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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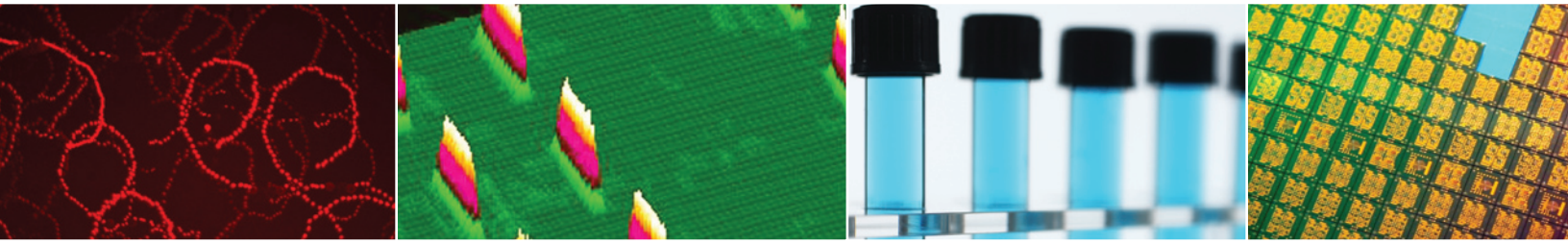

IN THIS ISSUE

Accelerating Translation

REALIZING THE POTENTIAL OF RATIONALLY DESIGNED NANOPARTICLE THERAPEUTICS

By: Jason Rolland, PhD, Co-Founder and Director of Research & Development, Liquidia Technologies

As advances in imaging lead to early detection of disease, and discoveries in molecular biology and genomics reveal new therapeutic targets; the development of precisely engineered nanoparticles will play an increasingly important role in the delivery of imaging and therapeutic agents for the diagnosis and treatment of disease.

For therapeutic applications, nanoparticles can improve solubility of poorly water-soluble drugs, prolong half-life in circulation, enhance bioavailability, facilitate tissue targeting, minimize systemic side effects, and improve therapeutic efficacy. Nanoparticle therapeutics offer particular promise in the field of cancer, owing to capabilities such as targeted tumor localization and active intracellular delivery.

Over the past two decades a number of nanoparticle-based approaches have been explored. Of these a few have realized clinical success, and fewer still have achieved commercial success. These approaches, including liposomes, dendrimers, polymer-drug conjugates and self-assembled structures are limited by inherent particle heterogeneity and a narrow ability to modify key parameters such as shape and chemistry. Using a novel nanofabrication method known as PRINT® (Particle Replication In Non-Wetting Templates), it is possible for the first time to independently optimize the shape, size, surface functionality, flexibility, and chemical composition of nanocarriers, all of which may significantly influence biodistribution, bioavailability, and therapeutic efficacy.

Initially discovered by Professor Joseph DeSimone and colleagues at the University of North Carolina-Chapel Hill, PRINT Technology is currently being developed and commercialized by Liquidia Technologies, a privately-held nanotechnology company based in Research Triangle Park, NC. Liquidia was founded in 2004 and is currently focused on developing PRINT particles for inhaled therapeutics, vaccines, and siRNA delivery.

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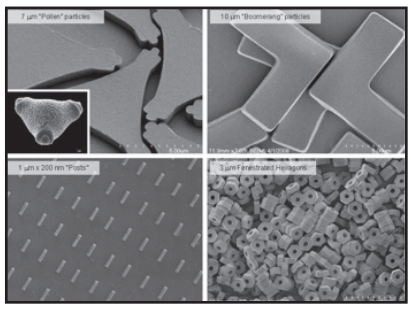

PRINT® particles of precise size, shape, and chemical composition offer more targeted, effective therapeutics for cancer and other diseases. (Courtesy of Liquidia Technologies.)

In the field of siRNA delivery, Liquidia is focused on modifying the shape and chemistry of PRINT particles to overcome barriers to effective systemic delivery. Unlike localized siRNA delivery, systemic delivery requires that particles have the ability to navigate the circulatory system and avoid uptake and clearance by non-target tissues. Upon leaving the bloodstream, the siRNA nanoparticles must diffuse through the extracellular matrix, be taken up into the target cell, and escape the endosome to reach the cytoplasm. Finally, the siRNA must be released from the carrier to induce gene knockdown.

To achieve these goals, Liquidia's PRINT particles are rationally designed with precise control of size, shape, and chemical composition. For cancer therapeutics, particles in the *size* range of 10 – 100nm are thought to be optimal based on the ability of these particles to be restricted from exiting the normal vasculature while still penetrating tumors following systemic administration. Particle *shape* may also play a particularly important role based on the ability of certain particle shapes to be selectively accumulated at different rates and in different tissues. Finally, the *chemical composition* of particles, including the use of stabilizing and targeting ligands on the surface of particles can facilitate active targeting to specific cells and tissues resulting in reduced off-target side effects. These characteristics combined with the ability of nanoparticles to carry a large therapeutic payload ranging from small molecules to biologics offer numerous advantages in terms of therapeutic potency and efficacy.

