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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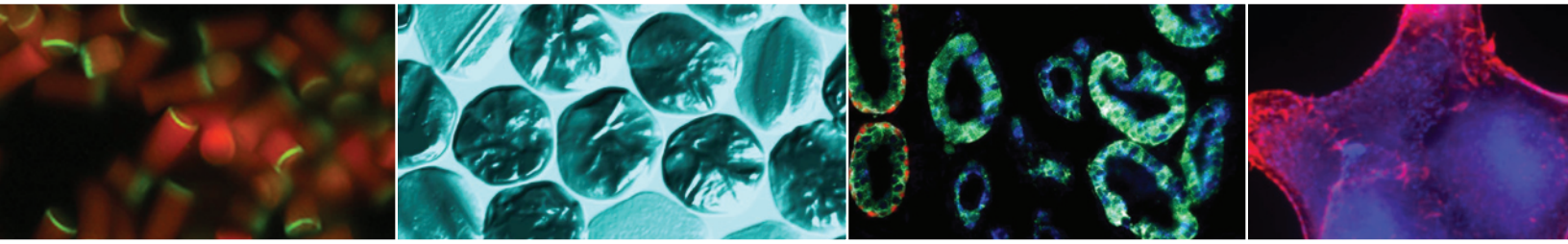

Building Team Science

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caNANOLAB: DATA SHARING TO EXPEDITE THE USE OF NANOTECHNOLOGY IN BIOMEDICINE

By: Sharon Gaheen[1], Krzysztof Ptak, PhD[2], Sue Pan[3], Elizabeth Hahn-Dantona, PhD[4], Qina Tan[5], Piotr Grodzinski, PhD[6], Anand Basu[7], Nathan Baker, PhD[8], David Paik, PhD[9]

Collaborating Centers/Organizations:
caNanoLab: NCI Nanotechnology Characterization Laboratory (NCL)
Emory-Georgia Tech (CCNE), Atlanta, GA
In Vivo Characterization Group: NCI, EPA, FDA, NIST, NIEHS, NIBIB
MIT-Harvard (CCNE), Boston, MA
Stanford University (CCNE-TR), Stanford, CA
Washington University (S-CCNE), St. Louis, MO

New scientific discoveries are being made at an enormous rate. According to National Library of Medicine, there were almost one million biomedical research articles published in 2008. The result of these scientific advances is an explosion of data that threatens to outstrip our capacity to analyze, absorb and reuse it. Maintaining knowledge of even our own specialized areas of research has become a major task, despite the availability of on-line journals and indexing systems as well as information exchange at scientific meetings. Moreover, as our ability to gather data continues to increase, the proportion that is analyzed, let alone published, becomes ever-smaller. A typical article in a scientific journal contains a summary of the experiments and their implications, but only a tiny fraction of the data on which they are based is ever presented.

[1]Science Applications International Corporation (SAIC)
[2]NCI Office of Technology Research (OTIR)
[3]Science Applications International Corporation (SAIC)
[4]Lockheed Martin
[5]Science Applications International Corporation (SAIC)
[6]NCI Office of Technology Research (OTIR)
[7]NCI Center of Biomedical Informatics and Information Technology (NCI CBIIT)
[8]Washington University in St. Louis
[9]Stanford University

The advantages of having all these data available a few clicks away are enormous. It allows researchers to make meaningful comparisons between their own results and those of others. It aids them in both finding answers to 'what if' questions and carrying out pilot studies without repeating experiments; this alone leads to more efficiency in terms of time, money and use of experimental animals. Databases of empirical data are an invaluable resource for modelers seeking to build and test theories based on realistic biological assumptions, and also can be useful to students, clinicians, educators, industry and the general public. The usefulness of data sharing is illustrated by work from The Cancer Genome Atlas (TCGA) project. TCGA is a collaborative effort involving specimen repositories, genome sequencing facilities, data curators, bioinformatics developers and the research community. The aim of the project is to facilitate the discovery of genetic variations that are associated with cancer occurrence by leveraging a large number of clinical samples and integrated multi-dimensional analysis tools. In their published study[1] the group was able to discern a relationship between genetic variations, DNA methylation, clinical treatment and the occurrence of glioblastoma. This disease usually responds poorly to current treatments and the results of study could lead to the future development of effective treatment regimens.

Progress in nanomedicine also depends on identifying valuable new discoveries, integrating the new information into existing hypotheses or formulating new ones, and then carrying out additional experiments to test these hypotheses and thus extend our knowledge. Nanomedicine is inherently interdisciplinary, and so this process can only work efficiently if researchers can integrate their own results with those obtained from other disciplines. Progress in the field has been impeded by the lack of a knowledge-management infrastructure for comparing and combining results within and across disciplines as well as the lack of standards describing the complexity of nanoparticles and their polydisperse nature. Nanoparticle-based vehicles come in a wide variety of physical structures and chemical compositions. This polydispersity of nanoparticles leads to diverse effects on live organisms, and impedes development and implementation of nanotherapies. Providing researchers with access to the characterizations of nanoparticles as well as the conditions under which they were characterized will assist in expediting the use of nanoparticles in biomedicine. Informatics is an essential component of the nanotechnology data-sharing process. In particular, it encompasses both terminology standardization and data handling which promotes interdisciplinary communication, allows data and protocol storage, and facilitates search, retrieval and modeling of data output.

FIGURE 1. *caNanoLab Portal: Facilitates data sharing of nanoparticles, characterizations, protocols, and publications.*

To address the challenges of data sharing, efforts are now underway by the National Cancer Institute (NCI) and collaborating organizations to define standards for representing nanoparticles and their characterizations and to create a cancer Nanotechnology Laboratory Portal (caNanoLab). The goal of this project is to lay the basic groundwork for a paradigm shift in which primary nanotechnology research data are standardized and shared within the scientific and clinical community.

caNanoLab (Figure 1) is a web portal designed to facilitate data sharing in the research community. caNanoLab allows researchers to submit and retrieve information on nanoparticles including the composition of the particle, the function of the particle (e.g. therapeutic, targeting, diagnostic imaging), the experimental characterization of the particle from physical (e.g. size, molecular weight) and *in vitro* (e.g. cytotoxicity, immunotoxicity) assays, the protocols for these characterizations, and related publications. Web based forms are available to facilitate data submission and data submitters can customize the visibility of their data at multiple levels ranging from private to available for public consumption to ensure data security. Using caNanoLab, researchers also can discover information on the research being conducted by other organizations through searching the results of all the publicly available physical and *in vitro* characterizations and obtain access publications from investigators at the Cancer Centers of Nanotechnology Excellence (CCNE).

caNanoLab was designed using caBIG™ principles and technologies enabling semantic interoperability and leverages a federated model for data sharing. Semantic interoperability is achieved via the use of concepts from the NCI's Enterprise Vocabulary Services (EVS) and the Washington University Nanoparticle Ontology (NPO), available at http://bioportal.bioontolog.org/. Since caNanoLab is engineered for caBIG™ compliance, public data stored within caNanoLab are readily searchable across the caBIG grid (caGrid) which facilitates integration with other caBIG data services. caNanoLab is currently deployed at the NCI Nanotechnology Characterization Laboratory (NCL), NCI, Washington University, Stanford, and Georgia Tech. caNanoLab provides access to publicly available data from characterizations performed at the NCL; information on over 300 nanoparticles curated from scientific publications through Washington University's data curation efforts; and the list of 600+ publications from the Cancer Centers of Nanotechnology Excellence (CCNEs). caNanoLab can be accessed at NCL site: http://cananolab.abcc.ncifcrf.gov/caNanoLab/ or other caNanoLab nodes participating in the federation. Feature requests and project direction are coordinated with the caBIG™ Integrative Cancer Research (ICR) Nanotechnology (Nano) Working Group, which is aimed at developing a vision for nanotechnology informatics and is composed of key members of the nanoinformatics community. caNanoLab enhancements

are suggested by the nanotechnology community through the caNanoLab Users Group, which is welcoming new member participation.

