of recurrent disease to adjuvant treatments, and, importantly, the ability to inform patients of a no evidence of disease status" says Shad. Ultrasensitive measurement of PSA levels in men following prostate cancer surgery is currently being collaboratively explored prospectively and retrospectively by Thaxton, the Northwestern University Department of Urology, Nanosphere, Inc., and Professor Mirkin. This multidisciplinary effort is a direct result of the Northwestern CCNE.

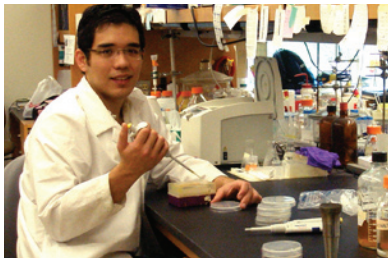
In 2008, Shad became the newest research faculty member in the Department of Urology at the Northwestern University Feinberg School of Medicine. He continues to be an important member of the NU-CCNE research team.

In addition to prostate cancer and diagnostics, Shad's research interests focus on the fabrication of the next generation of nanoparticle therapeutic and diagnostic agents, as well as translating current state-of-the art nanostructures into the clinical realm. Clinical translation of new and currently available therapeutic agents will require a thorough investigation of the *in vivo* distribution, short and long term toxicity profile, and *in vivo* efficacy of these nanostructures. A number of these tasks will be facilitated by fostering relationships with other CCNE investigators and laboratories.

"Being part of the NU-CCNE has given me the opportunity to rapidly translate the bio-barcode assay into the clinic where nanotechnology may have the profound impact that I envisioned as a medical student. The future success of this project and others will be dictated by my ability to communicate with others, foster new relationships, and collaborate across disciplines. It is in this framework that we will make the promise of nanotechnology a reality."

Dr. Thaxton lives in Chicago with his wife Maggie, and their two children, Aidan Erva and Marin.

Training Across the Alliance



Richard Ahn, NU-CCNE, Evanston/Chicago, IL

PROMISING YOUNG RESEARCHER EFFECTIVELY LEVERAGES SUPPORT FROM THE ALLIANCE

NU-CCNE researcher, Richard Ahn was recently awarded a Predoctoral Traineeship Award from the Department of Defense Congressionally Mandated Medical Research Programs to explore therapeutic nanobins for the treatment and imaging of Her2/neu positive breast cancers.

Pursuing thesis research in the MD/PhD program with Professor Thomas O'Halloran, Richard joined the NU-CCNE project on Nanoscale Encasement and Targeted Delivery of Multifunctional Therapeutic Agents for Hematological Cancer and Solid Tumors in 2006. This prestigious award effectively leverages the support from the NCI Alliance.

Ahn's work targets Her2/neu-positive cancers, which make up about 20% to 30% of the total breast cancers and are targeted by Herceptin, a therapeutic antibody used in the treatment of these cancers.

"For women in the United States, breast cancer is the most common type of cancer and the second leading cause of cancer death," stated Richard. "We are working on the development of a new class of smart chemotherapeutics for breast cancer that specifically deliver chemotherapeutic agents to cancer cells. By targeting cancer cells, normal tissues will be spared high doses of toxic drugs, thus preventing the dose-limiting toxicities that ultimately limit the usefulness of chemotherapy drugs and cause severe side effects.

The first objective of this work is to expand the pharmacological scope of therapeutic compounds that may be encapsulated in liposomes. Liposomes are formed from fatty acids, like those found in cell membranes, and can be induced to form microscopic vessels that may be used to carry chemotherapy. Using methods developed in our lab, we aim to encapsulate very high levels of chemotherapy drugs. These drugs will provide oncologists with more options for cancer treatment. The second aim is to incorporate Herceptin into our liposomes.

Current systemic cancer chemotherapy does not discriminate between normal tissue and cancerous tissue. Targeting liposomes will direct higher doses of chemotherapeutics to cancerous cells and limit the exposure of healthy tissue to drug compounds. The final aim is designed to provide a method to determine the efficacy of delivery of chemotherapy to the tumor site using noninvasive imaging methods in real time. The incorporation of magnetic resonance imaging (MRI) contrast agents will allow the visualization of the drug targeting agent in vivo and give immediate feedback on the success of drug targeting. Currently, a course of cancer chemotherapy is given, and weeks may pass before the effects of therapy can be evaluated. The incorporation of MRI contrast agents will provide a rapid indication of proper drug delivery, potentially allowing for faster assessment of drug efficacy. In addition, the liposomal methods we develop will be broadly applicable to other forms of cancer.

"As a future physician scientist, the training I am receiving has introduced me to current methodologies in nanoscale drug delivery and bioinorganic chemistry," explained Richard. "The techniques and knowledge that I am acquiring are critical to my success as a future Principal Investigator at the interface between nanotechnology and medicine."

Richard is a native of Minneapolis and completed his undergraduate work in chemical biology at University of California, Berkeley. He intends to ultimately, pursue a career as an academic radiologist and researcher.

For women in the United States, breast cancer is the most common type of cancer and the second leading cause of cancer death.