Liquidia is currently working with Abbott in the field of cancer to develop novel siRNA-based therapeutics, as well as several other partners to develop small molecule or biologic based therapeutics. Combining the research and development capabilities of pharmaceutical partners with Liquidia's particle design and delivery expertise will facilitate rapid advancement of novel products towards the clinic and ultimately towards commercialization.

In addition to developing breakthrough siRNA-based therapeutics for the treatment of cancer and other diseases, Liquidia is also focused on advancing PRINT nanoparticle-based vaccine products which could influence the future development of therapeutic cancer vaccines based on the ability to rationally design products for relevant targets and patient populations. Furthermore, Liquidia is applying the same PRINT technology to unlock new discoveries in the field of inhaled therapeutics, which could allow for more convenient dosage forms, as well as advantages in safety and efficacy, for patients with respiratory and systemic disease.

The full potential of this technology and its limitations remain to be seen. However, the ability to precisely tune a variety of particle characteristics and answer fundamental questions about the role of particle size and shape on biological processes is unlocking new capabilities in drug discovery and driving scientists at Liquidia and its partner institutions to develop and commercialize rationally designed products that will significantly improve human lives.

PHARMACOKINETICS AND PHARMACODYNAMICS OF NANOPARTICLE ANTICANCER AGENTS

By: Ninh M. La-Beck, PharmD[1,3], William C. Zamboni, PharmD,PhD[1,2,3,4,5] University of North Carolina at Chapel Hill, Chapel Hill, NC

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Introduction

Nanoparticles, which include nanosomes (nano-sized liposomes), conjugates, micelles and other nano-sized carriers, represent a promising platform for enhanced tumor delivery and activity of anticancer agents. The mechanism by which nanoparticles achieve increased tumor drug exposure as compared with traditional anticancer agents is believed to be due to the enhanced permeation and retention (EPR) effect. However, there may also be other important factors affecting tumor drug delivery [1]. Nanoparticle agents have higher variability in pharmacokinetic (PK; drug clearance, systemic exposure, distribution, etc.) disposition with potentially higher variability in pharmacodynamic (PD; antitumor response and toxicity) disposition as compared with traditional small molecule chemotherapy [2]. Unlike traditional anticancer therapies which are cleared by the liver and kidneys, nanoparticles are believed to be cleared by the reticuloendothelial system (RES) which include monocytes, macrophages and dendritic cells located primarily in the liver and spleen [3]. Non-stabilized (e.g. non-pegylated) nanoparticles are cleared relatively quickly via the RES. Stabilized (e.g. pegylated) nanoparticles also are cleared via the RES but at a much slower rate (**figure 1**). In addition, the RES may have a critical role in the release of drug from nanoparticles [1,2].

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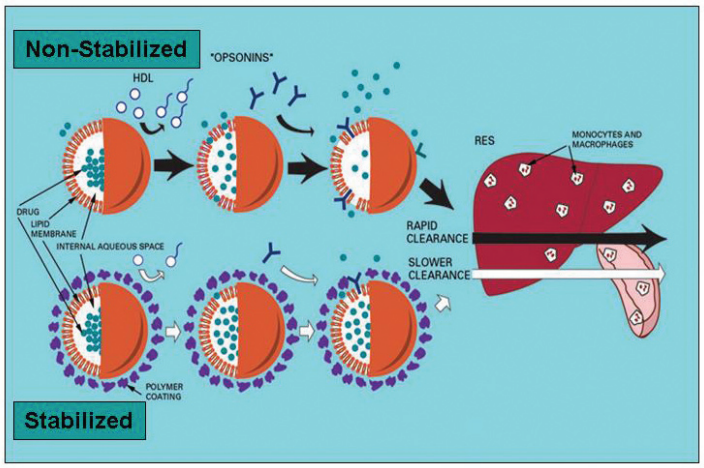

FIGURE 1. *Clearance of stabilized (e.g. pegylated) and non-stabilized (e.g. non-pegylated) nanosomes via the reticuloendothelial system (RES) in the liver and spleen.*

PK and PD Disposition

The PK disposition of carrier-mediated agents, such as nanosomes, nanoparticles and conjugated drugs, is dependent upon the carrier until the drug is released from the carrier. The drug that remains encapsulated within nanosomes or nanoparticles, or linked to a conjugate or polymer is an inactive prodrug, thus the drug must be released from the carrier to be active. After the drug is released from the carrier, the PK disposition of the drug will be the same as following administration of the non-carrier form of the drug [2,3,4]. Thus, the pharmacology and PK of these agents is complex, and detailed studies must be performed to evaluate the disposition of the carrier-associated form of the drug and the released form in plasma and tumors.

The nomenclature used to describe the PK disposition of carrier-mediated drugs includes encapsulated or conjugated (drug within or bound to the carrier), released (the active drug released from the carrier), and sum total (encapsulated or conjugated drug plus released drug). The ability to evaluate the various forms (encapsulated, released, unbound) of the drug after administration of nanosome or nanoparticle formulations is dependent upon specific sample processing methods [4].