Currently, the caNanoLab portal supports the submission and retrieval of physical and *in vitro* characterizations for nanoparticles. To further facilitate translational research, the project is expanding to include support for *in vivo* characterizations of nanoparticles and their functionalizing entities, which are analogous to those required for small molecules and other medical devices. These characterizations include rigorous testing to determine toxicity and PK/ADME properties. However, the *in vivo* characterization of nanoparticles presents additional challenges stemming from the relationship of particle structural properties to biological activity. The caNanoLab project is collaborating with members of the NCI, EPA, FDA, NIBIB, NIST, and other organizations to identify and define concepts and measurements needed to support *in vivo* characterizations.

The capture of nanoparticle information and characterizations in a structured fashion is essential to future facilities supporting cross-particle analysis, advanced visualization of structure-activity-relationships, and ultimately computer-aided nanoparticle design. These facilities will assist in engineering nanoparticles for optimal biodistribution and identifying the impacts of particle physiochemical structure on biological activity. Key to achieving these future goals is data sharing. *"caNanoLab is the primary resource for nanoparticle data related to nanomedicine. Together with curation activities and voluntary data entry from the cancer nanotechnology research community, it has laid the foundation for informatics efforts ranging from computer-aided nanoparticle design to toxicity analysis and prediction."* — Dr. Nathan Baker, Principal Investigator, Washington University.

References:

1. The Cancer Genome Atlas Research Network Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature* (2008) **455**, 1061-1068.

NCL caNanoLab: http://cananolab.abcc.ncifcrf.gov/caNanoLab/

Wash U caNanoLab: http://cananolab.wustl.edu:8080/caNanoLab/

caNanoLab Project Wiki: https://wiki.nci.nih.gov/display/ICR/caNanoLab

caNanoLab Download Site: http://gforge.nci.nih.gov/frs/?group_id=69

Washington University NPO: http://bioportal.bioontology.org/ontologies/39047

Young Investigator Highlight

Jianghong Rao, PhD
Stanford University (CCNE-TR),
Stanford, CA

COLLABORATING ACROSS THE ALLIANCE

By: Jianghong Rao, PhD
Stanford University (CCNE-TR),
Stanford, CA

Dr. Rao is an investigator at the Stanford NCI Centers of Cancer Nanotechnology Excellence (CCNE). He was trained in Chemistry at Harvard University and is currently an assistant professor in radiology and chemistry at Stanford University.

His lab is interested in developing novel imaging probes and strategies for *in vivo* imaging applications of cancer, and one of the emphases is on the nanoparticle based imaging probes and systems. For example, by combining quantum dots (QDs) with bioluminescence resonance energy transfer (BRET) technology, his laboratory has developed a unique and versatile QD-BRET nanosensing system with potentially wide-ranging applications in biology and medicine. BRET is a natural process of nonradiative transferring energy from a donor (usually a light emitting enzyme during the catalysis of the oxidation of its substrate such as luciferase) to a fluorescent protein, occurring widely in marine creatures such as the jellyfish *Aequorea victoria* and the sea pansy *Renilla reniformis*. In collaborating with the laboratory of Dr. Sanjiv Gambhir, the PI of Stanford CCNE, they have shown that semiconductor fluorescent nanocrystals quantum dots can substitute the fluorescent protein as the acceptor in the BRET process (*Nature Biotechnology* 2006, 24, 339). With the size-tunable emission of quantum dots, this system creates self-illuminating quantum dots with a long emission in red to near-infrared range which are particularly useful for *in vivo* imaging applications in minimizing light absorption from hemoglobin, and background autofluorescence from native blood and tissue chromophores, such as collagens, porphyrins, and flavins. Zymera, Inc., a biotechnology company based in South San Jose, California, licensed this technology from Stanford, and is working to bring this technology to the market.

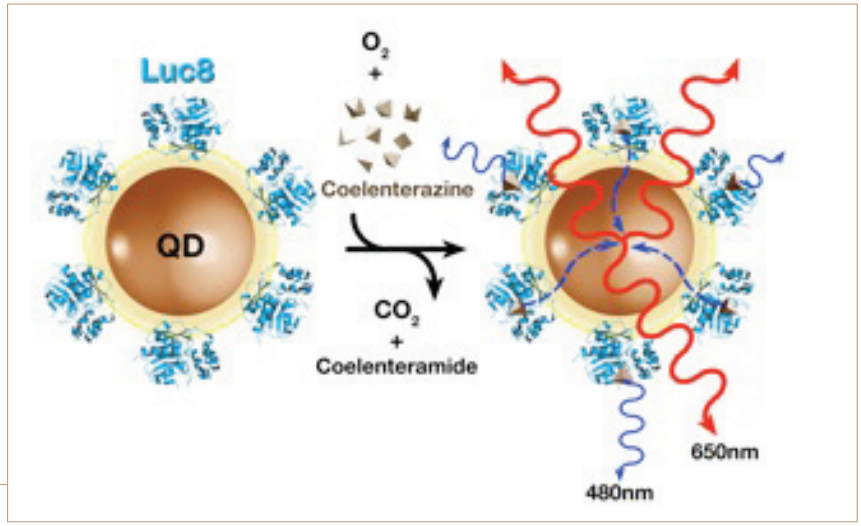


FIGURE 1. *Design of the BRET-QD conjugate and the BRET-QD catalytic reaction. Each quantum dot (QD) may have several copies of the luciferase enzyme (Luc8) covalently linked to the surface, as shown at left. Exposure to the luciferase substrate, coelenterazine, causes the emission of light peaking at 480 nm. Because the quantum dot is closely linked to the luciferase enzyme, the energy from this reaction transfers non-radiatively to the acceptor quantum dot (shown by the arrows with dotted lines). In this example, the quantum dot emits light in the red to near-infrared regions (655 nm). The Luc8 enzyme is a mutant with 8 mutations that confer a 200-fold increase of stability in serum and a 4-fold improvement in light output over the native enzyme.*

In addition to imaging applications, they have recently demonstrated this system in multiplexed detection of active matrix metalloproteinases (MMPs), which are upregulated in almost every type of human cancer, and whose overexpression correlates with advanced tumor stage, increased invasion and metastasis, and shortened patient survival (*Analytical Chemistry* 2008, 80, 8649). Far from being limited to protease detection, the BRET-QD technology may serve as a general nanotemplate for sensing and detecting many other analytes in biological samples (Figure 2). The forward reaction brings the QDs and bioluminescent proteins together through the interaction of X and Y (each of which is fused or conjugated to a QD, or bioluminescent protein) for BRET to occur, and it may be designed to detect protein-protein interactions, analytes (e.g. ions, DNA, RNA that mediate the interaction of X and Y), or enzymatic activities that act to join X and Y directly (e.g. ligases) or indirectly (e.g. kinases that catalyze the phosphorylation dependent X-Y complexation). The backward reaction breaks BRET and thus may be used to sense analytes (via competing off the binding site in the X-Y complex), and cleaving enzymes (such as proteases, nucleases).

The Rao laboratory is actively working with other researchers within and outside of the Stanford CCNE. For example, they have been closely working with the Gambhir laboratory in developing the QD-BRET technology, and applying them to the clinical samples in detecting target MMP activity. His lab is currently working on extending this system to other nanoparticles. For example, he is collaborating with Professor Xiaogang Peng, an expert in fluorescent nanoparticles at University of Arkansas, to develop new generations of QD-BRET particles. His laboratory is also working with Dr. Chad Mirkin (Northwestern CCNE) on developing the gold nanoparticle based BRET system for highly sensitive detection and imaging. In the future, Rao and colleagues plan to adapt the QD-BRET technology to a portable nanofluidic device to allow routine detections of biomarkers in a clinical setting through the collaborations with other CCNE investigators and clinicians.