Ji-Ho Park, Ph.D. Candidate in Material Science, NANO-TUMOR CCNE

SHARING IDEAS AMPLIFYIES RESULTS IN CANCER NANOTECHNOLOGY: AN INTERVIEW WITH JI-HO PARK, PH.D. CANDIDATE IN MATERIAL SCIENCE, UCSD CCNE (NANO-TUMOR CENTER)

By Adriana Vela
Project Lead, Educational Core
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Years ago, the mantra among research communities was 'publish or perish'. While publishing continues to be important, the mantra appears to be evolving into 'partner or perish' given the overwhelming evidence that demonstrates the impact collaborations have on the speed at which research is conducted and new discoveries are made. The advent of communication tools and the internet have become important enablers for information exchange and collaborations. Despite this, collaboration and sharing of ideas is not necessarily a given in all research environments especially across different disciplines. The NCI Alliance leads in this area by actively encouraging interdisciplinary collaboration and training. Similarly at UCSD, researchers benefit from a culture rich with collaborative spirit. One notable example demonstrating this spirit is Ph.D. candidate, Ji-Ho Park, a research member of Michael Sailor's lab. Following is an interview with Ji-Ho about his role in Sailor's lab and his experience in a collaborative-intense environment.

AV: What lured you to UCSD in 2004 after completing your bioengineering degree in South Korea?

JHP: After researching many options, I chose UCSD for its reputation in the bio-related research. UCSD is also widely known for its academic record and culture that encourages interdisciplinary collaborations. These were two very important factors in my decision.

AV: Tell me how you got started with this research team and how you leveraged your background to make contributions.

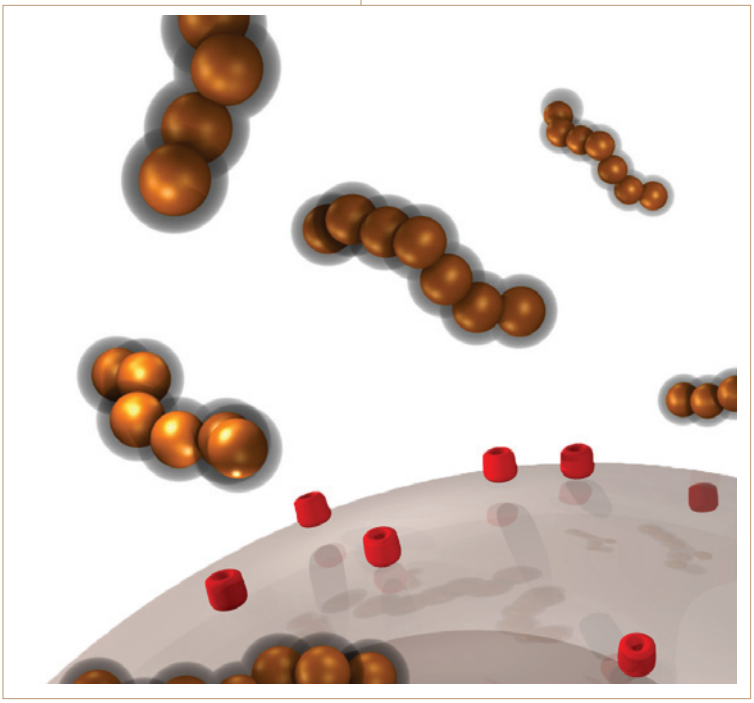
JHP: When I first joined the project in the collaborations with the research groups of Michael J. Sailor (my advisor, UCSD), Erkki Ruoslahti (Burnham Institute for Medical Research), and Sangeeta N. Bhatia (MIT), the team was developing the strategies to amplify *in vivo* tumor targeting of diagnostic and therapeutic nanoparticles by mimicking biological phenomena occurring in the body. However, since they have been using commercially available nanomaterials for this project, it seemed difficult to me that they modify the nanoparticle surface or structure for their specific purposes. Since I have had a lot of experiences to synthesize several types of nanomaterials, I thought that the use of our own nanomaterials would help us develop new nano-tools in cancer research more readily, at that time, I have decided to be involved in providing our team with well-characterized and *in vivo*-applicable nanomaterials I synthesize.

AV: Earlier this year you were sited as 'being the motivating force behind the discovery that gummy worm aggregates of nanoparticles stayed for hours in the bloodstream despite their relatively large size. Dubbed "Nanoworms", this discover was featured in ABC News and also was the subject of the cover of Advanced Materials's May issue where it also achieved recognition by the publication's deputy editor as being the 'Most Accessed' article. How did that come about?

JHP: While many discoveries often come about by accident, my material science experience and focus has been on synthesizing new nanomaterials and taking advantage of important new properties. We constructed the nanoworms from spherical iron oxide cores that joined together, like segments of an earthworm, to produce tiny gummy worm-like structures about 50 nanometers long. Their iron-oxide composition allows the nanoworms to show up brightly in an MRI allowing us to locate tumors earlier. We believe that the nanoworm's flexibly moving one dimensional structure may be one reason for its long life in the bloodstream and ability to evade the body's protective mechanism that would otherwise eliminate them from the bloodstream before reaching its target.

AV: How does this interdisciplinary team effectively work and how does each member contribute?

JHP: In the present collaboration, our multidisciplinary team has been engineering multifunctional nanoparticles that will exploit biological processes to guide the targeting, self-assembly, and remote actuation of these materials to treat tumors in mouse models of cancer. Particularly, I have focused on synthesizing new nanomaterials that can be used to allow the early diagnosis and effective treatment of cancer *in vivo*. In order to accomplish our goal, multiple backgrounds such as clinical cases in tumor therapy, tumor biology, materials science, and bioengineering are required. As a materials scientist, I could not understand complex biological processes in tumors or generally of the body as much as oncologist and tumor biologist could. Likewise, they also would not solve problems in the aspect of materials science easily. Thus, the training through collaboration allowed me to share ideas with other groups, discuss problems together, inter-compensate for the parts which folks in other field may not be familiar with, and proceed to develop the new nanomaterial-



An image of nanoworms from the cover of *Advanced Materials* magazine. Nanoworms are constructed from spherical iron oxide cores that are joined together, like segments of an earthworm, to produce tiny gummy worm-like structures about 50 nanometers long. The iron-oxide composition allows nanoworms to show up brightly in an MRI, helping to locate tumors earlier.

based tools for cancer diagnosis and therapeutics which can be translated to clinics in near future.