Factors Affecting PK and PD Variability

The factors affecting the PK and PD variability of these agents remain unclear, but most likely include the RES. S-CKD602 is a pegylated nanosomal formulation of CKD-602, a semi-synthetic camptothecin analogue. The PK disposition of nanosomal encapsulated and released CKD-602 in plasma was evaluated as part of a phase I study in patients [5]. The interpatient variability in the disposition of encapsulated CKD-602 was 10-fold greater than non-nanoparticle CKD-602. We also have reported that the PK variability of S-CKD602 was related to the age, body composition and monocyte function of patients [6,7,8].

The effect of age on the disposition of pegylated liposomal doxorubicin (PLD) as part of prior phase I studies of PLD in patients with solid tumors was also evaluated[9]. The mean sum total doxorubicin AUC in patients that were ≥ 60 years was 2-fold greater than in patients who were < 60 years old suggesting that patients that are ≥ 60 years of age have a lower clearance and increased exposure (e.g., AUC) of PLD and may have increased risk of toxicity as compared with patients < 60 years of age.

To examine the relationship between S-CKD602 disposition and monocytes in patients, the degree of neutropenia and monocytopenia in patients with refractory solid tumors was evaluated [8]. After administration of NL-CKD602, the ratio of percentage decrease at nadir in monocytes versus neutrophils was 1.1, whereas the ratio of percentage decrease at nadir in monocytes was 2.1 after administration of S-CKD602 [8]. This suggests that monocytes are more sensitive to S-CKD602 as compared with neutrophils, and that the increased sensitivity is related to the nanosomal formulation and not

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the encapsulated drug. It is possible that monocytes engulf nanosomal anticancer agents via their phagocytic function as part of the RES, which causes drug to be released from the nanosome and cytotoxicity to the monocytes. Consistent with the PK and PD interaction between S-CKD602 and monocytes, decreases in PLD clearance from cycle 1 to 3 are also related to a reduction in monocyte count on day 1 of each cycle [10]. In addition, the tumor delivery of nanosomal encapsulated drug, the release of the active anticancer agent from the nanosomal carrier into the tumor ECF and the antitumor activity of nanosomal agents also are related to monocytes, dendritic cells and macrophages in tumor models of ovarian cancer [11].

Summary

The therapeutic index of anticancer agents is smaller compared with other non-chemotherapy drugs. In addition, the PK and PD variability of nanosomal anticancer agents administered IV is several fold higher compared with small molecule anticancer agents administered orally or IV. Furthermore, it appears that nanosomal, nanoparticle and conjugated agents are all cleared via the RES and have high PK and PD variability. These factors raise serious issues about the translational development and clinical utility of nanoparticle anticancer agents. Thus, there is a need to identify and reduce the factors associated with the high PK and PD variability of nanoparticle anticancer agents as methods to improve response. Imaging and cellular phenotypic probes of the RES may be predictive of toxicity and response associated with nanoparticles, and represent a promising approach for individualizing therapy with nanoparticle anticancer agents (**Figure 2**).

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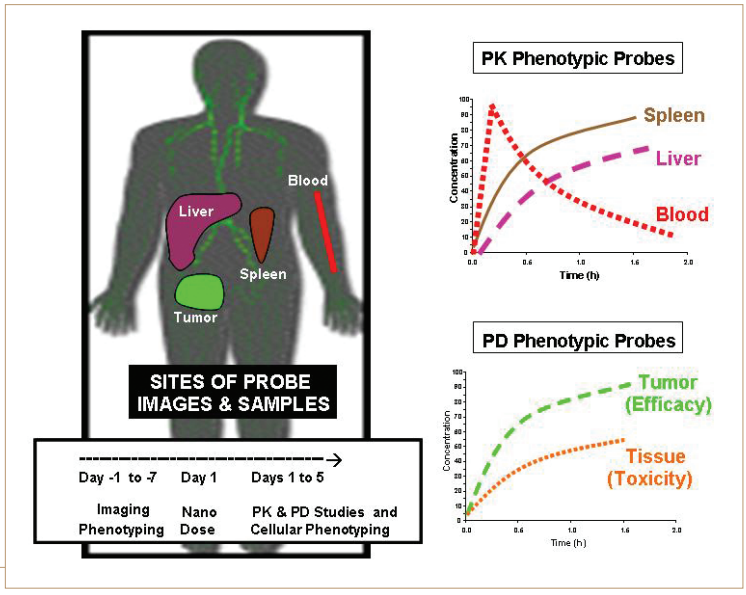

FIGURE 2. *Individualized nanoparticle therapy may be possible by combining pharmacokinetic and pharmacodynamic studies with imaging and cellular phenotypic probes that predict response and toxicity associated with nanoparticle agents.*

If you are interested in learning more about pharmacokinetics and pharmacodynamics of nanoparticle anticancer agents, please contact:

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Young Investigator Highlight

Muhammad Yousaf, PhD

The Yousaf Group uses a multidisciplinary approach that broadly interfaces surface chemistry and material science with biology to study fundamental questions in cell biology (ranging from Cell Migration to Cell Division) and to develop new tools applied to biotechnology (new types of microarrays).