For more information about Jianghong Rao and his research group please visit the group's website at: http://raolab.stanford.edu.

About Zymera: *It is a technology developer and manufacturer of reagents, assays, and detection platforms. The unique features of the BRET-QD assay platform allow development of a wide variety of nanodevice-mediated assays with potential impact on cancer diagnostics and therapeutics.*

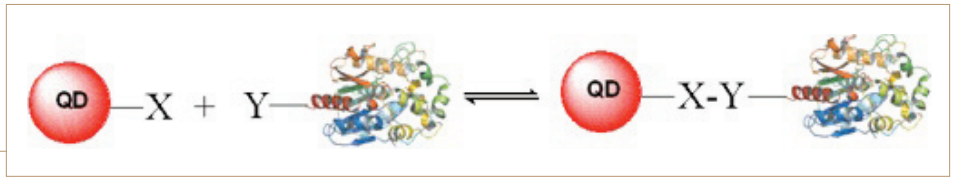


FIGURE 2. *QD-BRET system as a general platform for biosensing; X and Y are interacting partners that are linked to a QD and luciferase protein, respectively.*

Young Investigator Highlight

David Sept, PhD

Since joining the Biomedical Engineering department at Washington University in 2001, Dr. Sept's lab has focused on understanding the molecular basis of protein-protein and protein-drug interactions, and this interest has grown to include the interations of drugs and nanoparticles, in particular their pharmacokinetic and pharmacodynamic properties.

PHARMACOKINETICS OF NANOPARTICLES

David Sept, PhD
Washington University (S-CCNE), St. Louis, MO

Dr. Sept is a member of the Siteman Center for Cancer Nanotechnology Excellence (SCCNE) in the Washington University School of Medicine. He is an associate professor in the Department of Biomedical Engineering and is Co-PI for one of the SCCNE pillar projects, *An Informatics Resource for Targeted Nanoparticle Therapeutics* (together with Dr. Rohit Pappu, Biomedical Engineering, and Dr. Nathan Baker, Biochemistry & Molecular Biophysics).

Sept began his training in physics, receiving his Ph.D. in Theoretical Physics from the University of Alberta, in Edmonton, Canada. He then moved on to a postdoctoral position with Andrew McCammon in the Chemistry & Biochemistry department at UCSD where his research interests shifted more towards molecular biophysics and computational biology. Since joining the Biomedical Engineering department at Washington University in 2001, Sept's lab has focused on understanding the molecular basis of protein-protein and protein-drug interactions, and this interest has grown to include the interactions of drugs and nanoparticles, in particular their pharmacokinetic and pharmacodynamic properties. In collaboration with Baker and Pappu, this project expanded from simple pharmacokinetics into the development of a complete nanoparticle informatics resource. This resource includes a comprehensive taxonomical database of available nanoparticle technologies as well as a general toolbox for pharmacokinetics and pharmacodynamics modeling of targeted drug delivery and diagnostics using nanoparticles. Baker and Pappu have directed the development of a nanoparticle ontology that will characterize and relate the physical, chemical and pharmacological properties of nanoparticles used in cancer diagnostics and therapeutics, and Sept's lab has led in the development of general pharmacokinetics software (*NanoPK*) for modeling targeted and non-targeted nanoparticles.

The pharmacokinetics of nanoparticles exhibit some unique features, but modeling this system becomes much more complicated when one considers a drug-nanoparticle combination and the aspects of drug release. *NanoPK* offers the unique ability to simultaneously capture the behavior of the drug-nanoparticle complex as well as the pharmacokinetics of the free drug and free nanoparticle. Further, this software can simultaneously fit for multiple observations (eg. free and bound drug and/or nanoparticle concentrations in the plasma and at the tumor or other region of interest) and fit over multiple experiments (eg. identical nanoparticles carrying different drugs or drug concentrations). These features allow the researcher to determine the adsorption, distribution and clearance properties of the drug and nanoparticle separately and observe how factors such as the drug loading capacity and rate of drug release relate to bioavailability, toxicity, and therapeutic response.

NanoPK is being released as a web-based service that will allow users to model both simple and complex nanoparticle entities using one, two or three compartment pharmacokinetic models. This resource will be open to the entire scientific community, but it is anticipated that it will be particularly useful for researchers in the CCNE/NCI Alliance. Nanoparticle pharmacokinetics form only one aspect of the larger nanoparticle informatics effort within the SCCNE. This project has already greatly benefited from interaction with other CCNE members and data sharing from individual researchers, however with the ability to now model pharmacokinetic behavior, it is hoped that these interactions will increase, allowing us to gain critical insight into the complex relationship between pharmacokinetics and the chemical and physical properties of nanoparticles.

NanoPK offers the unique ability to simultaneously capture the behavior of the drug-nanoparticle complex as well as the pharmacokinetics of the free drug and free nanoparticle.

Training Across the Alliance

Keith B. Hartman, PhD, Postdoctoral Fellow

It was important for Dr. Hartman to find a mentor with the ability to place the basic science in the context of the end clinical application. He found Dr. Gambhir's Multimodality Molecular Imaging Lab at Standford University to be the perfect fit.

THE IMPORTANCE OF INTERDISCIPLINARY COLLABORATIONS

Keith B. Hartman, PhD, Postdoctoral Fellow Stanford University (CCNE-TR), Stanford, CA

As is often the case in life, my career path has not been one that I would necessarily have predicted, even as recent as 5 years ago. I originally had little interest in medical research. Trained as a chemist, my interests were in understanding and rationally manipulating the fundamentals of matter. For this reason, I was fascinated with the emerging field of nanotechnology which promises to revolutionize tomorrow's materials. I chose to complete my PhD in chemistry at Rice University, the birthplace of carbon nanotechnology. My thesis research did not initially have a strong medical component, rather it focused on the intercalation of atoms and small molecules inside carbon nanotubes. Serendipitously, loading magnetic materials into these structures enhanced their magnetic properties, yielding an exciting new magnetic resonance imaging (MRI) contrast agent, and thus, beginning my journey into medical research.

Following a successful PhD career, I realized that if I was to truly have an impact in the world beyond the bench top, I needed a better appreciation of the biological aspects of the problem. Thus, as I sought a postdoctoral advisor and institution, I wanted an opportunity with both a strong clinical and interdisciplinary aspect. It was important to find a mentor with the ability to place the basic science in the context of the end clinical application, and I found the Gambhir laboratory within the Stanford University CCNE to be a perfect match for me. In many ways, I have found this laboratory to be a microcosm of the CCNE paradigm — it brings together physical and biological scientists, engineers, medical scientists, and clinicians to solve medicine's most challenging problems.

Though I have found the learning curve steep, it has been an intellectually-challenging and rewarding postdoctoral experience. My current research focuses on the development of new imaging techniques (Raman and Photoacoustic) for early cancer detection. I can appreciate the project on the physical level because it implements basic fundamentals of physics and chemistry, while I can utilize my chemistry training to design contrast agents.

However, the most insightful aspect of the project has been understanding the eventual clinical implementation and developing clinically viable imaging solutions. Too many times, this end focus is lost on the basic science when done in isolation from medical facilities.