AV: Has the model for collaboration been effective so far?

JHP: I believe that face-to-face discussion and collaboration between graduate students is most effective and necessary to better understand what is going on in each group and the level of give and take from one another considering the physical distance between the institutions. I frequently visit the Bhatia group at MIT crossing the country and spend some time in their lab to discuss the problems in each side, perform experiments together, and sometimes use the instruments we don't have in our institute to complete experiments. Additionally, some of our collaborative work have been done simultaneously at both institutes (e.g. nanomaterial synthesis and characterization in the Sailor group at UCSD and *in vitro* and *in vivo* targeting and therapeutic study using the nanomaterials in the Bhatia group at MIT). This collaboration enables me to focus on studying the research area more specialized to me (e.g. nanomaterial development) and contribute to the overall collaboration more effectively.

AV: How has your experience with collaborative projects shaped the way you see research in general? How has it shaped the way you view your career developing?

JHP: The training across the alliance has encouraged me to carefully listen to various opinions from other experts such as pathologists and clinical surgeons and design new nanomaterial platforms for biomedical applications. My research interest in bionanotechnology requires me to work on the interface between biology and nanotechnology and I will need a lot of help from experts in biology and medicine. Thus, the collaboration experience I have been through will allow me to choose my research topic in future post-doctoral position or career from more diverse and interdisciplinary fields. I am very happy to participate in the collaboration with world-class research groups through the UCSD CCNE program.

AV: What do you consider to be the most important lesson this experience has taught you?

JHP: I would say that opening my mind is the most important lesson I got from this experience. Generally, we don't try to listen to opinion from people working in other fields and keep our already-made decision or opinion to solve problems or do research. But through this collaboration, I realized that totally different approaches from people who have different backgrounds would help solve problems quicker in research.

AV: What are you goals after you graduate?

JHP: I would like to proceed with post-doctoral training and later become a professor at the University level teaching and doing research related to bioengineering and material science.

Training Across the Alliance

Adam Braunschweig, NU-CCNE, postdoctoral

NIH KIRSCHSTEIN POSTDOCTORAL FELLOWSHIP IN CANCER PROVIDES NEW OPPORTUNITIES

NU-CCNE, Evanston/Chicago, IL

Northwestern University postdoctoral scholar Adam Braunschweig is the newest recipient of the National Institute of Health's Kirschstein Postdoctoral Fellowship in Cancer Nanotechnology Research.

"Besides being a great honor, this prestigious fellowship provides the flexibility necessary to branch off into new research directions," stated Adam. His work will investigate the potential of nucleotide-nanoparticle conjugates in cancer therapy and research.

Adam's Ph. D. training was in the field of physical-organic chemistry, and the move to cancer research is a significant departure from his previous work. While working on his thesis, he developed new thermodynamic models and synthetic pathways for the design of molecular machines. Although these nanoscale machines were built for molecular electronic and nanoelectronic mechanical systems, "I believe the interdisciplinary experience I acquired building intricate molecular systems is a strong foundation for dealing with the complexity inherent to cancer" says Adam.

The interdisciplinary mindset Adam has used in his previous work is reflected in the project he will undertake in Professor Chad Mirkin's laboratory. The Mirkin lab is a world leader in nanomaterials synthesis, particularly in the development of gold nanoparticle-oligonucleotide conjugates. These materials are small clusters of gold (< 100 nm) that are covered with a well-ordered shell of nucleic acids. By decorating these nanomaterials with a shell of oligonucleotides, they are able to combine the recognition abilities of the DNA and the structural properties of the nanoparticles, which results in a host of new characteristics that result from working on the nanoscale dimension. Importantly, these materials penetrate the cell wall easily and have negligible cellular toxicity, making them the ideal systems to study cellular function.

Adam will study the ability of these nucleotide-nanoparticle agents to knockdown oncogene expression as both therapeutic agents and to understand signaling pathways that lead to cancer. Because the oligonucleotide-nanoparticle agents both carry DNA into cells and bind complementary mRNA with high affinity, they behave as effective knockdown agents of gene expression. Using the specificity of complementary nucleotide interactions, these conjugates can be tailored to knockdown the expression of almost any gene, and the subsequence effects on cellular function can be explored. In particular, Adam is interested in genes, such as Survivin, that imbue cancer cells with resistance to programmed cell death, apoptosis. Genes that inhibit apoptosis are an interesting therapeutic target because unlimited cell division results in tumors, and researchers hope understanding and stopping this growth has therapeutic potential.

From the collaborative environment that exists within the Northwestern CCNE, Adam hopes to extend this project from the construction of nanostructures to testing them in real cancer models. By exploiting both preexisting collaborations within the Mirkin lab as well as the interdisciplinary nature of the CCNE, he hopes to make steps towards translating the recent progress in nanotechnology to real, clinical benefits for cancer patients.

Accelerating Translation

FROM THE LABORATORY TO THE MARKETPLACE — ACCELERATING COMMERCIALIZATION OF NEW TECHNOLOGIES

NU-CCNE, Evanston/Chicago, IL

Rapid commercialization of new technologies helps to ensure key discoveries have immediate impact, but the path from laboratory hypothesis to commercially relevant product can be challenging. Even once the promising new technologies has been conceived, developed, and tested, the development of a compelling business plan that can launch that technology into the market can remain as a significant road block to commercialization for scientists, engineers, and clinicians untrained in business development.

