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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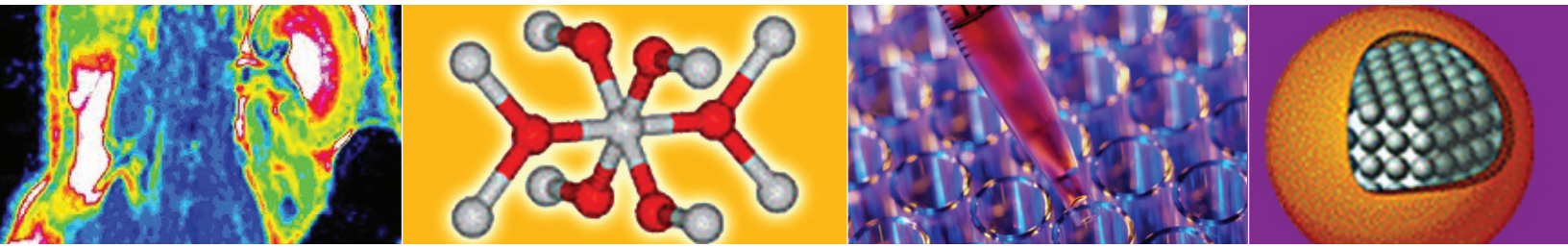


IN THIS ISSUE

Building Team Science

TACKLING METASTASIS THROUGH TEAM SCIENCE: CANCER BIOLOGISTS LEAD THE CHARGE SYNERGIZING THEIR DISCOVERIES BEHIND COMMON NANOTECHNOLOGY PLATFORMS

By Leland W. K. Chung[1], Jianjun Cheng[2], Douglas Hanahan[3] and Kattesh V. Katti[4]

[1]Emory/Georgia Tech CCNE, Atlanta, GA

[2]University of Illinois at Urbana-Champaign, Siteman CCNE, St. Louis, MO

[3]University of California at San Francisco CNPP, San Francisco, CA

[4]University of Missouri CNPP, Columbia, MO

Cancer mortality and morbidity remain a challenge, considering that only 2.1% of the patients who underwent curative and adjuvant cytotoxic chemotherapy had a 5-year survival in the United States. The root of this problem is cancer metastasis. Metastatic cancer is lethal and disseminating cancer cells are extremely difficult to tame. This problem can only be resolved by pursing an increased understanding of cancer biology, new technology for early cancer detection and novel therapy for the management of advanced cancer metastases even after cancer has spread to vital organs. Alliance CCNE/CNPP scientists, Dr. Douglas Hanahan from the University of California at San Francisco, Dr. Jianjun Cheng from the University of Illinois at Urbana-Champaign, Dr. Kattesh Katti from the Univeristy of Missouri at Columbia and Dr. Leland Chung from Emory University in Atlanta have worked together in a way that would not have been possible without CCNE Nanotechnology Platforms. These team scientists have recently formed an interdisciplinary group to begin tackling this problem. We met at various Alliance meetings/events and followed up with emails and teleconferences. Unlike other "traditional" team science projects, our team scientists did not know each other when we began our efforts, had no prior joint publications, and were not likely to meet

each other because of disparate scientific disciplines. Yet remarkably, because of our common passion to defeat cancer metastasis, and the collaborative network generated by the NCI Alliance program, we have come together over the past few months, sharing ideas, chemical reagents, cell lines, and laboratory models. We are happy to report that in our short time together, the exciting results have already shown that by working together on cancer biology, early detection and innovative treatment of cancer metastasis without prior conditions and in the spirit of cooperation, we can accelerate the pace of scientific discovery.

For over a decade, Dr. Douglas Hanahan's laboratory has worked on understanding the molecular events underlying multi-step carcinogenesis, cell proliferation and angiogenesis (1). They created a transgenic pancreatic cancer progression model that recapitulated the histopathology and behavior of human disease (2). Dr. Jianjun Cheng is a polymer and material scientist with strong commitment to translational research. He holds numerous patents on the design and synthesis of novel drug-nanoparticle for cancer drug delivery (3). Dr. Kattesh Katti's laboratory has synthesized gold and silver nanoparticles for improved cancer diagnosis and therapy (4). His laboratory discovered bombesin, an effective targeting ligand for the delivery of these metallic nanoparticles tagged with radioactivity to human cancer epithelial cells (5). Dr. Leland Chung is a cancer biologist with a special interest in prostate cancer bone metastasis. His laboratory established a number of cancer metastasis models closely resembling human androgen-independent and lethal bone-metastatic prostate cancer (6). Recently, Dr. Chung's laboratory, in collaboration with Dr. Lucjan Strekowski's laboratory at Georgia State Univeristy, discovered a class of near infrared (NIR) heptamethine cyanine dyes that have the unique ability to be uptaken by human and mouse cancer cells but not normal cells.

Since pancreatic cancer and hormone-refractory bone-homing prostate cancers are considered the most aggressive and lethal forms of human cancers, Drs. Hanahan and Chung collaborated to demonstrate that one of the heptamethine cyanine dyes, IR-783 (Sigma-Aldrich), can be readily uptaken by several pancreatic and prostate cancer cell lines and pancreatic and prostate tumor xenografts in mice (Figure 1). Although this NIR dye can be photosensitized by light to yield tumoricidal derivatives, it requires high concentrations difficult to achieve in live animals. This problem attracted the attention of Dr. Cheng, who then worked with his graduate student, Rong Tong and