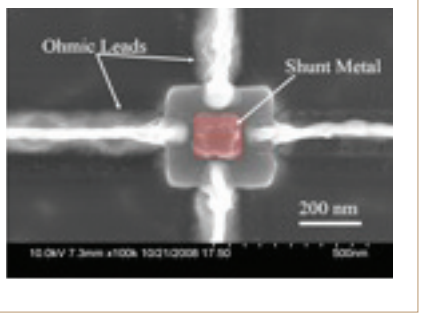
Having been trained as a chemist, I was taught to analyze problems in terms of atoms and bonds, molecules and materials, and entropies and thermodynamics. However, I have learned that this is not enough to solve problems in complex fields such as medicine. I wandered into the medical research arena through my interest in nanotechnology. It is my belief that the CCNE program is laying the foundations for the future design of medical research, combining expertise across the science and clinical spectrum to solve problems. It is this exciting horizon that propels so many scientists forward into new directions.

Although I am a firm believer in the impact nanotechnology will play in the future, I am convinced that a far greater impact will result from the interdisciplinary collaborations that are fostered and nurtured by programs like the CCNE initiative.

PREPARATION OF THE NEXT GENERATION NANOMEDICINE WORKFORCE

By: Irfan S. Ahmad, PhD and Rashid Bashir, PhD

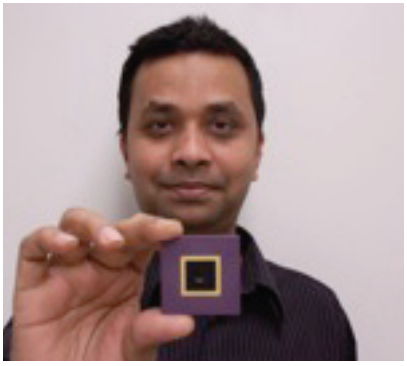
FIGURE 1. *The SEM image of an EEC device.*



Center for Nanoscale Science and Technology, University of Illinois at Urbana-Champaign, in collaboration with the Siteman Center of Cancer Nanotechnology Excellence at Washington University in St. Louis

The University of Illinois Center for Nanoscale Science and Technology (CNST www.cnst.illinois.edu) is leading Core 6 as part of the NCI-funded Siteman Center of Cancer Nanotechnology Excellence (SCCNE) at Washington University in Saint Louis. Core 6 addresses fundamental issues pertaining to nanomaterials and nanofabrication toward the development of nanodevices and nanotubes for targeting cancer, provide access and training for nanofabrication for pillar and pilot projects (Overall Project: Bashir, R. PI; co-PIs: Adesida, I; Sweedler, J., and Ahmad, I).

Washington University Professor Stuart Solin's postdoctoral research associate



Dr. AKM Newaz has been developing a device for simultaneous *in vivo*, multimodal nano-volume imaging of biological cells, in conjunction with researchers from Professors Ilesanmi Adesida and Rashid Bashir's groups at Illinois. The ultimate goal is to develop an efficient nanosensor array with 50nm pixel size and separated by 50nm having 100nm spatial resolution. Newaz has received nanofabrication training at the University of Illinois Micro and Nanotechnology Laboratory (MNTL), under the auspices of the CNST.

The nanosensor and the arrays are being fabricated at the state of the art clean room facility at the Micro and Nanotechnology Laboratory (www.mntl.illinois.edu) at the University of Illinois (www.illinois.edu). Fabrication of these devices required three steps of aligned electron beam lithography (EBL) as well as several steps of optical lithography.

Due to the complex structure of our nanosensor and nanosensor arrays, the fabrication required wide range of equipments, such as JEOL JBX-6000FS/E EBL system, Hitachi S-4800 field emission scanning electron microscope, Karl Suss MJB3, Contact Mask Aligners, PlasmaTherm SLR-770 Inductively Coupled Plasma Reactive Ion Etcher, PlasmaLab Freon/O2 Reactive Ion Etcher (RIE) System, CHA SEC-600 E-Beam/Thermal Evaporator, STS Mixed-Frequency Nitride PECVD System, Rudolph FE-III Focus Ellipsometer, and Tencor Alpha-Step 200 Profilometers.

FIGURE 2. *University of Illinois Micro and Nanotechnology Laboratory, platform resource for nanofabrication and training.*

"I wanted to investigate the fundamental physics of biological systems and biosensors at the nanoscale, which may bring new engineering ideas and solutions for applications in different areas, ranging from bio-processing in industry to nanomedicine", said AKM Newaz, postdoctoral research associate at Washington University. He added, "This post doctoral research project at SCCNE in collaboration with the University of Illinois Center for Nanoscale Science and Technology provided me with a unique opportunity with a vibrant research environment at the Micro and Nanotechnology Laboratory to receive training at the forefront of bionanotechnology research. I was able to work with experts from diverse research backgrounds ranging from electrical engineers to biomedical scientists. This SCCNE-University of Illinois collaboration helped me to develop vital skills and gain research expertise in bionanotechnology and nanomedicine, and helped fabricate creatively demanding and challenging devices". This multidisciplinary effort is a direct result of the SCCNE.

Prior to joining the Siteman Center of Cancer for Nanotechnology Excellence (SCCNE) at Washington University as a post doctoral research associate, Newaz conducted research in the field of quantum transport at the State university of New York at Stony brook. Despite my research success in quantum transport in low dimensional physics, I was attracted to the interdisciplinary research of nanobiotechnology. I wanted to investigate the fundamental physics of biological systems and biosensors at the nanoscale, which may bring new engineering ideas and solutions for applications in different areas, ranging from bio-processing in industry to nanomedicine. This post doctoral research project at SCCNE in collaboration with the University of Illinois provides a unique opportunity for me to get the proper training in the forefront interdisciplinary research of nanobiotechnology. Thanks to the vibrant research environment in our SCCNE-UIUC collaboration, I was able to work with experts from diverse research backgrounds ranging from electrical engineers to biomedical scientists. This SCCNE-UIUC collaboration helps me to learn a lot and develops my research expertise in the field of nanobiotechnology.

"SCCNE-UIUC provided me with a unique opportunity to work at the interface between nanotechnology and biology. I feel very fortunate to work in this cutting edge and rapidly expanding research field, which is constantly bringing in new ideas to develop tools to fight diseases. The tools and techniques that I have acquired working in collaborative environment at the SCCNE-UIUC, is an invaluable experience for me and will help me to be successful as a principle investigator in the field of Nano-biotechnology" said Newaz.

Newaz was born and raised in Bangladesh, completing undergraduate degree in Physics at the University of Dhaka. Later he moved to State University of New York at Stony Brook for his graduate studies in physics. He lives in St. Louis with his wife. He intends to pursue a research career in academia in nanobiotechnology and nanoscale physics.

Accelerating Translation

Nano Research Facility at Washington University in St. Louis cultivates an open and shared research environment.

NANO RESEARCH FACILITY (NRF) AT WASHINGTON UNIVERSITY IN ST. LOUIS

By: Dong Qin, PhD, National Nanotechnology Infrastructure Network Director at Washington University in St. Louis

Today, nanotechnology plays a vital role in expediting a revolution in technology and industry that benefits our society. Advances in nanotechnology — the ability to engineer, manipulate, and manufacture materials at the nanoscale — have enabled an industry to produce and use engineered nanomaterials in a wide variety of consumer products. It is anticipated that the escalating use of these materials in industrial and consumer products will result in greater exposure of workers and the general public to these nanomaterials. Therefore, it is essential to embark on responsible development of nanotechnology — a commitment to develop and to use these materials to meet human and societal needs, while making every reasonable effort to anticipate and mitigate adverse effects and unintended consequences.