To address this need, researchers at the Northwestern University (NU) CCNE can turn to the Small Business Evaluation and Entrepreneur (SBEE) program. This unique program provides opportunities for researchers to work in partnership with advanced MBA students. The researchers are assisted in determining market viability of their technologies and in the development of comprehensive business plans. The MBA students are introduced to the latest technological advances while gaining real-world experience.

Developed by Professor Chad Mirkin, NU-CCNE Director and Director of the International Institute for Nanotechnology (IIN), and Professor Barry Merkin from the Management and Strategy Department in Northwestern's Kellogg School of Management, the SBEE program has resulted in the launch of 14 start-up companies and $330 million in venture capital support to-date.

The SBEE program capitalizes on the strength of NU's Kellogg School of Management, which is consistently named among the top management schools in the world in surveys conducted by publications including *BusinessWeek*, *the Economist Intelligence Unit, Financial Times, U.S. News & World Report* and *The Wall Street Journal*. Kellogg students hear presentations on new technologies in the exciting field of nanotechnology at open forums held throughout the year. Students evaluate prospective opportunities and form teams to evaluate, research, and assist with the development of business plans that are then presented to potential investors. "The SBEE program brings together people from two different worlds," explained Professor Mirkin. "The business students have unique opportunities to be in on the ground floor of the latest technologies, and the researchers are assisted in successfully transitioning their discoveries from the laboratory to the marketplace. It's a win-win situation."

The test case for the SBEE program was a new nanoparticle-based diagnostic tool to detect disease targets ranging from HIV to methicillin-resistant bacteria. "Working with the MBA students from Kellogg, we were able to develop an award-winning business plan and generate the capital necessary to launch a new business," stated Mirkin. In November 2007, this business (Nanosphere, Inc.) raised $113 million in its initial public offering.

Additionally, the company recently received clearance from the Food and Drug Administration for the Verigene® System — a gold nanoparticle-based medical diagnostic platform for clinical use — and two nanotechnology-based assays. The Verigene® System is the basis for an ultrasensitive prostate-specific antigen (PSA) immunoassay that is being developed by researchers at the NU-CCNE and the technology was licensed to Nanosphere.

Some recent examples of technologies successfully launched through the SBEE program include: Nanotope, Inc., launched in 2005 by Professor Samuel Stupp to commercialize the use of his self-assembling amphiphilic molecules for drug discovery and novel therapeutic tissue regeneration; PreDx, Inc., launched in 2006 to commercialize the bio-activated contrast agents for imaging diagnostics developed by Professor Thomas Meade; and SAMDITech, Inc., launched in 2007 by Professor Milan Mrksich to commercialize high-throughput biomarker screening for in vitro nanodiagnostics. Pharocore, Inc. is currently under development to commercialize the application of nanoprisms for diagnostics and therapeutics.

DEVELOPING THE NEXT GENERATION "SMART" CONTRAST AGENT NANOPARTICLES FOR MAGNETIC RESONANCE IMAGING AND TREATMENT OF CANCER

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Magnetic resonance imaging (MRI) uses magnetism, radio waves, and a computer to produce images of internal body structures and function. This powerful radiological tool is noninvasive, provides high spatial resolution, and tomography.

During the imaging process, magnetic resonance (MR) contrast agents are used to highlight specific internal organ features making them easier to see. Unfortunately, many commercially-available MR contrast agents lack imaging sensitivity, which significantly limits their effectiveness in cancer diagnosis.

An interdisciplinary team of researchers at the Northwestern University (NU) CCNE is exploiting the rapidly advancing field of nanotechnology to develop new classes of MR contrast agents. By coupling the unique properties of nanomaterials that function as a platform-diagnostic with new types of biochemically activated probes, entirely new generations of contrast agents are being developed that are capable of detecting cancer at the cellular level in whole organisms and potentially delivering targeted treatment.

"We are focusing on developing contrast agents for early staging of cancer that are 10 to 100 times more sensitive than currently available, while simultaneously reporting on the physiological properties of lesions and tumors," stated Professor Meade.

A primary focus has been the investigation and optimization of particle size and composition on the magnetic properties of nanoparticles used as T_2 (dark) MR contrast agents. The results of these studies indicate that the size of the magnetic nanoparticles modulates the magnetic moment and strongly affects the T_2 MR contrast effects (Figure 1). As the size of a Fe_3O_4 nanoparticle increases from 4 to 12 nanometers, MR contrast is substantially enhanced. Moreover, doping the crystalline lattice of Fe_3O_4 with atoms (such as Mn, Co, and Ni) increases the contrast. Mn-doped iron oxide nanoparticles, in particular, have a higher magnetic moment and exhibit a 5.8 times higher MR relaxivity as compared to conventional iron oxide nanoparticles. The team has also found that when a 12 nm doped iron oxide nanoparticle is conjugated