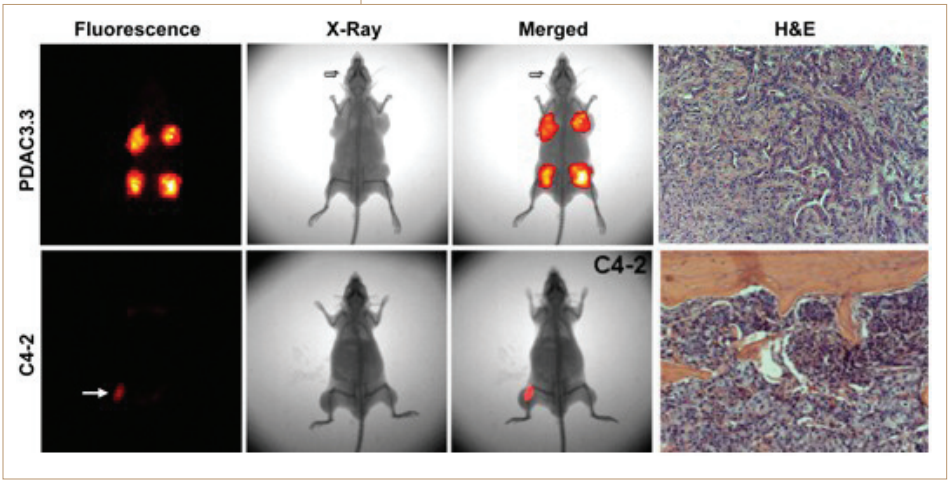
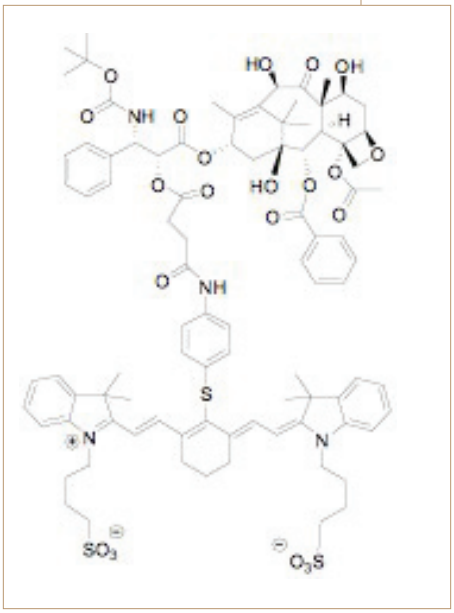


FIGURE 1. *Imaging pancreatic tumors grown subcutaneously and prostate tumor grown in bone of immune compromised mice. A pancreatic tumor cell line, PDAC3.3, and a bone metastatic prostate tumor cell line, C4-2, were implanted respectively at subcutaneous and intratibial site of nude mice. Tumor growth can be clearly imaged without interference background (left panels). The presence of the tumors was confirmed by histopathology (right panels).*

FIGURE 2. Chemical structure of IR-MUT-1. IR-MUT-1, a dye docetaxel conjugate, was synthesized and tested in human prostate and pancreatic tumor models.



Dr. Chung's student Dr. Xiaojin Yang, to develop a family of novel IR-783-taxol and –taxotere (or IR-MUT-1, see Figure 2) conjugates. They evaluated the cytotoxicity and biodistribution of these organic dye-drug conjugates and demonstrated that these conjugates could accumulate in cancerous but not in normal tissues for a prolonged period of time (over 4 days, see Figure 3). The attractive and promising properties of the dye-drug conjugates in pancreatic and prostate tumor models will soon be expanded into large scale studies of efficacy and safety with the hope that these designed drugs can be applied in human cancers as a new class of highly effective targeted therapeutics with minimal toxicity to normal tissues and cells.

Dr. Katti's laboratory has completed a series of basic studies documenting the effectiveness of bombesin as a cancer cell-surface-specific ligand that can guide gold nanoparticles to cancer cells without accumulating in normal cells. In collaboration with Dr. Chung's laboratory, they demonstrated that bombesin-guided gold nanoparticles can be delivered systemically to cancer cells. These new guided nanoparticles offer promise for cancer detection and also can be activated by external energy to induce focal hyperthermia to specifically kill cancer cells, which has the potential to improve cancer metastasis therapies.

In sum, the Alliance research network provides unprecedented opportunities for research collaborations between biologists, material scientists and polymeric and synthetic chemists who share a common research interest in defeating cancer metastasis. A meaningful synergy has already been achieved among CCNE and CNPP investigators through open communication and collaboration without preconditions. The group has already discovered a new class of cancer homing NIR-drug conjugates that offer hope for both imaging and targeting metastatic pancreatic and prostate cancers. Their collaboration was made possible by support and encouragement from the NCI administrative staff of the Alliance program, who assisted with communication and provided budgetary, personnel and administrative flexibility allowing collaborative efforts by the team scientists to flourish. The Alliance represents a new model of effective management of team science and resources which hopefully can be expanded within the National Cancer Institute extramural support portfolio to accelerate discovery and the rapid translation of bench science to the clinic.

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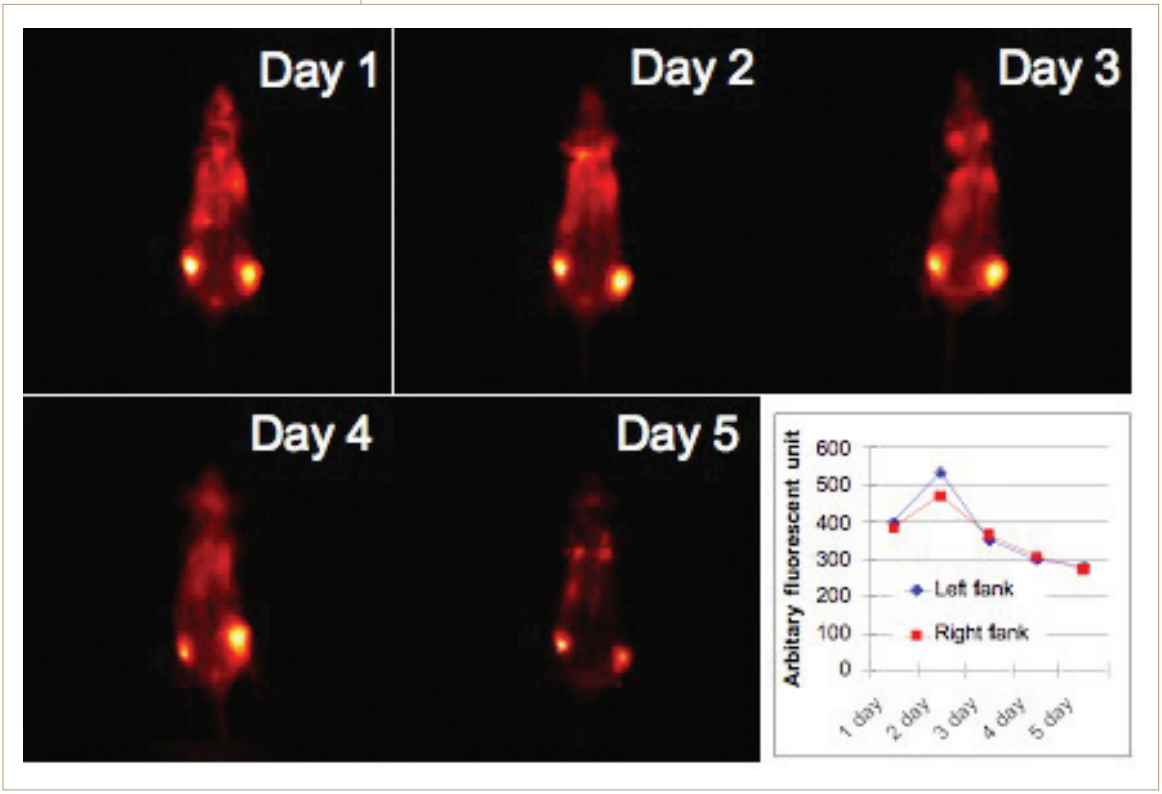
FIGURE 3. Prolonged retention of IR-MUT-1 in tumor tissues for days. Unlike small molecule drugs are typically clearly from body within minutes or a few hrs, IR-MUT1 retained in tumor tissues for several days and induced apoptosis in tumors without affecting the normal tissues.