Washington University Engineering has technical expertise to build our niche at the intersection of nanotechnology and important needs in public health and environment with a focus on:

- Nanostructured Materials — the bottom up approach to nanofabrication
- Nanotoxicology — nanotechnology in the context of public health and environment
- Photoacoustic Microscopy — nanotechnology as an enabler for early cancer detection

Nano Research Facility (NRF) cultivates an open and shared research environment that brings researchers across disciplines together, particularly in the emerging area of nanomaterials with applications in the energy, environment, and biomedical fields. NRF includes a micro- and nano-fabrication lab (clean room), surface characterization lab, particle technology lab, and bio-imaging lab. As a member of the National Nanotechnology Infrastructure Network (NNIN), supported by the National Science Foundation, NRF is available to both academic and industry users nation-wide. Our commitment is to provide unique technical capabilities in areas of:

- Knowledge-based synthesis of nanostructured materials
- Article instrumentation tools for toxicity studies
- Non-invasive imaging modalities for nano and biological applications

For more information on the NRF, please visit www.nano.wustl.edu.

Nanotechnology Highlights

IMAGING NANOARRAYS

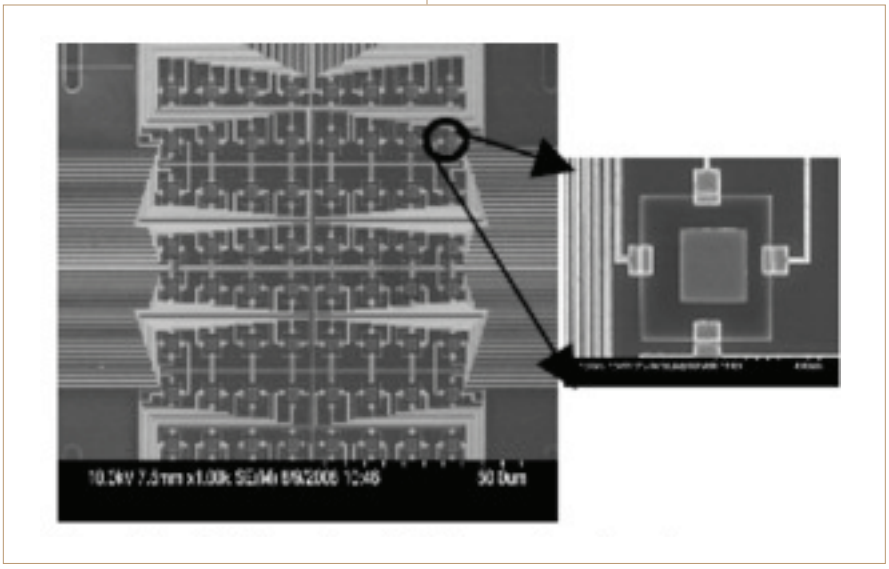
By: Stuart Solin[1]

Washington University, St. Louis, MO

[1]Department of Physics; Center for Materials Innovation; Siteman Center of Cancer Nanotechnology Excellence

A number of techniques including scanning probe microscoposcy[i], confocal microscopy[ii], etc. have been developed to image biological entities on the nanoscale. Essentially all of these techniques are cumbersome, relatively time-consuming, costly, and require highly trained specialized personnel. Moreover, the nano imaging techniques developed to date typically reveal the atomic or molecular structure of the specimen under examination but usually do not image other physical properties that have important biological implications.

FIGURE 1. *The SEM image of an 8×8 EEC array. The blow-up figure shows the SEM image of one of the pixels.*



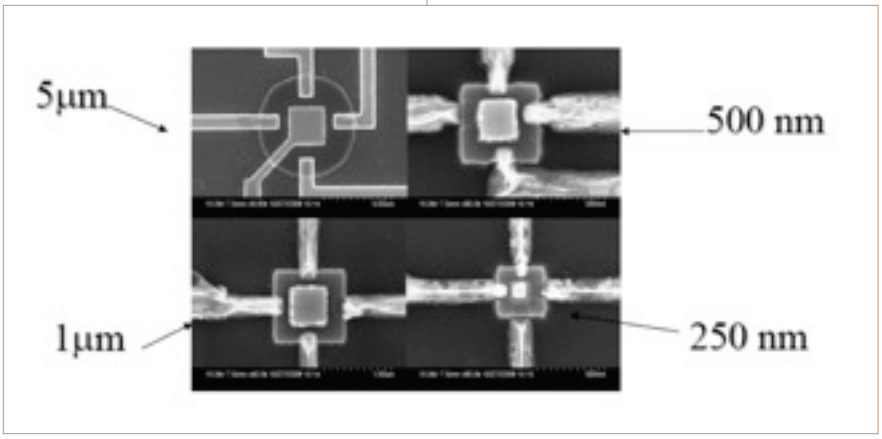
Our research group has been developing a series of inexpensive, nano-sensors and nano-arrays that are designed to produce contact images of various physical properties of cancer cells with ultra high spatial and unprecedented temporal resolution. These new sensors and arrays are based on the recent discovery of EXX phenomena by Solin and co-workers.

The electrical transport properties of any device depend on two factors, one physical and one geometric. The physical contribution arises from the material properties such as doping level, impurities, bulk mobility etc. On the other hand, the geometric contribution comes from the configuration of the device such as the device dimensions, shape, lead contact area, lead arrangement etc.[iii] Solin and co-workers have shown that by careful design, the geometric contribution can be made dominant in the transport properties and have validated this notion by demonstrating a new class "EXX" phenomena where E = Extraordinary and XX = magnetoresistance (MR),[iv] piezoconductance (PC),[v] optoconductance (OC),[vi] and Electroconductance (EC).[vii] They have further shown that EXX devices can function as very effective sensors of the relevant external perturbation, e.g. strain in the case of EPC. The scaling of EXX devices to the micro and nano regimes is a prerequisite to their use in the study of the biological properties of live cancer cells.[viii]

Our EXX devices, examples of which are shown in Figs. 1 and 2, were prepared using lattice matched GaAs epitaxial layers grown by molecular beam epitaxy (MBE) on semi-insulating GaAs substrates. The device has a simple design of a van der Pauw hybrid structure with a metal (Ti) and semiconductor (GaAs) in a close contact. Figure 1 shows an SEM image of a fabricated 8 x 8 EEC array consisting of individual devices of size 5 μm x 5 μm. The smallest feature size of this array corresponding to the width of the contact leads is 100 nm. Nanoscopic devices having submicron dimensions and the EEC arrays were fabricated using three steps of aligned electron beam lithography and reactive ion plasma etching (RIE). The mesa of the device has been fabricated using negative electron beam resist Hydrogen silsesquioxane (HSQ), followed by controlled Inductively Coupled Plasma (ICP) RIE. The nanoscopic metal features for Ohmic leads and the shunt metal were accomplished by using positive electron beam resist, PMMA. The metallization was done using both thermal and e-beam evaporation. Finally, 250 nm of a Si_3N_4 dielectric layer was deposited on top of the device using the plasma enhanced chemical vapor deposition technique to isolate the electrical circuit of the devices from the aqueous environment necessary to study a living cancer cell. Individual EEC pixels such as those shown in Fig. 2 have exhibited a field sensitivity of 3.05 V/cm[vii] whereas cancer cells have a known surface charge density that produces a field of order several kV/cm.

The EEC arrays described above were fabricated in the University of Illinois Urbana-Champaign Center for Nanoscale Technology. Travel to this facility on a regular basis is cumbersome and time consuming. Accordingly, we plan to further our studies of the physics of EXX phenomena and the development of EXX nano sensors and nano arrays in our new Washington University Center for Materials Innovation/Nantional Nanotechnology Infrastructure Network nano fabrication facility that is due to be commissioned in February, 2009.