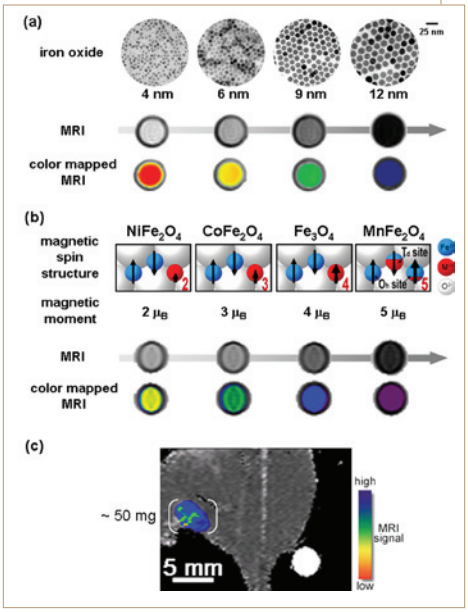


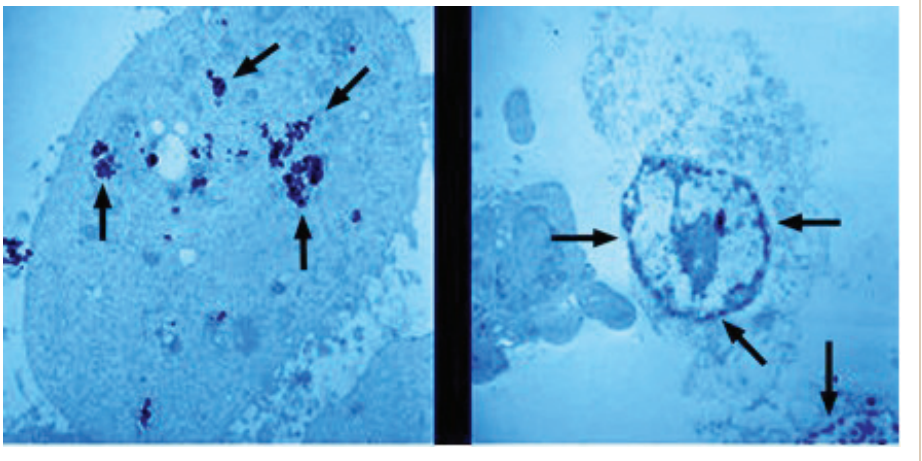
FIGURE 1. (a) (a) Nanoscale size effects of Fe_3O_4 nanoparticles on MR contrast effects. (b) Magnetic spin structures of metal-doped Fe_3O_4 nanoparticles, MFe_2O_4 (M=Mn, Fe, Co, Ni) and their effect on MR contrast. (c) MR image of a small tumor (~50 mg) in a mouse after injection of 12 nm MnMEIO-herceptin (antibody) conjugates.

to herceptin (Figure 1c) it targets the cancer marker Her2/Neu and enables selective detection of a small tumor (~50 mg).

The team has also recently reported some exciting developments with the synthesis of an array of magnetic nanostructures that are conjugated with brain tumor specific antibodies. Co-localization experiments with these conjugated nanostructures demonstrate an affinity for them to simultaneously target the TGF-β and NCAM surface receptors of medulloblastoma (i.e., highly malignant primary brain tumor) cells. Extensive analysis by SEM (scanning electron microscopy) has indicated that the mechanism for cellular uptake of these nanostructures is receptor-mediated translocation versus passive uptake through internalization by the cells (Figure 2) — meaning that the conjugated magnetic nanostructures are selectively entering only the cancer cells. Researchers hope that coupling a radio-frequency (RF) system could provide targeted thermal activation and subsequent destruction of the cancer cells, allowing the tumors to be detected and simultaneously eliminated.

The NU-CCNE team is also pioneering the synthesis of "smart" small-molecule gadolinium contrast agents that are biologically activated. They have successfully developed probes that are "activated" by calcium, zinc, β-galactosidase, and β-glucuronidase. Additionally new nanomaterials have been created through the design of a unique class of multimodal contrast agents for MRI that contain a super-paramagnetic nanoparticle core, biocompatible shell, and covalently-linked paramagnetic Gd(III) chelate (multi-MR). Results indicate that the covalent attachment of the Gd(III) chelate results in a significant change in the relaxivity of the particles that can be visualized with MR imaging. This class of agent can provide a means to co-localize the agent using two MR modalities (T_1 and T_2) that make diagnosis far more certain. These results demonstrate the promise of the Gd(III) chelates to be high performance, next-generation molecular imaging agents (Figure 3).

FIGURE 2. TEM photomicrographs of medulloblastoma cells targeted by unlabeled (left) and antibody-functionalized magnetic nanostructures (right).



By gaining a thorough understanding of fundamental magnetic nanoparticle properties, exploring new ways to implement increased versatility and biocompatibility, and synthesizing probes that are biochemically activated, the NU-CCNE team is developing new classes of MR contrast agents that could significantly enhance the use of MRI for *in vivo* cancer diagnostics. With the added potential for *in vivo* therapy, these next generation contrast agents could transform MR imaging from simple cancer diagnostic tool to a cancer treatment option.