Young Investigator Highlight

Scott Manalis, Ph.D.
MIT CNPP, Boston, MA

COLLABORATING ACROSS THE ALLIANCE

Scott Manalis, Ph.D.
MIT CNPP, Boston, MA

Dr. Manalis is the co-PI for the NCI Cancer Nanotechnology Platform Partnership (CNPP) entitled *Integrated System for Cancer Biomarker Detection*. He was trained in Applied Physics at Stanford University and is currently an associate professor in biological and mechanical engineering at MIT.

Manalis is interested in exploiting the unique physical properties associated with micro- and nanoscale dimensions to develop precision measurement methods for single cells and biomolecular interactions. His lab has recently developed a technology that enables mass to be measured in the aqueous environment with a resolution that is a million-fold better than existing methods. Their technology, known as the suspended microchannel resonator (SMR), places the fluid inside of the resonator instead of immersing the resonator in the fluid and thereby solves the long-standing problem of signal degradation from viscous drag. This has enabled single cells, nanoparticles and biomolecules to be weighed in solution with femtogram resolution. *(Nature 2007, 441 1066).* The Manalis lab is also developing high performance fluidic interfaces to micro- and nanofluidic sensors such as the SMR. These interfaces utilize novel Teflon valves and pumps that are resistant to virtually all chemicals. *(Lab on a Chip 2008, 7 347).* They are currently developing a microfluidic Autosampler Chip that will be capable of automating all fluidic manipulations necessary for performing precision measurements with the SMR sensor.

Within the NCI CNPP, Manalis together with Jongyoon Han (MIT) and Bruce Zetter (Harvard Medical School) are developing a general approach for improving the performance of ligand — receptor assays. While immunoassays such as ELISA are well established for antigen-based biomarker detection, the fidelity of the assay is governed by the disassociation constant, K_d, of the antibody-antigen complex. If the antigen concentration is significantly below K_d, then the binding kinetics are slow and readout precision of the antigen-antibody complex can be degraded by noise. Their approach is based on a nanofluidic

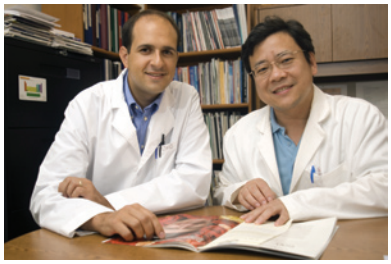
Within the NCI CNPP, Manalis together with Jongyoon Han (MIT) and Bruce Zetter (Harvard Medical School) are developing a general approach for improving the performance of ligand — receptor assays.

device that controllably concentrates a dilute sample and an ultra-sensitive SMR mass sensor that detects specific biomarkers within the concentrate. Since the amplification (or gain) of the concentrator is adjustable, the dynamic range and detection limit of the immunoassay can be governed by the properties of the concentrator and not K_d. The devices are batch fabricated by conventional foundry-level processing techniques, and the cost per device could potentially be suitable for routine use in a clinical setting.

The environment fostered by the NCI Alliance has led to several productive collaborations for the Manalis laboratory. For example, he is working with Dr. Parag Mallick and other investigators within the Stanford CCNE on a project to determine if the response of cancer cells to pathway-directed therapeutics can be classified according to subtle changes in growth. The project leverages the Stanford CCNE's discovery of numerous cell-surface protein biomarkers indicative of therapeutic response and an ultrasensitive mass sensor that has been advanced within his CNPP. In the future, Manalis and colleagues plan to use the SMR's ability to resolve mammalian cell mass with a precision near ~0.01% to investigate how cell growth relates to progression through the division cycle, and if the response of cancer cells to pathway-directed therapeutics can be classified according to subtle changes in growth. He is also working with Dr. Sangeeta Bhatia (Harvard/MIT CCNE) and Dr. Katti Kattesh (University of Missouri CNPP) on the development of gold nanoparticles for ultrasensitive mass-based detection of cancer biomarkers. Finally, he is participating within a consortium (which includes Dr. Jim Heath, Caltech CCNE and Dr. Grzybowski, Northwestern CCNE) to integrate super-low fouling poly(carboxybetaine) surfaces that are currently being developed by Shaoyi Jiang (University of Washington) with various nano- and microscale detection platforms that are suitable for routine use in a clinical setting.

For more information about Scott Manalis and his research group please visit the group's website at: http://www.media.mit.edu/nanoscale/index.html.

Training Across the Alliance



On the left: Aaron Mohs, Ph.D., Emory CCNE Distinguished Fellow

On the right: Shuming Nie, Ph.D., Director for Nanotechnology and Bioengineering, Winship Cancer Institute

CONNECTING ACROSS DISCIPLINES — EMORY/GT CCNE'S DISTINGUISHED FELLOWS PROGRAM

By Quinn Eastman, Ph.D.
Science Writer, Emory University

An organic chemist dons scrubs to work side by side with a thoracic surgeon and test a new tumor imaging probe in animals. An electrical engineer is enlisted to make sense of the huge amounts of data new biophysical techniques produce.