FIGURE 2. *The SEM image of an individual EEC sensors scaled to the nano regime.*



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THE USE OF NANOTECHNOLOGIES FOR MONITORING TREATMENT RESPONSE IN MOUSE MODELS OF HUMAN CANCERS

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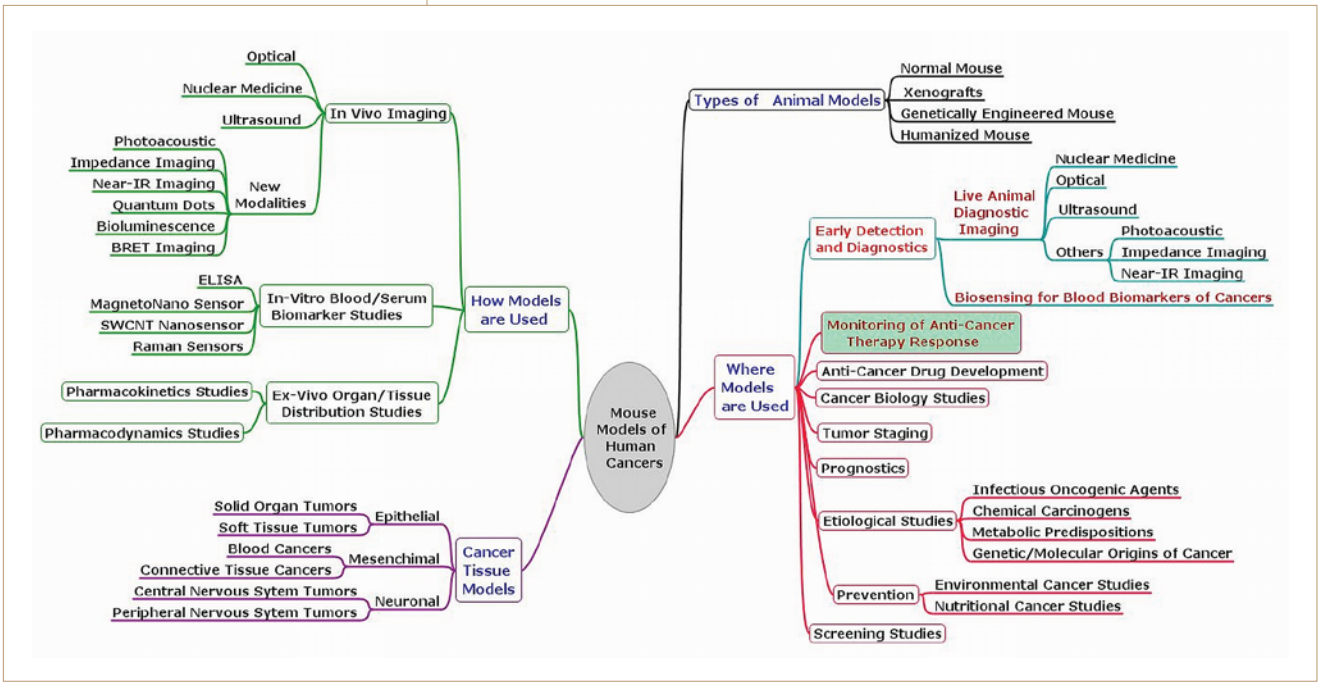
The development and the use of mouse models that mimic human cancers have been playing an essential role in our improved understanding of cancer biology and the host response to cancer. These mouse models of human cancers (MMHC) also enable the development and testing of novel tools for cancer diagnosis, targeted therapies and anti-cancer therapy response monitoring (Figure 1). Cancer is a disorder with multiple types of clinical manifestations as a result of a wide range of poorly understood causes; hence, the types of currently available mouse models of cancers are very diverse. The MMHCs can generally be classified into 3 main groups: i) cancer xenografts in normal or immunologically compromised

FIGURE 1. *An overview of mouse models of human cancer (MMHC). Shown are different models, how they are used, and the applications they are used for.*



mice, ii) genetically engineered mice, iii) humanized mice. In the first group of cancer xenografts, cancer cells of human origin, grown in culture or derived from primary human tumors, are typically implanted surgically or injected sub-cutaneously in either normal fully immunocompetent mice or mice that are immunologically deficient so that they do not reject the human cancer cells. The second group of genetically engineered MMHCs contain the models that are developed either through chemical induction of tumors and subsequent mutagenized strains with germline mutations of cancer relevant genes or genetically engineered, knock-out or knock-in, strains with deficiencies in tumor suppressor genes, over-expression of oncogenes, or other types of transgene expressions that predispose these animals to the development of intended tumors or are protective against tumor formation. The third group of MMHCs includes the mice that are genetically modified to replace some of the mouse genome with human genes that are important for oncogenesis and the medical management of its clinical manifestations. MMHCs mimicking a few predefined aspects of human cancers can be chosen from a wide range of existing model pools representing a variety of cancer types or tumor sites, histopathologies, or age of cancer onset among other important factors relevant to the field of oncology. These cancer models are typically used for studying the oncogenic processes, live animal imaging, blood biomarker studies, and extensively for drug development and monitoring of response to anti-neoplastic therapy.

Annually billions of dollars of money and significant resources are wasted in the U.S. healthcare system by prescribing cancer drugs to patients who will not likely benefit from them. If nanotechnology is developed and applied properly, it could significantly change how we predict and monitor anti-cancer treatments. Patients could receive simple blood tests where changes in blood proteins could help to monitor response to a given therapy, and this could then be further studied by molecular imaging of the patient. To realize this goal, MMHC have to be first studied with results/lessons from them then translated to the clinic.

The recent and continuing evolvement of targeted anti-neoplastic therapy drugs such as Iressa and Tarceva are leading the way towards personalized medicine. Both drugs are targeting the epidermal growth factor receptor (EGFR) tyrosine kinase. Certain cancers, e.g. lung and breast cancers, over expresses the EGFR receptor resulting in an increased activation of the Ras signaling pathway that has an anti-apoptotic effect on the malignant cells leading to increased cell proliferation. The anti-neoplastic effects of the drug will be most pronounced only in patients with highly EGFR expressing cancers. However, mutations of the EGFR receptor or alternation of the signaling pathway downstream of the receptor might turn patients that should respond to treatment into non-responders. With the growing number of targeted drugs available, identifying responders from non-responders early in the treatment course are thus becoming increasingly important in cancer therapy management.

Computed tomography (CT) is currently the primary tool for monitoring treatment response by measuring changes in tumor volume pre and post therapy. Unfortunately, changes in tumor volume may take a long time to occur and it is difficult to differentiate viable from non-viable cells. More recently, ^{18}F 2-deoxy-glucose (FDG) positron emission tomography (PET) has allowed for significant improvements in response monitoring, since FDG images tumor glucose metabolic rates. Significant decreases in FDG accumulation at tumor sites often correlate with better long term outcomes. Unfortunately, FDG also accumulates in inflammatory sites, and transient increases in FDG uptake sometimes occur even in responding tumors.