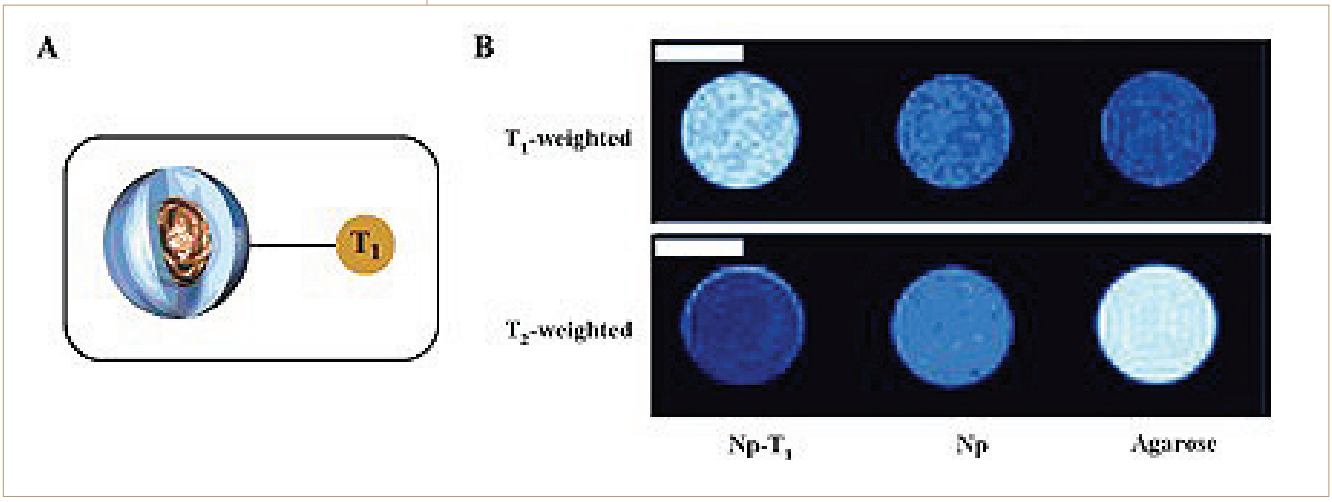


FIGURE 3. (A) Illustration of dual-contrast MRI contrast agent; (B) in vitro phantom MRI images of dual-contrast agent and controls.

SELF-ASSEMBLED PEPTIDE AMPHIPHILE (PA) NANOSTRUCTURES DESIGNED TO TARGET BREAST TUMORS AND INDUCE CANCER CELL DEATH

By Samuel Stupp[1], Vincent Cryns[2], SonBinh Nguyen[3], Karl Scheidt[3]

Northwestern University, Evanston and Chicago, IL

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[3]Department of Chemistry; Robert H. Lurie Comprehensive Cancer Center

Breast cancer is the leading cause of cancer death among women worldwide, and the fifth leading cause of cancer death including both sexes. Breast cancer treatments currently rely heavily on the use of chemotherapeutic agents. While often a valuable course of treatment, the use of these substantially toxic agents also significantly affects normal tissue. The ability to specifically target tumor cells to deliver therapeutic agents would therefore be a tremendous breakthrough.

A considerable fraction of breast cancers exhibit an excess of a particular protein called ErbB2 on the surface of cells — a protein that might be related to a high number of abnormal or defective cells. ErbB2 is a receptor tyrosine kinase belonging to the epidermal growth factor (EGF) receptor family involved in cell differentiation, proliferation, and tumor growth. Researchers at the Northwestern University (NU) CCNE are developing nanostructures that will target ErbB2 and act as selective drug delivery vehicles.

One platform that has shown particular promise as a nanotechnology-based cancer therapeutic is the cylindrical supramolecular nanofibers created through the self-assembly of peptide amphiphiles (PA). Fundamentally, PA molecules are comprised of a hydrophilic peptide sequence covalently linked to a hydrophobic fatty acid tail. Unique to the research at the NU-CCNE, these particular PA molecules organize through intermolecular bonding into nanofibers that are nanometers in diameter and up to microns in length (Figure 1). "By taking full advantage of the elegant yet simple self-assembly capability of the PA molecules, multifunctional and complex structures can be created," stated Professor Samuel Stupp. "*In vitro* investigations of PA structures bearing drug conjugates and

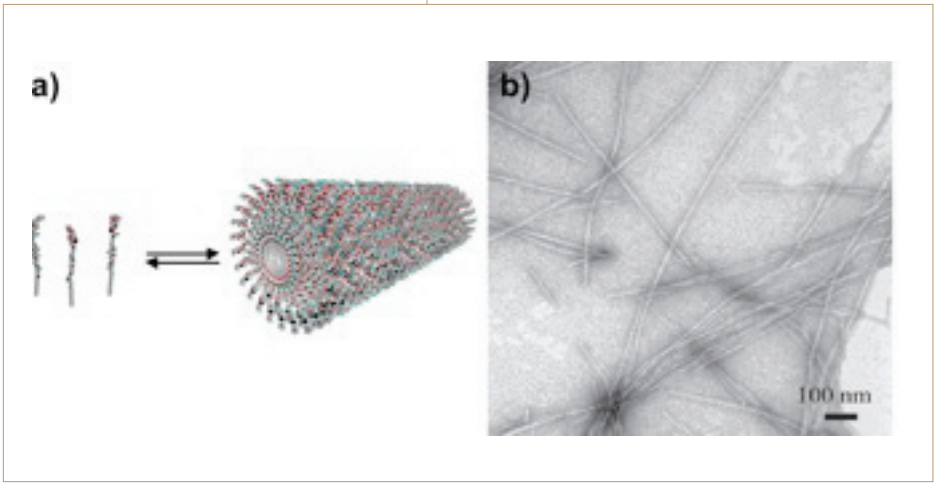
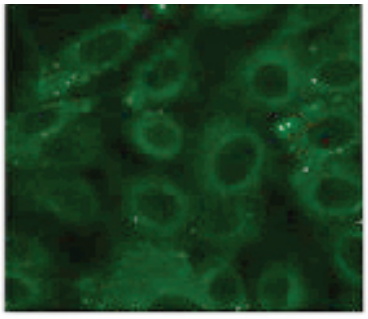
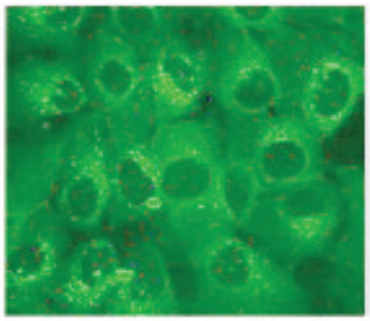


FIGURE 1. A) Schematic representation of a peptide amphiphile supramolecular assembly forming high aspect ratio nanostructures. B) Transmission electron micrograph of PA nanofibers displaying pro-apoptotic sequences on their surfaces.