These examples of collaboration at Emory and Georgia Tech's Center for Cancer Nanotechnology Excellence show how the field of cancer nanotechnology touches several disciplines. They also illustrate how participants in an innovative postdoctoral fellow program at Emory/Georgia Tech are connecting those disciplines.

"Our goals are to attract the best people possible and form bridges between the research programs of various faculty," says CCNE director Shuming Nie.

Emory-Georgia Tech Distinguished CCNE fellows are required to be assigned to at least two principal investigators. The program includes scientists with a wide range of backgrounds and skills, ranging from electrical engineering to molecular biology.

For medicinal chemist Debatosh Majumdar, "nanotechnology offers a little bit of everything. The chemistry can be relatively simple, but after that the challenge is biology."

As a Distinguished CCNE Fellow, "the demands and expectations are higher, because there will be more things on your plate," says Aaron Mohs, the first fellow to begin work in 2006.

For his graduate work, Mohs explored how to create biodegradable contrast agents for MRI (magnetic resonance imaging). Now, he is evaluating the potential toxicity of nanoparticles as vehicles for tumor imaging and treatment. His work spans several types of nanoparticles studied by CCNE investigators, including those made of gold, iron oxide, polymers and semiconductor quantum dots.

"Part of the challenge comes because we don't know whether some nanoparticles' toxicity will come from their chemical composition or from physical characteristics like size and shape," Mohs says. He is beginning to explore how effectively nanoparticles might cross intestinal barriers if they enter the body orally.

His "pre-pre-clinical" work harmonizes with the NCI's Nanotechnology Characterization Laboratory, he says: "They provide a structure and we apply it to the unique technologies we're developing here."

Although most of his work is on cultured cells, Mohs has teamed up with a new Emory surgery faculty member, Sunil Singhal. In a new "intraoperative suite" they designed, their team demonstrated the ability of fluorescent probes to visualize tumors within the lungs of pigs during surgery.

To provide the targeting power to the nanoparticles Mohs is testing, his colleague Hari Sajja is involved in producing, purifying and conjugating proteins such as ATF-plasminogen, which binds to a receptor overexpressed in many cancers. An experienced chemical engineer, Sajja previously worked on selecting RNA molecules that specifically bind various compounds.

He became interested in targeting treatment to a tumor because it offers the possibility of avoiding the side effects of traditional chemotherapy, and says that what he likes the most in the lab is imaging using animals.

"That is the acid test — when you find out whether the preparation you have made really works," Sajja says.

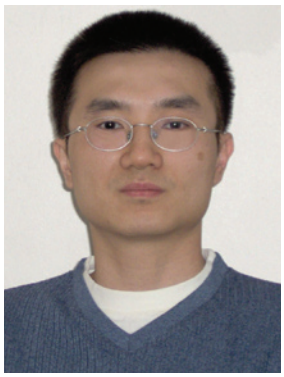
Mitch Parry, a computer science PhD with expertise in signal processing, is building computing infrastructure for the CCNE group. Working with Georgia Tech bioinformatics professor May Wang, Parry is also developing computing tools for tissue mass spectrometry.

With a minimum of processing, tissue mass spectrometry could be used to rapidly evaluate biopsy samples, but it presents a challenge in sorting through immense amounts of raw data and making sense of it.

Director Nie is aiming for an expansion of the Distinguished CCNE Fellow program from four to six fellows, and envisions that they will stay for around three years. The fellows lunch with the CCNE's monthly visiting speakers and have access to reserved travel funds.

"Our goals are to attract the best people possible and form bridges between the research programs of various faculty," says Emory/GT CCNE director Shuming Nie.

Training Across the Alliance



Ken-Tye Yong, Ph.D.,
Postdoctoral Fellow
State University of
New York at Buffalo CNPP,
Buffalo, NY

INTERDISCIPLINARY EXPERIENCE FOR SUCCESS IN CANCER RESEARCH

By Ken-Tye Yong, Ph.D.,
Postdoctoral Fellow
State University of New York
at Buffalo CNPP, Buffalo, NY

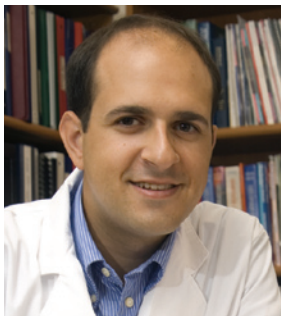
During my PhD years, my research has focused on the synthesis, functionalization, and application of nanomaterials. These materials have various applications in fields ranging from electronics to biology due to their unique properties. After graduation in 2006, I joined Dr. Paras N. Prasad's group as a postdoc in the Institute for Lasers, Photonics and Biophotonics at State University of New York at Buffalo. At that time, I was given the freedom to choose my own research career path either in biomedical or solar energy field, which are among the best programs available in the Institute.

I have a series of discussions with my advisors, Dr. Paras N. Prasad, Dr. Earl J. Bergey and Dr. Anirban Maitra. They inspired me to apply background in nanomaterials to biomedical research. Because of the support from the SUNY/ Buffalo CNPP (Cancer Nanotechnology Platform Partnership), I am able to work with colleagues from different disciplines (e.g. physicians, engineers, chemists, and physicists) and dedicate myself to pancreatic cancer research. Because pancreatic cancer often evolves without early symptoms and the majority of patients are diagnosed at an advanced, and hence incurable, stage, we note that it is of vast importance to develop ultrasensitive imaging probes for diagnosing pancreatic cancer at an early stage in order to potentially improve the survival rate of pancreatic cancer patients.

One promising nanomaterial which could serve as an imaging probe for early detection of pancreatic cancer is quantum dots (QDs). Quantum dots are inorganic luminescent semiconductor nanoparticles which allow control of their electronic and optical properties by varying particle sizes. Though I was able to use chemical approaches to reproducibly provide precise control of composition, size, and shape of the QDs formed, there remain challenges in making them compatible with biological systems. My colleagues and I have developed methods to make these particles more biocompatible and at the same time locate the cancerous area. After treating QDs with several coatings, they can serve as glowing markers that clearly identify several types of pancreatic cancer cells. These encouraging results justify further investigation of the use of quantum dots as imaging agents for pancreatic cancers.