CELL BEHAVIOR

By: Muhammad Yousaf, PhD
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Dr. Yousaf is an investigator at the University of North Carolina at Chapel Hill NCI Carolina Center of Cancer Nanotechnology Excellence (C-CCNE). He was trained in chemistry at the University of Chicago and Cell Biology at Harvard University and is currently an assistant professor in chemistry and the Carolina Center for Genome Science at the University of North Carolina at Chapel Hill. His lab is interested in developing new surface chemistries applied to studying cell behavior ranging from cell adhesion, migration and differentiation. For example, by collaborating with Klaus Hahn (a C-CCNE member) a combined surface chemistry approach with a FRET-based biosensor was used to investigate the effect of changes in the extracellular microenvironment on the spatio-temporal dynamics of RhoA activation in cell protrusions. This approach is based on the use of microcontact printing to pattern self-assembled monolayers of alkanethiolates on gold, to generate cell adhesive and inert regions on the model surface, and the development of a compatible high-resolution fluorescence microscope that overcomes the intrinsic quenching of low concentration and intensity of fluorophores in live cells by the gold surface. Mouse embryonic fibroblasts expressing the RhoA biosensor, confined within the cell adhesive pattern, periodically extend protrusions to sample the inert region of the monolayer outside the pattern. They observed for the first time that RhoA activity is elevated at the leading edge of protrusions in the absence of substrate adhesion (Figure 1) (J. Am. Chem. Soc. 2007, 129, 9264).

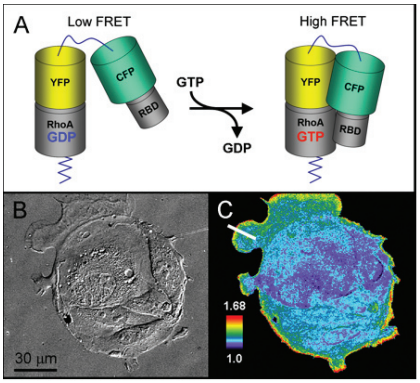

FIGURE 1. *A Genetically encoded single-chain biosensor of RhoA nucleotide state. (A) RhoA is fused to Citrine YFP followed by ECFP and a small binding domain derived from the RhoA effector protein Rhotekin. Activated RhoA (GTP-bound state) binds the small binding domain and changes the relative orientation between Citrine YFP and ECFP, thereby affecting FRET. By monitoring the ratio of FRET and CFP emissions upon CFP excitation, changes in RhoA activation states can be monitored in real time. (B) Differential interference contrast image of mouse embryonic fibroblasts (MEF) stably expressing the RhoA biosensor, confined to a circular pattern of 130 micron diameter. (C) Ratiometric image of FRET emission over CFP emission, with pseudocolor indicating the extent of RhoA activation.*

The Yousaf group has also developed dynamic surfaces for spatial and temporal control of cell behavior. The system is based on an electroactive and catalytic dynamic substrate strategy that captures and subsequently releases ligands and cells in-situ via an electrochemical potential. The surface is catalytic for multiple rounds of immobilization and release with a quantitative functional group transformation. By combining this strategy with a photochemical approach, the Yousaf Group showed the capture and release of peptide ligands that mediate biospecific cell attachment on defined surface gradient patterns (Fiugre 2) (Angew. Chem. Int. Ed. 2008, 47, 6267).

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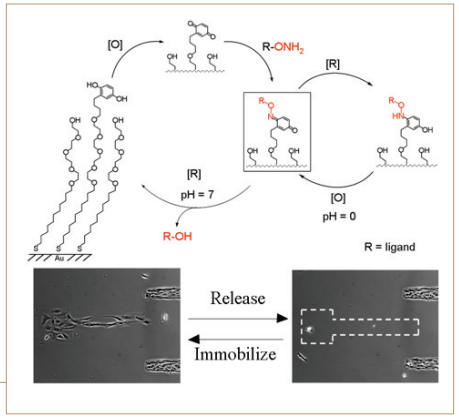


FIGURE 2. *A scheme describing the interfacial reaction between soluble oxyamine and quinone terminated self-assembled monolayers. Electrochemical oxidation [O] of the mixed monolayers presenting hydroquinone and tetra(ethylene glycol) groups converts the hydroquinone to the corresponding quinone. The resulting quinone then reacts selectively with a soluble oxyamine tagged ligands ($R\text{-}ONH_2$) to give the redox active oxime conjugate on the surface. The oxime is chemically stable and undergoes reversible redox couples in 1M $HClO_4$ (pH 0). Electrochemical reduction [R] of the monolayer in buffer solution at pH > 0 spontaneously reverts the oxime to the hydroquinone via release of the surface bound ligand as a hydroxyl. By combining with a photochemical approach, the capture and release of peptide ligands that mediate biospecific cell attachment on defined gradient patterns is demonstrated.*

Another application of surface nanopatterning is the production of symmetric and asymmetric cell adhesive peptide nanoarrays for the study of single cell polarization. Yousaf's group used dip pen nanolithography to pattern nanometer-sized spots of hydroquinone terminated alkanethiol on gold substrates. After electrochemical activation of the surface, the corresponding quinone can then undergo a reversible chemoselective reaction with an oxyamine terminated ligand. Substrates presenting both symmetric and asymmetric nanoarrays of immobilized linear Arg-Gly-Asp (RGD) peptides and cyclic (RGD) peptides were used to examine the effect of the spatial distribution of cell adhesive ligands on the polarization of adhered Swiss Albino 3T3 fibroblasts by determining the directional vector between the nucleus centroid, centrosome centroid, and Golgi center. This methodology is extended to investigate the effect of spatial arrangement of immobilized ligands, affinity of ligands, and nanospot size on polarity and focal adhesion formation within the adherent cells on the symmetric and asymmetric nanoarrays (Figure 3)(J. Am. Chem. Soc. 2008, 130, 3280).