FIGURE 2. An anti-ErbB2 PA nanostructure (labeled with a fluorescent dye) shows more selective binding to ErbB2 positive cells *in vitro*.



ErbB2 Negative Cells



ErbB2 Positive Cells

apoptotic epitopes show excellent potential thus far," he added. The PA nanofibers, additionally, posses the very relevant feature of being completely biocompatible, therefore allowing cells to degrade these materials through natural metabolic pathways. These characteristics, along with the fact that PA nanostructures can be produced with a peptide synthesizer on a relatively large scale in comparison to other nanotechnologies, could significantly transform breast cancer treatment.

Using the PA supramolecular nanofiber architecture, these researchers are exploring a number of avenues to directly target breast cancer cells. For example, researchers have introduced a PA molecule with an ErbB2-specific antibody mimetic peptide sequence within its supramolecular structure. *In vitro* experiments have shown that the PA nanofibers are selectively taken up by ErbB2 positive cancer cells (Figure 2). The team has also discovered new targeting sequences using phage display screening techniques against a fusion protein bearing the extracellular portion of the ErbB2 receptor.

PA nanostructures composed of pro-apoptotic peptide sequences are also being used directly as anticancer therapeutics. Using the nanofiber itself as the vehicle to destroy malignant cells, this mode of therapy is distinctive in its use of natural amino acids as the cytotoxic agent, as opposed to synthetic chemotherapy drugs. In particular, the $(KLAKLAK)_2$ sequence, which induces cell death by disrupting the mitochondrial membrane, has shown increased cellular uptake (Figure 3) and subsequent bioactivity *in vitro* when incorporated into nanofibers as compared to peptide alone and other PA controls. *In vivo* efficacy experiments are being performed with the hope that the size scale of the nanostructures will cause selective accumulation in tumor tissue due to the enhanced permeability and retention (EPR) effect. An additional pro-apoptotic signal being explored for incorporation into PA systems is a Smac-derived sequence, which antagonizes inhibitor of apoptosis proteins (IAPs).

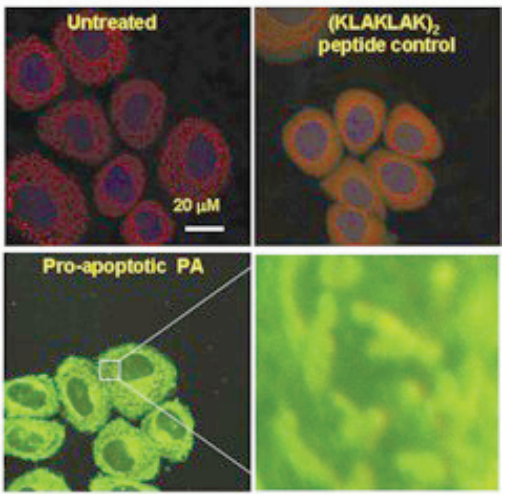


FIGURE 3. SK-BR-3 breast cancer cells treated with fluorescein-labeled $(KLAKLAK)_2$ PA or peptide for 6 h. The internalization of the pro-apoptotic epitope is enhanced when incorporated into PA nanostructures. Additionally, co-localization of the PA nanostructures with cell mitochondria is observed. Mitochondria are stained in red, while the PA nanofibers exhibit green fluorescence. Yellow areas in the merged image (bottom right) indicate co-localization of PA nanostructures with mitochondria.

Alliance Activities

SYMPOSIUMS

Northwestern University CCNE, Evanston, IL
2008 International Institute for Nanotechnology Symposium
November 20, 2008 from 7:45 am-6:30 pm
Location: Hotel Orrington, Grand Ballroom, 1710 Orrington Avenue, Evanston, IL 60201
Featured Speakers:
Alan Heeger, University of California, Santa Barbara
Paul McEuen, Cornell University
Donald Eigler, IBM Almaden Research Center
J. Fraser Stoddart, Northwestern University
David Leigh, University of Edinburgh, Scotland
Julius Rebek, Jr., The Scripps Research Institute
Lars Samuelson, Lund University, Sweden
Jeffrey Moore, University of Illinois at Urbana-Champaign
Cherry Murray, Lawrence Livermore National Laboratory

For more information, please visit: www.iinano.org/symposium/2008.

C-CCNE, Chapel Hill, NC
Annual Cancer Nanotechnology Symposium
Friday, November 14, 2008
Location: Carolina Club at UNC Chapel Hill

For more information, contact Susan Wohler Sunnarborg at susan_sunnarborg@med.unc.edu.

COURSES

Siteman CCNE at Washington University, St. Louis, MO
Biomedical Applications of Nanotechnology
This course is intended to survey the field of nanobiomedicine in a lecture format given by invited experts. Topics will range from multimodality imaging to targeted therapeutics to molecular diagnostics.

Benefits and toxicities will be presented and the translational aspects of commercialization of nanosystems for medical use will be covered. For an outline of course lectures and additional information about the course, please contact Lynn Coulter at lcoulter@cmrl.wustl.edu.

MIT-Harvard CCNE, Boston, MA
Access to all MIT undergraduate and graduate courses can be found at: http://mit.edu/ocw/.