This bioimaging of pancreatic cancer cells relied on QDs mainly concentrates on the in vitro, experiments done outside of a living body in a controlled environment. Throughout the process, I have observed QDs lack some critical features for in vivo study and they can be improved by adding other functions. During that time, I noticed American Association for Cancer Research-PanCAN has actively engaged in funding young scientists to conduct research in pancreatic cancer treatment and detection. Because I was familiar with the limitations and difficulties of using QDs in experiments conducted in the living body, I generated ideas to enhance their capabilities as diagnostic tools and wrote a proposal about these plans. My advisors were very supportive and encouraged me to apply for the funding sponsored by AACR-PanCAN. I am very fortunate and honored to have been selected as the recipient for the AACR-PanCAN Fellowship Award this year. I am proud to participate in SUNY/Buffalo CNPP program, in which I have learned how to fuse my research experience in nanomaterials to a multidisciplinary field and interact and cooperate with scientists from all over the world. The training not only allows me to realize the challenges faced by current cancer research but also helps me initiate and formulate independent ideas based on the findings and discoveries in the project. I am really grateful to be part of it.

One promising nanomaterial which could serve as an imaging probe for early detection of pancreatic cancer is quantum dots (QDs).



Aaron M. Mohs, Ph.D.
Emory — Georgia Tech
CCNE Distinguished Fellow
Emory/GT CCNE,
Atlanta, GA

DISTINGUISHED FELLOWSHIP HONOR LEADS TO GREAT OPPORTUNITIES

By Aaron M. Mohs, Ph.D.
Emory — Georgia Tech CCNE
Distinguished Fellow
Emory/GT CCNE, Atlanta, GA

Receiving the Emory-GT CCNE Distinguished Fellowship has been a great honor and also an excellent opportunity to explore several of the new technologies developed at our center. One of the primary responsibilities of being a CCNE Fellow is to interact with multiple investigators within our CCNE and to serve as a bridge between projects or groups to increase collaboration. To highlight the opportunities provided by my Fellowship, one project that I am involved with focuses on developing nanoparticles and instrumentation for intraoperative imaging to dramatically improve patient outcome following cancer surgery. My role in this project is to interface novel technologies in nanoparticle imaging probes and imaging devices with clinical need by closely working with faculty in the Department of Surgery at Emory. This interdisciplinary interaction compels scientists to design technology for immediate patient impact and exposes clinicians to the benefit of bringing the latest technology into the hospital. Another area of my research focuses on the toxicology of nanomaterials, or nanotoxicology. Evaluating the safety of nanomaterials, both *in vitro* and *in vivo,* is a decisive point in the development of any nanomaterial designed for use in a living organism, regardless of the platform used, e.g. polymeric, gold, iron oxide, or semiconductor nanoparticles. Therefore, understanding the interaction between each of these technologies being developed within our CCNE and the biological environment puts this project in a unique position to evaluate potential lead candidates of nanotechnology for further development and identify potential roadblocks or requirements for the next generation of nanomaterials. Traditional postdoctoral research projects may not always provide these opportunities for multidisciplinary research and collaboration at the interface of engineering, science, and medicine, but by being a CCNE Fellow, these highly collaborative interactions are my primary focus.

Aside from research responsibilities, my CCNE Fellowship has provided me with many opportunities to build networks within the scientific community. My fellowship put me in a position where I can actively contribute to NCI Alliance for Nanotechnology in Cancer working groups, such as the Nanoinformatics and the Diagnostic, Imaging, and Sensing Working Groups. Within our CCNE, I have been able to interact with many research and clinical faculty and meet with outside professors and clinicians in our Distinguished Seminar series. Because of the scientific and clinical components of my research and the excellent opportunity to network with the scientific community both internally and externally, the Emory-GT Distinguished Fellowship has provided me with an extraordinary opportunity to build my scientific career at the forefront of biomedical research.

Accelerating Translation

Commercialization of Nanotechnology
By Deborah Halber

Once the domain of high-tech startups, the area surrounding the Massachusetts Institute of Technology (MIT) in Cambridge, Mass., is attracting a growing cluster of biotech and drug companies. Two of the newest are spinning off technologies from the laboratories of MIT's David H. Koch Institute for Integrative Cancer Research and Massachusetts General Hospital (MGH)/Harvard University.

BIND Biosciences, Inc. and T2 Biosystems Inc. seek to revolutionize the detection, diagnosis and treatment of cancer and other life-threatening diseases. They are both commercializing cutting-edge research supported by the MIT-Harvard Center for Cancer Nanotechnology Excellence, part of the National Cancer Institute's $144M commitment to nanotechnology.

Dr. Omid C. Farokhzad, assistant professor of anesthesia at Harvard Medical School, co-founded BIND Biosciences in 2006 with $2.5 million in funding from Polaris Venture Partners and Flagship Ventures of Cambridge. The company, which raised an additional $16 million in 2007, develops therapeutic targeted nanoparticles that deliver drugs directly to diseased cells while minimizing systemic exposure, thereby increasing efficacy and reducing side effects.

"Taking biomedical advances associated with cancer treatment and diagnosis from the bench to the market requires partnering with many different groups as exemplified in these two cases out of the NCI-funded Centers for Cancer Nanotechnology Excellence," said Thomas M. Stackhouse, assistant director of the NCI's Technology Transfer Center (http://ttc.nci.nih.gov/). "Through a complete range of services including day-to-day transactional agreements, the NCI's Technology Transfer Center is able to help create and advance partnerships with the NCI to bring the benefit of new technologies to the patients."

BIND Biosciences' initial efforts are in cardiovascular and inflammatory disease and cancer — a clinical test for cancer treatment is slated for 2009 — while ongoing research at MIT and Harvard-affiliated Brigham and Women's Hospital is pioneering the technology to a myriad of clinical and research applications, including RNA interference.