The Yousaf laboratory is actively working with other researchers within and outside of the Carolina CCNE to integrate microfluidics and new materials to study a range of cancer cell behaviors. For more information about Muhammad Yousaf and his research group please visit the group's website at: http://www.chem.unc.edu/people/faculty/yousaf/index.html

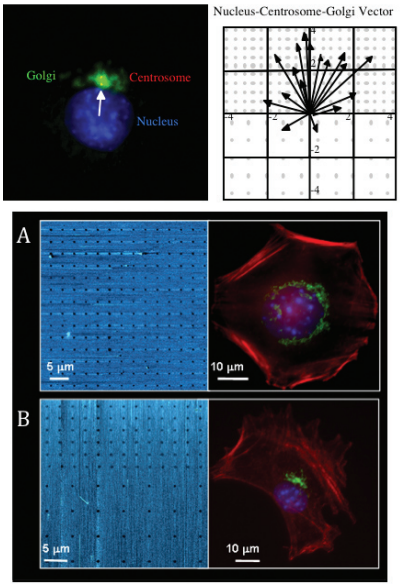
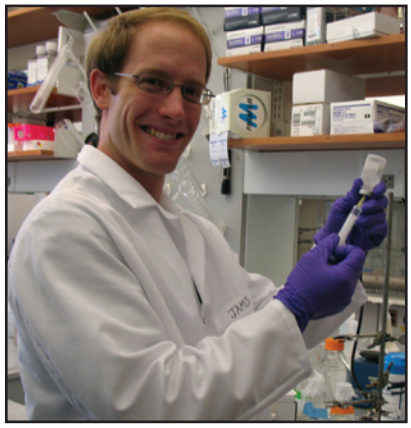


FIGURE 3. *(Top Left) Polarty vector defining the distance between Nucleus center, Centrosome center and Golgi center. (Top Right) Vector was used to define internal polarity on symmetric and asymmetric peptide nanoarrays. (A) (Left) Lateral force microscopy image of an expanded region of the control symmetric nanoarray (20 x 20, 500 nm spots spaced 3 um apart). (Right) Representative fluorescent micrograph of 3T3 Swiss Albino mouse fibroblast adhered to a symmetric nanoarray of immobilized linear RGD peptide. The diffuse distribution of the Golgi surrounding the nucleus indicates that the cell is not polarized on the symmetric nanoarray. (B) (Left) Lateral force microscopy image of an expanded area of an asymmetric nanoarray composed of two arrays of 500 nm spots 20 x10 (spaced 3 um apart) and 10 x 5 (spaced 6 um apart). The vector between the concentrated golgi with respect to the nucleus and centrosome indicates the cell is polarized towards the higher density region of the array. The cells were stained for nuclei (blue), Golgi apparatus (green), and actin (red).*

Young Investigator Highlight



James Byrne, C-CCNE researcher and DoD National Defense Science and Engineering Graduate Fellow in pursuit of the dual MD/PhD degree.

IN SEARCH OF ENHANCING DRUG DELIVERY

By: James Byrne, Graduate Fellow
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The five-year survival rate for patients with pancreatic cancer remains less than 5%. Current treatment options for pancreatic cancer include surgical resection for localized disease, or systemic delivery of chemotherapy for patients with metastatic disease. Unfortunately, gemcitabine, the current standard of care chemotherapy for pancreatic cancer, is effective only in a minority of patients. A recent study has suggested that impaired drug delivery is perhaps one major reason why gemcitabine and other chemotherapies are ineffective[1]. This and other studies suggest that poor tissue perfusion plays a substantial role in preventing adequate exposure to drug.

C-CCNE researcher and DoD National Defense Science and Engineering Graduate Fellow, James Byrne, is focused on overcoming this problem. In pursuit of the dual M.D./Ph.D. degree, Byrne is working with chemistry professor Dr. Joseph DeSimone and surgical oncologist Dr. Jen Jen Yeh to develop a medical device that will enhance and optimize the delivery of chemotherapies to pancreatic and other difficult to treat solid tumors.

"Pancreatic cancer is one of the most lethal cancers in part because of the lack of good drug perfusion. We are working on a method to treat pancreatic cancer using a minimally invasive local drug delivery device, which will increase tumor exposure to gemcitabine," states Byrne.

The medical device being developed by Byrne and the team utilizes electric field-assisted delivery (EFAD) to deliver small molecule drugs and nanoparticles loaded with a therapeutic agent to the site of the tumor. The principle of EFAD is the application of an electric potential to drive charged species into tissues; this technique is also known as iontophoresis and electrophoresis. EFAD allows for increased flux of the drug when compared to passive diffusion. As many chemotherapeutic agents and nanoparticles are inherently charged or can be tailored to have a known charge, EFAD is an attractive approach for delivering chemotherapies.