SEMINARS

Emory-Georgia Tech CCNE, Atlanta, GA
2008 Frontiers of Cancer Nanotechnology Seminar Series — These seminars will be webcast.
November 10, 2008 at 3:00 pm
Location: Winship Cancer Institute, Room C5012
Joseph DeSimone, PhD Department of Chemistry & Chemical Engineering University of North Carolina, Chapel Hill
Title — Monodisperse, Shape-Specific Nano-Biomaterials for Cancer Therapeutics and Imaging Agents

December 8, 2008
Location: Winship Cancer Institute, Room C5012
Charles Lieber, PhD Department of Chemistry and Chemical Biology Harvard University Title — Nanoelectronic-Biology Interfaces: From Ultrasensitive Detection to New Biomaterials

For more information, please visit: http://www.wcigtccne.org/index.php.

Or contact, Ryan Jowers — Ryan.jowers@bme.emory.edu — phone 404-778-3033 or Michelle Denney — Michelle.denney@bme.emory.edu — phone 404-727-0391.

Nano-Tumor CCNE, San Diego, CA
"Nanoplatforms for Targeted Molecular Imaging in Living Subjects" by Weibo Cai, Ph.D., Assistant Professor, Departments of Radiology and Medical Physics, School of Medicine and Public Health, University of Wisconsin — Madison, Wisconsin and University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, Madison, Wisconsin

Wednesday, Nov 19, 2008 at Goldberg Auditorium, Moores UCSD Cancer Center

For more info contact: adriana@nanobionexus.org

Northwestern University CCNE, Evanston, IL
Frontiers in Cancer Nanotechnology Seminar Series
November 5, 2008 at 4:00 pm
Location: Northwestern University, 2145 Sheridan Road, Evanston, IL 60202
Professor Mohammad Yousaf, University of North Carolina at Chapel Hill, Carolina Center of Cancer Nanotechnology Excellence

For more information, please visit: www.ccne.northwestern.edu.

CCNE-TR, Stanford, CA
2008 Nanobiotechnology Seminar Series
November 13, 2008
Chad Mirkin, Ph.D. "Nanostructures in Biodiagnostics and Gene Therapy"

For more information, and to view archived webcasts of seminars, please visit http://mips.stanford.edu/public/nanobiotech_seminar.adp.

C-CCNE, Chapel Hill, NC
Seminar Series 2008-2009
All seminars will be at noon in the Lineberger Pagano Conference Room

December 9, 2008
Mark Dewhirst, D.V.M., Ph.D., Department of Radiation Oncology, Duke University
"Development of imageable thermally sensitive liposomes for cancer therapy: Rationale and implementation"

January 13, 2009
Samir Mitragotri, Ph.D., Department of Chemical Engineering, University of California at Santa Barbara
"Designing Carriers for Drug Delivery: Does Shape Matter?"

February 10, 2009
Russ Mumper, Ph.D., School of Pharmacy, UNC-Chapel Hill
"Nano-based Approaches to Address Multidrug Resistance or Target Reactive Oxygen Species to Cancer"

March 10, 2009
Veena Misra, Ph.D., Department of Electrical and Computer Engineering, North Carolina State University
Title TBA

April 14, 2009
Scott Manalis, Ph.D., Department of Biological Engineering, Massachusetts Institute of Technology
"Microdevices for Biomolecular Detection and Single Cell Analysis"

May 12, 2009
Teri Odom, Ph.D., Department of Chemistry, Northwestern University
"Diagnostics and Therapeutics using Multifunctional Nanopyramid Probes

For more information, contact Susan Wohler Sunnarborg at susan_sunnarborg@med.unc.edu.

Alliance Classifieds

Job Postings

MIT-Harvard CCNE, Cambridge, MA
Post-Doctoral Fellow (Laboratory for Multiscale Regenerative Technologies)

Post-doctoral fellow position available in the laboratory of Dr. Sangeeta Bhatia, M.D., Ph.D. (MIT / Brigham and Women's Hospital), to (1) develop novel nanotechnology-based approaches for cancer therapy and imaging, (2) exploit microtechnology tools in the study of the cellular microenvironment, (3) engineer liver tissue models.

LMRT is a multidisciplinary environment with membership in the Koch Institute of Integrated Cancer Research, the Harvard-MIT Division of Health Sciences and Technology, the Department of Electrical Engineering and Computer Science, the Microscale Technologies Laboratory, the Center for Environmental Health Sciences, the Division of Medicine at the Brigham & Women's Hospital, and the Harvard Stem Cell Institute. In 2008, Dr. Bhatia was invited to become a Howard Hughes Medical Institute Investigator.

Minimum requirements for this position include a Ph.D. and/or M.D. Successful candidate will have a strong background in engineering, physics, materials science, chemistry, biology or medicine with an interest in interdisciplinary research.

Send brief statement of research interests, CV, and names of three references to:
Sangeeta N. Bhatia, M.D., Ph.D.,
sbhatia@mit.edu
website: http://lmrt.mit.edu/

The NCI Alliance Nanotechnology in Cancer Bulletin is a collaborative effort developed and facilitated by the Communications and Integration Working Group (CIWG) of the Alliance program. The group is currently led by Alliance co-chairs, Ryan Jowers (Emory-GT CCNE) and Diane Clark Robinson (NSBCC-CCNE), with coordination from NCI co-chair, Krzysztof Ptak, Ph.D.

The CIWG's mission is to catalyze effective Alliance-wide and external communications, facilitate Alliance team science integration, create education outreach opportunities, and leverage best practices.

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