"Our goal is to develop and invent technologies with near-term and long-term impact that will change the face of how medicine is practiced," Farokhzad said.

T2 Biosystems is creating a new generation of small, affordable lab-quality diagnostic tools for use in the emergency room, the ambulance, the physician's office, the home and the field. By exploiting the physics underlying the interaction of magnetic nanoparticles with biological substances and detecting the results with miniaturized magnetic resonance systems, the company is seeking FDA approval for its innovative new approach to medical diagnostics.

T2 Biosystems' six co-founders at MGH and MIT raised $5.5M in 2006 and 10M in 2008. CEO John McDonough joined in 2007, after helping launch startups in medical and Internet applications.

T2 Biosystems' prototype portable device will test blood, urine, saliva or any other water-based biofluid within minutes for a wide variety of targets, including viruses, cells, proteins, enzymes, nucleic acids and small molecules, McDonough said.

Because there is no visual analysis involved, the test is more accurate and faster than traditional methods. "Because of the work involved in taking a technology from the lab to the marketplace, it helps to determine where there is an immediate need for the technology," McDonough said. "Where does it save someone's life and take costs out of the health care system? For us, the answer is our ability to provide a rapid diagnostic test."

It doesn't hurt that MIT engineering powerhouse Robert S. Langer, whose ideas have spawned a string of biotech startups and who holds over 600 issued or pending patents, helped found both BIND Biosciences and T2 Biosystems. But McDonough and Farokhzad agree that other factors are critical for success. "My recommendation for people who do not have folks like Bob as a collaborator would be to seek out mentors and advisors who have experience in taking great science from the university into a commercial setting," McDonough said. "Advisors can include people from the universities, angel and venture investors along with people who have experience and may currently be working in a commercial setting."

Farokhzad agreed. "Reach out to mentors who will help you avoid some key mistakes," he said. He also urged young researchers to file patents for their innovative new work. "The one way you make sure your technology goes nowhere is if you don't patent it," he said. "Companies will develop your technology only if they are secure that if they spend tens of millions on it, nobody is going to scoop them."

THE NANOTECHNOLOGY CHARACTERIZATION LABORATORY

By: Jennifer Hall, Ph.D.
Data Coordinator/Scientific Writer
Nanotechnology Characterization Lab
NCI-SAIC Frederick, Frederick, MD

The Nanotechnology Characterization Laboratory (NCL) provides infrastructure support to the National Cancer Institute (NCI)'s Alliance for Nanotechnology in Cancer program — including the CCNEs and CNPPs, as well as the larger nanotechnology and cancer research communities. NCL's primary mission is to accelerate the translation of promising and safe nanotechnology-derived cancer therapeutics and diagnostics from the advanced discovery-phase towards clinical trials. Towards this goal, NCL conducts thorough preclinical characterization of nanomaterials intended for cancer applications. NCL characterization services are available by application to developers and researchers from academia, industry, and government. NCL characterization is offered at no cost to the developer.

The NCL was conceived on paper at NCI in 2003 in response to the growing number of promising proof-of-concept studies involving nanotech cancer therapies. At that time, this exciting work had not yet translated into clinically used cancer drugs and diagnostics. NCI recognized that this issue couldn't effectively be addressed without interagency collaboration and the involvement of the public, private, and academic sectors. Within a year, relationships were established with the National Institute of Standards and Technology (NIST) and the US Food and Drug Administration (FDA) and the NCL was founded at NCI's Federally Funded Research & Development Center at SAIC/NCI-Frederick.

The first objective of the newly-founded laboratory was to work with NIST and the FDA to develop a set of standardized methods for safety and efficacy testing of nanomaterials (i.e. the NCL assay cascade). By the beginning of 2006, the NCL fully operational with a working set of characterization assays specifically designed to help nanotech cancer therapies and diagnostics meet regulatory requirements.

Once its assay cascade was established, the NCL began actively soliciting collaborations with developers of promising nanotech cancer therapies and began several translational projects. Among these are projects from several Alliance for Nanotechnology in Cancer CCNEs and past and present grantees. The NCL produced its first client report for Dendritic Nanotechnologies, Inc. (DNT) in late 2006. The data in this report helped DNT obtain equity in its operation, resulting in its acquisition by a larger pharmaceutical development firm.

In 2007, the NCL almost doubled the number of its collaborations with academia, industry, and government. The NCL now has over 30 such collaborations aimed at bringing particular nanotech products to clinics. This encompasses over 100 unique nanoparticle constructs undergoing NCL characterization. In 2007, NCL also began contributing to the progression of nanotech candidate drugs through clinical trials. One NCL submission is scheduled for an IND submission in 2008 and another has completed Phase I and will enter Phase II in 2008. In 2007 the NCL also produced four client reports, five peer-reviewed articles in prestigious scientific journals, and had three of its protocols accepted in final ballots as American Society for Testing and Materials (ASTM International) standards. These represent the first internationally recognized formal standards for biocompatability-testing of nanomaterials intended for medical applications.

The NCL's primary focus is to work with the developers of nanotech cancer drugs and diagnostics to help move their products towards clinical trials. The NCL also collaborates with scientists who have not yet selected their lead compound, but need assistance with physicochemical, safety or efficacy studies. NCL is comprised of staff from the fields of chemistry, physics, immunology, cell biology and toxicology — and now has experience with the majority of nanoparticle tyles intended for medical applications, including liposomes, nanoshells, nanorods, metal colloids, functionalized gold, titanium dioxide, derivatized fullerenes, dendrimers, quantum dots, nanoemulsions, nanocrystals, iron oxides, and polymer-based nanomaterials.

As those experienced with nanotechnology understand, multifunctional nanoparticles are intricate, often delicate systems, and their characterization is challenging. Nanoparticles have to be characterized quite rigorously, as there are multiple components that must work in concert to achieve functionality. Meaningful physicochemical characterization of a multifunctional entity like a nanoparticle includes assessment of the individual parts, the stoichiometry and connections between the parts, and the chemical stability of those associations (e.g., covalent and van der Waal bonds).