Applying EFAD to pancreatic cancer has the potential to provide localized and therapeutically valuable concentrations of drugs to pancreatic tumors, with the aim of shrinking and potentially eradicating the tumor. The EFAD approach can also be combined with other treatment modalities, such as surgery and systemic therapies

[1]Olive, K.P., et al. Inhibition of hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science 2009; 324 (5933): 1457-1461.

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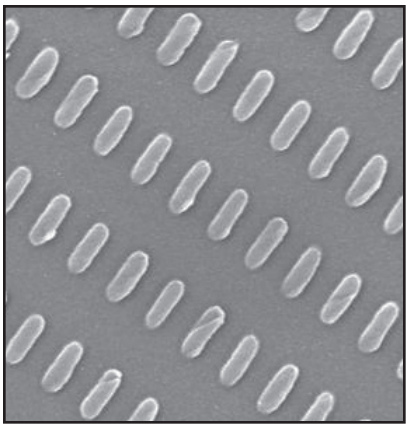
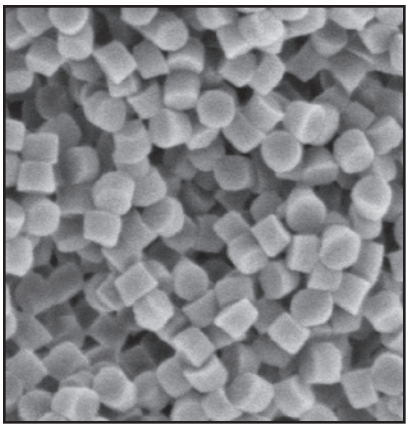
to improve outcome. Additionally, this innovative approach for local delivery of chemotherapies to the pancreatic tumor offers the capacity for a safe and efficacious therapy while eliminating the detrimental effects of systemic delivery. This device leverages the ability to make chemotherapy-loaded nanoparticles of various sizes, shapes and charge densities, using the Particle Replication in Nonwetting Templates (PRINT) technology scheme, a technique developed in the DeSimone lab. The PRINT® technology provides a way to fabricate nanoparticles with high drug loading capacity and highly charged nanoparticles made with biologicals and uncharged drug species. Delivery of these nanoparticles by EFAD can provide substantial concentrations of chemotherapies to the tumor in a controlled release setting.

Collaborations with UNC physicians and scientists provide a multidisciplinary approach to the creation of an EFAD device. Gastroenterologist, Dr. Lisa Gangarosa, and radiation oncologist, Dr. Joel Tepper work closely with Byrne to offer clinical input for device development. In conjunction with Liquidia Technologies and Synecor LLC, the device is being prototyped and developed for pre-clinical testing. "This device has the ability to shift the paradigm in delivery of current and future chemotherapies to solid tumors. We hope that it can improve the lives of people suffering from pancreatic cancer and other challenging solid tumors by providing a more effective way to deliver chemotherapies," added Byrne.

The progression of a benchtop concept into the clinic is a fundamental part of Byrne's training in nanotechnology and translational medicine. Byrne, a native of Texas, completed his undergraduate work in biomedical engineering at the University of Texas at Austin. He intends to pursue a career in translational medicine as an academic oncologist and researcher.





Working Across the Alliance

Kattesh V. Katti, M.Sc.Ed, PhD, DSC, FRSC

TRANSITION FROM MACRO TO NANOSCIENCE AND THEN ON TO NANOMEDICINE

By: Kattesh V. Katti, M.Sc.Ed, PhD, DSC, FRSC
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Throughout my undergraduate and graduate studies, I have been very fortunate to have undergone extensive training and formal education in interdisciplinary areas interfacing the areas of Chemistry, Physics, Biology and Materials science. My graduate studies (at the Indian Institute of Science, 1979-1985) involved the development and characterization of hybrid Inorganic-Organic phosphazene monomers and polymers. My training at the graduate level prepared me to undertake my first stint of post doctoral effort (through an internationally prestigious Alexander von Humboldt fellowship in Germany [1985-1987]) in the interdisciplinary area of metal-organic chemistry. As an Alexander Von Humboldt fellow in Germany, I was attempting to develop quasi aromatic systems incorporating transition metals within cyclic organic and inorganic systems. The intent was to develop cycometallaphosphazenes and related heterocyclic systems embedded with transition metals to subsequently use such hybrid materials as precursors for the development of metal containing polymers. After a highly successful endeavor, I further attempted the applications of various functionalized organo metallic compounds as catalyst precursors for initiating catalytic transformations of organic compounds with biological significance. With my strong backgrounds in organic, inorganic chemistry and materials science, I began to apply chemical principles for the construction of non linear optical materials. The objective was to utilize non linear optical materials in biomedical imaging as potential diagnostic agents. I also recognized the importance of interdisciplinary approach for research and product development, especially in medical fields.