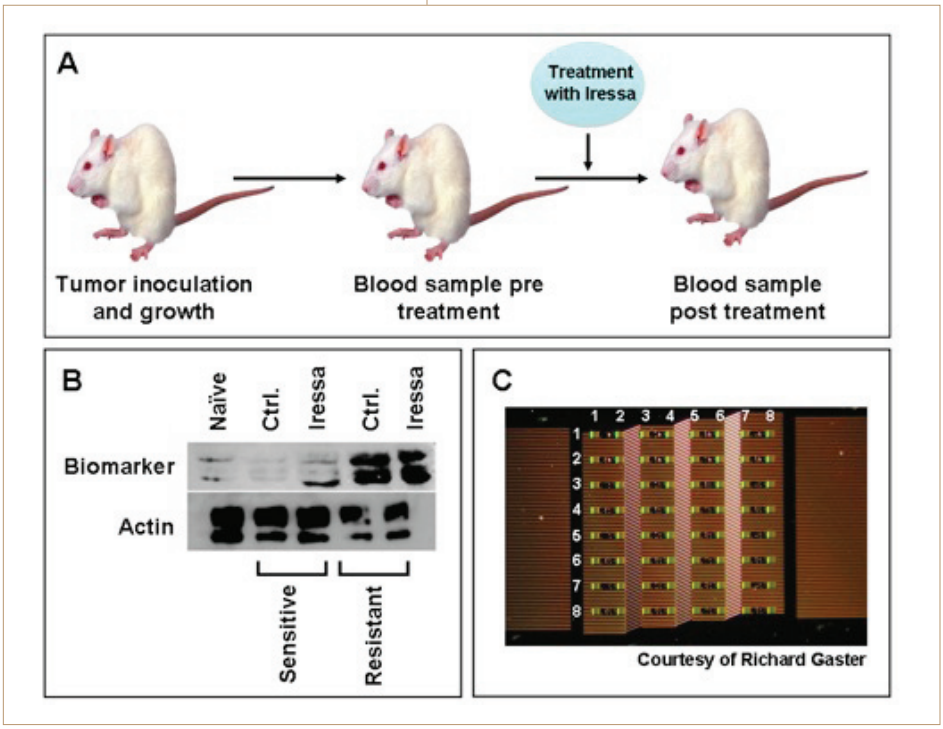
Blood levels of a series of tumor markers might change in specific ways as a response to therapy and enable one to predict and monitor the response of treatment. To test this hypothesis, cancer mouse models have been developed at Cedar Sinai Medical Center. In a xenograft model with a human cancer sensitive to Iressa, Iressa resistance was induced *in vivo* by prolonged treatment of the mouse with Iressa. Mice inoculated with either the sensitive or resistant human cancer cell lines underwent treatment with Iressa and multiple blood serum and tumors samples were obtained pre and post initiation of therapy. The mice blood serum and tissue samples were applied in a large mass spectrometry based proteomic study aiming at identifying biomarkers that change differentially due to treatment with Iressa between the sensitive and resistant mouse models. The mass spectrometry study has been carried out as a multicenter collaboration between groups at the Fred Hutchinson Cancer Research Center, Cedar Sinai Medical Center, University of California Los Angeles, and Stanford University. More than 4000 proteins were identified in the mass spectrometry data from the blood serum and tumor tissues samples. By incorporating cell culture data and multiple validation steps, the list of proteins has been narrowed down to ~16 proteins or biomarkers that changes differentially in the sensitive and resistant mouse models due to treatment with Iressa.

Concurrent with the blood biomarker discovery process, Dr. Shan Wang's group at Stanford University has developed a magnetonanosensor chip which allows for simultaneous measurement of up to 64 different protein levels from a single blood sample. The magnetonanosensors allow quantification of proteins down to the low fM range with a dynamic range of six orders of magnitude.

Currently researchers at Stanford University are trying to show that it is possible to predict and monitor therapy response hours after initiation of treatment by measuring specific changes in the mouse serum proteome. The study brings together elements from the development of the Iressa sensitive and resistant mouse models, the results of the biomarker discovery study with mass spectrometry, and the technology development of at high throughput magnetonanosensor chip for protein quantification (Figure 2).

FIGURE 2. ***A)*** *Schematic outline of the experimental design used to obtain the serum samples used in the mass spectrometry biomarker discover study.* ***B)*** *Biomarkers that were identified to change due to treatment in the mass spectrometry study were further validated by Western Blotting using mouse blood samples. Shown is a biomarker that in the sensitive model is up regulated in response to treatment with Iressa. The resistant cancer model shows no significant change due to the same treatment. Actin is used as a lane loading control.* ***C)*** *Close view of the magnetonanosensor chip developed in Dr. Shan Wang's group at Stanford. The chip consists of an 8x8 array of sensors that each can measure the concentration of a specific biomarker through a sandwich assay using two antibodies for the biomarker of interest. This enables measurements of up to 64 different proteins in the same blood sample with very high sensitivity and a large dynamic range. By combining biomarker discovery, MMHC, and nanotechnology, the ability to distinguish responding tumors form non-responding tumors should be possible.*

Using a blood sample to predict and measure response to therapy has the advantages of high sensitivity, high throughput, and potential low cost. The changes that occur in the serum proteome though, represent a pooled or averaged estimate of the response of each cancer nodule. The goal is to address this problem by developing highly specific imaging probes specific for complex events like "response to therapy". For example, a blood test could be highly sensitive in showing a response to therapy, but would have sub-optimal specificity. A highly specific imaging test could then be done to ensure that each cancer nodule within the patient is responding as predicted by the blood test — thereby combining the best of both a blood test and an imaging test. Future studies that incorporate imaging and blood testing of the mouse models are also planned. Hopefully, these and related studies of MMHC will be predictive of what will be seen when using patient serum as well as when imaging patients. Therefore, testing of clinical human samples in patients undergoing EGFR targeted therapies is also planned. Nanotechnology when properly married to biomarker discovery should deliver on the promise of fundamentally changing how we approach cost-effective cancer treatment response monitoring in the clinic.



DETECTION OF NANOPARTICLES TARGETED NEOVASCULATURE USING A REAL-TIME INFORMATION-THEORETIC DETECTOR

By: Michael Hughes PhD[1], Jon Marsh PhD[1], Kirk Wallace PhD[1], John McCarthy PhD[2], Victor Wickerhauser PhD[2],Gregory Lanza MD, PhD[1],Samuel Wickline MD[1]

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Our primary objective is to develop ultrasonic acquisition and analysis techniques to improve the detection and diagnosis of cancer through imaging of $\alpha_v\beta_3$-targeted, perfluorocarbon nanoparticle emulsion contrast agents. The integrin $\alpha_v\beta_3$, has been shown to be present in the formation of new vessels known as angiogenesis that is a necessary step in the growth of cancerous tumors. We are investigating the use of the nanoparticle platform to target the expression of $\alpha_v\beta_3$ by conjugation of an anti-$\alpha_v\beta_3$ peptidomimetic to the nanoparticle. We have demonstrated that perfluorocarbon nanoparticles act as ultrasonic contrast agents by modifying the acoustic impedance on the surface to which they bind. However, the clear delineation between non-targeted, normal tissue and cancer cells remains a challenge for conventional ultrasonic imaging. The sensitivity of *ultrasonic* detection is ultimately dependent on a physical difference in the way sound interacts with a surface coated in contrast agent and one that is untargeted. The sensitivity of this determination can be improved by applying new signal receivers to traditional ultrasonic echo data. (A signal receiver is a mathematical operation that reduces a digitized waveform value to a single number, which is then used to determine a pixel value. A well-known example is real-time integrated backscatter imaging). We have been investigating the application of a new class of signal receivers based on analogs of Shannon Entropy. Previously, the calculation of the information-theoretic receivers (ITR) required hours of computation on a Linux cluster. Recently, we have derived a new ITR that may be calculated essentially in real-time.