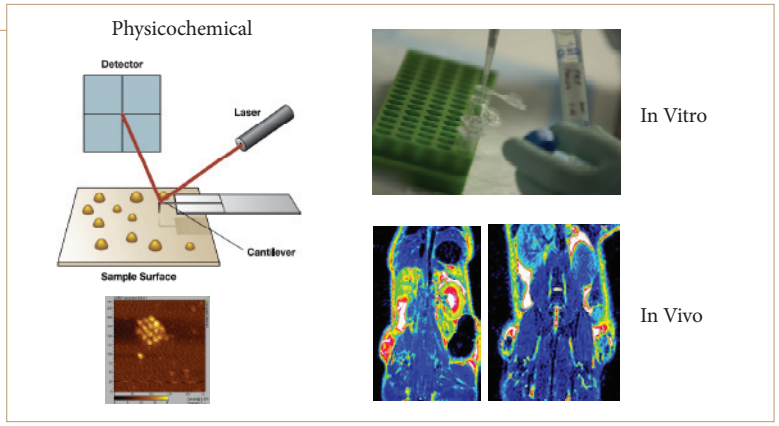
Nanoparticle biological characterization is also challenging. For instance, nanoparticles often absorb light and interfere with *in vitro* methods used to evaluate their physicochemical or immunological properties. Many nanoparticles have catalytic properties and can enhance assays that rely on enzymatic reactions, generating false-positive results. Assays routine to the preclinical characterization of conventional pharmaceuticals, such as the Limulus amebocyte lysate (LAL) test for endotoxin contamination detection may yield spurious results when applied to nanoparticle samples.

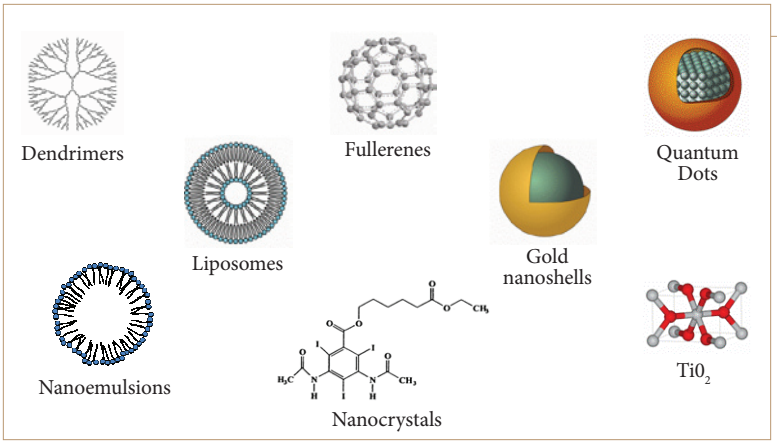
A plethora of data now exists in the scientific literature, as well as characterization data generated by NCL on proprietary formulations, demonstrating that each nanoparticle is unique. Slight changes to a nanoparticle's size or surface chemistry, for instance, can dramatically influence a physiological response. A thorough characterization of a nanoparticle-based therapeutic includes evaluation of physicochemical properties, sterility and pyrogenicity assessment, biodistribution (ADME or absorption, distribution, metabolism and excretion) and toxicity characterization — which includes both *in vitro* tests and *in vivo* animal studies. The NCL has experience in each of these tiers of a rational characterization cascade and has validated its assays on a wide variety of nanomaterials.

The NCL is currently accepting applications for characterization services. NCL characterization (including physicochemical, in vitro, and in vivo experiments) is offered at no cost to the developer. Please visit our website http://ncl.cancer.gov for more information.

NCL Extramural Collaborators (2004-2008). *New collaborations in 2007 include (from top left): Alnis BioSciences, Dr. James R. Connor of Pennsylvania State University, CytImmune Sciences, Dr. Julia Y. Ljubimova of Cedars-Sinai Medical Center, Dr. Esther H. Chang of the Lombardi Comprehensive Cancer Center at Georgetown University, Carigent Therapeutics, Dr. Andrew Miller of Imperial College London, Dr. Vladimir P. Torchilin of Northeastern University, Dr. William Zamboni of the University of Pittsburgh, Dr. Kattesh V. Katti of the University of Missouri-Columbia, Avidimer Therapeutics, and Dr. Alex Wei of Purdue University. New in 2008 include Luna Innovations and GE's Chemical Nanotechnology Laboratory.*

Characterizing Nanoparticles in the NCL Assay Cascade. *Nanotechnology strategies submitted to NCL are characterized in a standardized assay cascade developed in collaboration with the National Institute of Standards and Technology and the Food and Drug Administration. This three-tiered system for nanoparticle characterization consists of physicochemical,* in vitro, *and* in vivo *testing. NCL characterization services are offered at no costs to our collaborators.*





Portfolio of NCL Nanoparticles. *NCL has characterized many different types of nanomaterials, including liposomes, dendrimers, gold nanoshells, quantum dots, colloidal gold, nanoemulsions, fullerenes, TiO2 nanocrystals, iron oxides, and polymers. The majority of the nanoparticles submitted to NCL are functionalized with drugs and targeting agents. In June of 2008, there were a total of 122 unique nanoparticles undergoing NCL characterization.*

Alliance Activities

SYMPOSIUMS

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

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

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

LECTURES

Nano-Tumor CCNE, San Diego, CA
UCSD/Invitrogen Lecture Series
Thursday, October 23, 2008
Location: UCSD's Goldberg Auditorium at Moores UCSD Cancer Center
Scheduled speaker: Stephen Quake
Microfluidic Large Scale Integration (LSI), a technology that is helping to pave the way for large scale automation of biology at the nanoliter scale, and how this team has been exploring applications of "lab on a chip" technology in functional genomics, genetic analysis, and protein design.

For more information, contact adriana@nanobionexus.org

SEMINARS

CCNE-TR, Stanford, CA
2008 Nanobiotechnology Seminar Series
Dates and invited speakers:
September 16, 2008 — Jonathan Simons, M.D.
Nanotechnologies for Personalized and Predictive Prostate Cancer Care
October 14, 2008 — Charles Lieber, Ph.D.
Nanoelectronic-Biology Interfaces: From Ultrasensitive Detection to New Biomaterials
November 13, 2008 — Chad Mirkin, Ph.D.
Nanostructures in Biodiagnostics and Gene Therapy
Visit http://mips.stanford.edu/public/nanobiotech_seminar.adp for more information and to view archived webcasts of seminars.