As an independent faculty at the University of Missouri, Columbia in the Department of Radiology (1990 to present), my research focus has been toward the development of chemical frameworks for use in site specific localization of diagnostic and therapeutic agents. This type of research involved the development of bioconjugation chemistry to attach tumor specific vectors to radioactive diagnostic and therapeutic probes. Validation of hypothesis involved extensive testing in a variety of small and large animal models. With substantial funding from the National Institutes of Health, Department of Energy and Pharmaceutical industry (1990 through 2008), my research has successfully validated hypotheses toward the development of *in vivo* stable and tumor specific bioconjugates for applications in molecular imaging and therapy of cancer and other disorders. In particular, the stringent pharmacokinetic requirements of radiopharmaceuticals for use under *in vivo* profiles required careful reduction of the overall molecular sizes of active pharmaceutical ingredients. The relationship of molecular sizes, hydro/lipophilicity of

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pharmaceuticals to their target specificity, bio availability and uptake and bioclearance has been a continuous evolution process within my research focus. My contributions toward chemical architecture of molecules for the design of molecular imaging/ therapeutic agents have resulted in substantial intellectual property often meeting/exceeding industry standards. This effort has resulted in extensive publications in each of the above mentioned areas in high impact peer reviewed publications. I have also served as the principal inventor on patents dealing with catalysts, bioconjugates, peptide design, electronic material precursors, environment restoration agents, cancer diagnostic and therapeutic agents.

By 2000, I had worked in several traditional areas of basic, applied and interdisciplinary fields including, chemistry, physics, biology, materials science, radiopharmaceuticals for cancer diagnostics and therapy, chemotherapeutic agents design, wound healing agents, and polymeric systems in drug delivery. By 2002, I was considering to make a paradigm shift in my research focus by looking at ways to increase the diagnostic/therapeutic payloads at the tumor sites. This realization stemmed from the inherent drawbacks of traditional chemical bioconjuagtes which showed less than optimum uptake and retention at the tumor sites or sites of biological interest. Around 2003, I was concluding a pre-clinical trial effort of a new gold-containing chemotherapeutic agent which had shown efficacy in treating hormone refractory prostatic cancer in animal models. Our results compelled us to look at various alternatives toward increasing the therapeutic payload at the tumor sites. The non toxic nature of the proprietary gold-based chemotherapeutic agent prompted me to look at various ways of designing nanoparticulate analogs of the chemotherapeutic agent.

Around 2003-2004, the road map of the NIH toward creation of Cancer Nanotechnology Alliance came into existence. This announcement by the NIH catalyzed the overall emphasis of my acclivities to capitalize on the unique properties offered by nanoparticles and the application of the principles of Nanoscience/Nanotechnology for the development of diagnostic and therapeutic agents. Just around this time, we were also fortunate in discovering new processes for the synthesis of biocompatible gold nanoparticles. Because of my interdisciplinary backgrounds in the chemical, biological and biomedical fields, I found that the transition from the macro to nano domains was natural. As part of my ongoing biomedical research program, I had established partnerships with tumor biologists, isotope production experts, radiologists, medical physicists, veterinarians, and oncologists. Therefore, building a functional Cancer Nanotechnology Platform at the University of Missouri, in many ways, was seamless. However, the NIH road map definitely helped formalize interrelationships within various scientists to work together with common objectives.

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The founding of the first Nanoparticle Production Core facility (NPCF) at the University of Missouri provided uninterrupted supply of biocompatible gold, silver, palladium and various metallic nanoparticles for their research needs of our new interdisciplinary nanomedicine program. In many ways, the Cancer Nanotechnology Platform at the University of Missouri has provided a functional base to apply nanotechnology to solve medical problems beyond cancer. The Cancer Nanotechnology Platform at the University of Missouri (CNP at MU) has catalyzed the inception of collaborative research programs with over 12 research groups within the University of Missouri system. These programs are focused on utilization of gold nanoparticles for the development of nanomedical products in treating:

- Prostate cancer
- Breast cancer
- Lymphoma
- Age related macular degeneracy (AMD) and Pseudo Xanthoma Elastocum (PXE)
- Gene Therapy for eye disorders

The CNP at MU has established working relationships and partnerships with various alliance members and non-members including Leland Chung from the Emory CCNE, Sam Gambhir, Stanford CCNE, Priyabrata Mukherjee and Debabrata Mukhopadhyay from Mayo Clinic. Our CNP has also established collaborative endeavors in nanomedical programs at some of the finest medical institutions outside of the US. We are actively collaborating with Sankara Netralaya in Chennai, India — an internationally reputed institution with a solid track record in basic and clinical ophthalmic research. Our collaborative efforts with this institution are focused toward the utility of biocompatible gold nanoparticles in treating AMD and PXE. We are also working with this premier eye research institution in developing gold nanoparticle-based brachy agents in treating retinoblastoma and AMD.

New Directions In Nanomedicine:

Combination of nanotechnology with plant science provides a great future for medicine especially in the context of nanomedicine. Green nanotechnology is naturally poised to exploit the untapped potential of plant kingdom as non toxic resources for cancer specific phytochemicals. Nanoparticles can be efficiently used to extract cancer receptor specific phytochemicals and also for selective delivery of cancer specific agents for use in molecular imaging and therapy (Figure 1). Epigallocatechin gallate (EGCG) is a naturally occurring phytochemical present in tea with proven applications in cancer therapy. Gold nanoparticles, when conjugated with non toxic EGCG, show prostate tumor cell avidity. Indeed, AuNP-EGCGs can be used as new probes for molecular imaging of individual cancer cells as shown in Figure 2. Therefore green nanotechnology will provide new and highly effective pathways in molecular imaging and therapy of cancer and other diseases.