At this time these real-time ITRs have been employed in three different animal models: transgenic K14-HPV16 mice 13-16 weeks old (this model contains human papilloma virus-16 oncoproteins driven by a keratin promoter so that precancerous lesions develop in the skin), athymic nude mice implanted with Human MDA 435 cancer cells by injection, in the left hindquarters, and a larger sample of mice implanted with B16 cancer cells. Results from both HPV-16 and MDA 435 models indicate that the real-time algorithms have increased sensitivity, with detection of targeted nanoparticles occurring at 15 minutes post-injection ($p<0.05$), while our earlier Shannon entropy based approach detected accumulation

of targeted nanoparticles at 30 minutes. Moreover, conventional, energy-based, signal processing was unable to detect accumulation of targeted nanoparticles. One potential shortcoming of the real-time approach, its use of the derivative of the backscattered radio frequency (RF) ultrasonic signal, has been addressed by bandpass filtering the RF prior to analysis with the real-time ITR. The combined signal processing offers further improvements in sensitivity. It is now possible for us to detect accumulation of both $\alpha_v\beta_3$ targeted nanoparticles and nontarged nanoparticles mechanically trapped in the tortuous neovasculature of the tumor, with the rate of increase of ITR output in the targeted case being twice that observed in the nontargeted case (over a period of one hour post-injection; data from the HPV16 mice in the group receiving no injection showed no change in ITR output over the same time interval). This result appears to be relatively robust, being fairly insensitive to changes in filter type and filter parameters. Analysis of the B16 tumor data is currently underway. The raw data for this study was acquired by scanning the imager array over the tumor site. While this resulted in a significantly larger data set (~100x increase in size), it also eliminated the requirement that the transducer be clamped in a fixed position over the tumor during acquisition of images (as has been the case in all previous studies). This change in acquisition protocol is intended to realistically model the type of data that could be obtained clinically using a 3D probe, and is a test of the translational relevance of ITR-based imaging. Preliminary analysis indicates that data acquired in this mode results in the detection of the rapid accumulation of targeted nanoparticles and the slower accumulation of nontargeted nanoparticles, a result consistent with our previous studies. Further, more data must be collected from a control group of mice having no injection before our initial study can be completed. Moreover, we plan additional improvements in our new acquisition protocol (fabrication of an ultrasonic coupling adapter) that will more realistically model clinical reality and produce improved data.

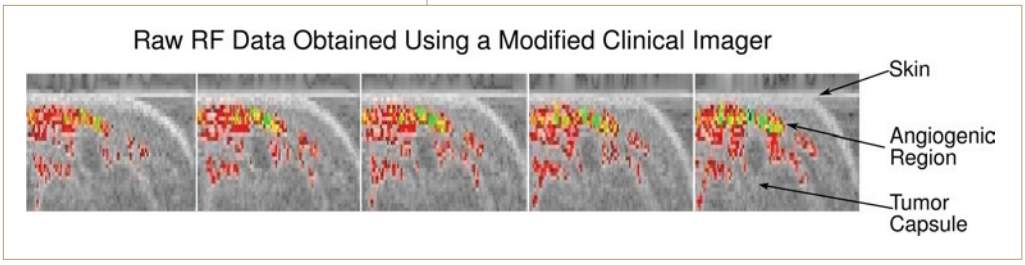

FIGURE 1. *A figure made by producing a colorizing the entropy image and then superposing the upper 5% of the colorized, pixels onto the conventional image. The image clearly shows the location of targeted tissue relative to the tumor capsule. This location is consistent with independent physiological constraints governing tumor recruitment of neovasculature, which indicate that the region of angiogenesis should lie proximal to the tumor-skin interface.*

Alliance Activities and Classifieds

SYMPOSIUMS

CCNE-TR, Stanford, CA
First Annual Center for Cancer Nanotechnology Excellence Symposium
May 28-29, 2009
Bechtel Conference Center, Encina Hall, 616 Serra Street, Stanford University

The symposium will feature world-renowned thought leaders, scientists, engineers, and clinicians as panel speakers on a variety of frontier cancer nanotechnology subject matters including Monitoring of Cancer Therapeutic Response via Nanosensors and Molecular Imaging, Cancer Biomarker Discovery and their Clinical Utilization, Frontier Nanobio Theranostic Devices, Clinical Translation Medicine for Cancer.

C-CCNE, Chapel Hill, NC
Cancer Nanotechnology Symposium
The Carolina C-CCNE announces the 3rd annual Cancer Nanotechnology Symposium to be held on November 18, 2009.

COURSES

CNST, Urbana-Champaign, IL
Cellular and Molecular Mechanics and Enabling Technologies Hands-on Summer Course
June 8-19, 2009

The course is open to all researchers, and is being coordinated by the MechSE, BioE, CNST, MNTL, SCCNE-UIUC, CCM, and the Colleges of Engineering and Veterinary Medicine. Funding for the course was obtained from the NSF, and the UIUC College of Engineering through the Center for Cellular Mechanics. To apply visit: www.gem4.org.

Sponsored by: The University of Illinois Center for Cellular Mechanics (CCM), Center for Nanoscale Science and Technology (CNST) in collaboration with the Global Enterprise for Micro-Mechanics and Molecular Medicine (GEM4) and the Siteman Center of Cancer Nanotechnology Excellence

SEMINARS

CCNE-TR, Stanford, CA
2009 Nanobiotechnology Seminar Series: Focused on Therapy Response
Location: Clark Auditorium, Bio-X
Times: Lectures 4:30-5:30 pm,
Reception: 5:30-6 pm

April 21: From Biological Design Principles to Bioinspired Nanotechnologies
Donald Ingber, MD, PhD
Children's Hospital Boston
Harvard University

May 12: TBD — Seminar begins at 2pm
Charles Lieber, PhD
Harvard University

May 19: A Systems Biology Approach to Personalized Medicine
Gordon Mills, MD, PhD
University of Texas
MD Anderson Cancer Center

June 16: Towards Next-Generation Nanoparticles
Sangeeta N. Bhatia, MD, PhD
Massachusetts Institute of Technology
Brigham & Women's Hospital

CNST, Urbana-Champaign, IL
The University of Illinois Center for Nanoscale Science and Technology (CNST) and Nano-CEMMS Seminar Series
Date/Time: April 22 at 4 pm
Location: Micro and Nanotechnology Lab, University of Illinois Room 1000

"A Hard Day in the Life of a Soft Cell"
Prof. Jeffrey J. Fredberg, Dept. of Bioengineering, and Physiology Program in Molecular and Integrative Physiological Sciences (MIPS), Department of Environmental Health Harvard School of Public Health

For more information visit: www.cnst.illinois.edu/seminars.htm.

C-CCNE, Chapel Hill, NC
Spring Seminar Series

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"

Contact ccne@med.unc.edu for more information.

EVENTS AND WORKSHOPS

Nano-Tumor CCNE, San Diego, CA
San Diego Science Festival
Nanotech Mashup!
April 2, 2009
5-7:30pm

Hilton Garden Inn, San Diego, CA
In conjunction with the San Diego Science Festival, NanoTumor Center and NTN, we invite you to meet cutting-edge nanotech researchers and scientists from various departments at UCSD in this special "mashup' event. Attendees will have the opportunity to engage in conversations with researchers from the chemistry, medical, physical sciences, engineering, physics and other disciplines who are all working together on innovative applied and translational nanotech research. Hands on demonstrations, videos and educational materials will be provided in this unique opportunity to learn more about these innovative technologies and how they address some of the world's toughest challenges in medicine and health.

For more information,
visit www.ntc-ccne.org or contact adriana@nanobionexus.org.

CNST, Urbana-Champaign, IL
The University of Illinois Center for Nanoscale Science and Technology (CNST) Annual Nanotechnology Workshop will be held during May 2009. More details to come.

C-CCNE, Chapel Hill, NC
4th Annual Chapel Hill Drug Conference
"The Use of Nanotechnology to Create Safe and Effective Therapeutic and Diagnostic Products"
May 13-14, 2009 at UNC-Chapel Hill
Information available at:
http://www.pharmacy.unc.edu/labs/4th-annual-chapel-hill-drug-conference.

Job Postings

The Nanotechnology Characterization Lab (NCL) has an opening for a postdoctoral scientist with experience in chromatographic separation techniques, mass spectrometry, and/or elemental analysis techniques for nanomaterials (http://www.saic-frederick.com/careers/). The NCL provides pre-clinical assessment and characterization of nanoparticles and devices that will be used for cancer research. This postdoctoral research opportunity will focus on the development and application of analytical techniques for the quantification of ligands, drugs, and polymer coatings on nanomaterials. This person will work with an interdisciplinary team of scientists at NCL and the National Institute of Standards and Technology (NIST) to characterize nanomaterials intended for therapeutics and diagnostics.

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.

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

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