Emory-GT CCNE, Atlanta, GA
2008 Emory-GT CCNE Frontiers of Cancer Nanotechnology Seminar Series
Location: Winship Cancer Institute, Atlanta GA, Room C501
Time: 3:00 p.m.
September 11, 2008 - Richard J. Cote M.D., FRCPath
New Approaches to Cell Capture, Analysis and Molecular Biosensing Using Novel Nanotechnology Platforms
October 13, 2008 – Dennis Liotta, Ph.D.
Novel Cancer Therapeutics
November 10, 2008 – Joseph DeSimone, Ph.D.
Monodisperse, Shape-Specific Nano-biomaterials for Cancer Therapeutics and Imaging Agents
December 8, 2008 — Charles Lieber, Ph.D.
Nanoelectronic-Biology Interfaces: From Ultrasensitive Detection to New Biomaterials

Nano-Tumor CCNE, San Diego, CA
Qdot® Nanocrystals for Biological Applications
Wednesday, October 29, 2008
Location: UCSD's Goldberg Auditorium at Moores UCSD Cancer Center
Schedule speaker: Eric Tulsky, Invitrogen, Inc.
For more information, please contact adriana@nanobionexus.org.

Alliance Classifieds

Job Postings

Emory-GT CCNE, Atlanta, GA

Post-Doc Fellow (Biomedical Engineering)

The Emory-Georgia Tech Center of Cancer Nanotechnology Excellence (CC NE) and the Bioengineering Research Partnership (BR P) invite applications for postdoctoral research associates in biomedical engineering, nanotechnology, medicinal chemistry and bioinformatics. Specific research topics include: (1) nanoparticles for gene and siRNA delivery; (2) nanotechnology for molecular analysis and detection of atherosclerosis plaques; (3) nanoparticle reagents for sensitive imaging of Alzheimer's and other neurodegenerative diseases; (4) nanoparticle organ uptake, distribution, and toxicology; (5) biomedical applications of Raman and surface-enhanced Raman spectroscopy; (6) cellular image processing and 3-D reconstruction; (7) synthesis of biocompatible and biodegradable polymers for targeted delivery of imaging and therapeutic agents; and (8) molecular histopathology and correlation of biomarkers with clinical outcome. The minimum requirements include a PhD or MD degree in engineering, chemistry, biology or medicine, at least two first-author papers in high-quality journals (impact factor>5.0), and an interest in collaborative work at the interface of science, engineering, and medicine.

Exceptional candidates will be considered for the prestigious CC NE fellowship at Emory University and the Georgia Institute of Technology. We offer competitive salaries plus fringe benefits. To apply, send a cover letter, an updated CV, and names of 3-5 references to Mr. Ryan Jowers, Cancer Nanotechnology Center Manager, Department of Biomedical Engineering, Emory University, 101 Woodruff Circle Suite 2007, Atlanta, GA 30322. Electronic applications are encouraged and should be addressed to Mr. Ryan Jowers at ryan.jowers@bme.emory.edu. For further information, see www.nielab.org and www.wcigtccne.org. All positions are open until filled.

MIT-Harvard CCNE, Cambridge, MA

MIT is an equal opportunity/affirmative action employer. Applications from women, minorities, veterans, older workers, and individuals with disabilities are strongly encouraged. For current employment opportunities, please visit: http://hrweb.mit.edu/staffing/.

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 Kathleen Cook (NU-CCNE), with coordination from NCI co-chair, Jerry Lee, 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.

For comments or article ideas, please contact your Alliance CIWG Primary Contact(s):

CCNEs

C-CCNE, Chapel Hill, NC
Susan Sunnarborg, Ph.D.
susansunnarborg@med.unc.edu

CCNE-TR, Stanford, CA
Billie Robles
brobles@stanford.edu

NANO-TUMOR CCNE, San Diego, CA
Davorka Messmer, Ph.D.
dmessmer@ucsd.edu
Adriana Vela
adriana_wp@yahoo.com

Emory-GT CCNE, Atlanta, GA
Ryan Jowers
ryan.jowers@bme.emory.edu

MIT-Harvard CCNE, Boston, MA
Shannon Cozzo
scozzo@mit.edu

NU-CCNE, Evanston, IL
Kathleen Cook
k-cook@northwestern.edu
Mary Drzewiecki
m-drzewiecki@northwestern.edu

NSBCC-CCNE, Pasadena, CA
Diane Clark Robinson
dianer@caltech.edu

S-CCNE, St. Louis, MO
Angela Benassi
benassia@ccadmin.wustl.edu

CNPPs

UCSF-CNPP, San Francisco, CA
Jessica Pahler
jpahler@diabetes.ucsf.edu

UMich-CNPP, Ann Arbor, MI
Jola KuKowska-Latallo

UMiss-CNPP, Columbia, MO
Jeanne Muse
musej@health.missouri.edu

MIT-CNPP, Boston, MA
pdextras@mit.edu

VCU-CNPP, Richmond, VA
Harry Dorn, Ph.D.
hdorn@vt.edu

SUNY/Buffalo-CNPP, Buffalo, NY
Indrajit Roy, Ph.D.
iroy@buffalo.edu

UWash-CNPP, Seattle, WA
Omid Veiseh
omid@u.washington.edu

SKCC-CNPP, San Diego, CA
Jan Schnitzer, MD
jschnitzer@skcc.org

Northeastern-CNPP, Boston, MA
Renata Nyul
r.nyul@neu.edu

MD Anderson-CNPP, Houston, TX
Chun Li, Ph.D.
cli@di.mdacc.tmc.edu

RPCI-CNPP, Buffalo, NY
Deborah Pettibone
Deborah.pettibone@roswellpark.org

MGH-CNPP, Boston, MA
Sung Chang
skchang@partners.org

CIWG Editor — Angela Benassi, S-CCNE CIWG Primary Contact
Article Contributors — Emory/GT CCNE, MIT/Harvard CCNE, Siteman CCNE, MIT CNPP, SUNY/Buffalo CNPP, UCSF CNPP, UMiss CNPP, and NCI
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