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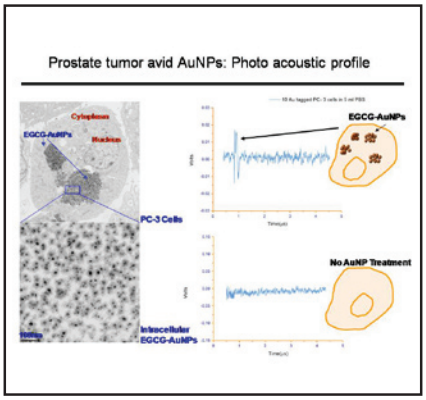

FIGURE 1. *TEM Profile and Photoacoustic Image of Prostate Cancer Cells Embedded with EGCG Gold Nanoparticles*

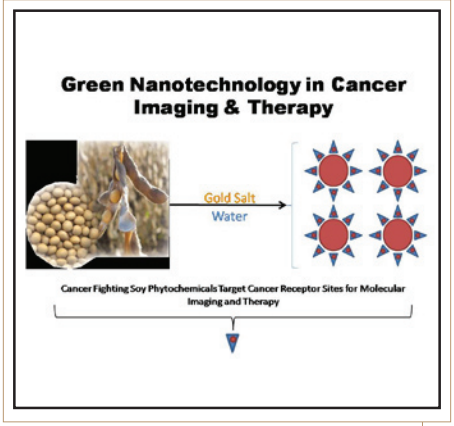

FIGURE 2. *Production of Tumor specific Gold Nanoparticles From Soy Phytochemicals (Featured in: **SCIENCE; as Editor's Choice.**, 2008; 322(5899):167.(AAAS Publication)*

We are now taking the next step of clinical translation of our findings for use in human patients. Toward this objective, we are developing non toxic gold nanoparticles using the 100% green nanotechnological processes. One such process involves the utility of phytochemicals and biocompatible proteins from Soy for use in the formation and stabilization of gold nanoparticles (Figure 2). Large scale manufacturing units for the production of biocompatible gold nanoparticles under cGMP units are being established through investments from the corporate sectors.

The synergistic relationships with research groups within the MU campus, with various alliance members and also with select medical/allied institutions in international locations has allowed smooth transfer of nanoparticulate conjugates for testing in animal models, and testing in disease models beyond cancer. Most importantly, this collective effort, initiated by the CNP at MU, has catalyzed the expansion of the research base, both in terms of the number of researchers and the target diseases, where the principles of nanoscience are being applied to bring about a paradigm shift in ways diseases would be diagnosed and treated.

My research and product development achievements, as summarized above, have been adequately rewarded by my peers through national and international awards which include:

- Gauss Professorship from Gottingen Academy of Science(2006)
- Outstanding Scientist and Academy Fellow awards by the St Louis Academy of Science (2007)
- Outstanding Missourian award by the Missouri House of Representatives (2008)
- One of 25 Most Influential Scientists In Molecular Imaging award by rt image (2008)
- Curators Professor award by the University of Missouri Board of Curators (2009)
- Doctor of Science award by the Chancellor/Vice Chancellor of Karnatak University, India (2009)

I take this opportunity to express my gratitude to all the members of our Cancer Nanotechnology Platform including Raghuraman Kannan, Evan Boote, Stan Casteel, David J. Robertson, Meera Chandrasekhar, Suchi Guha, Cathy Cutler, Dennis Lubahn, Sudarshan Loyalka, and Silvia Jurrison. I also thank our highly productive and scientifically skilled post doctoral fellows and scientific staff including Ravi Shukla, Nripen Chanda, Ajit Zambre, Kavita Katti and Genevieve Fent.

On behalf of my institution and my research group, I thank the National Cancer Institute and the office of the Alliance for Nanotechnology In Cancer for their continued generous support for our research work in nanomedicine.

NANOPARTICLE MEASUREMENTS: MONITORING NANOPARTICLE-BIOMOLECULE CONJUGATES UTILIZING MASS SENSING WITH RESONATING MICROCHANNELS

By: J.Christopher Luft[1], Scott Manalis[2], and Joseph M. DeSimone[1]†‡§

Departments of [1]Chemistry and Carolina Center of Cancer Nanotechnology Excellence, [2]Department of Mechanical Engineering, and Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, †Pathology, and ‡Pharmacology and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC 27599; and §Department of Chemical and Biomolecular Engineering, North Carolina StateUniversity, Raleigh, NC 27695

Current research exploring the therapeutic and diagnostic applications for nanomaterials is helping to identify critical parameters for the compatibility of various materials with biological systems. The most current findings implicate physical attributes such as size, shape, hydrophilicity, and surface chemistry as key factors contributing to the fate of a nanomaterial *in vitro* and *in vivo*. Therefore, one of the keys to advancing the field of nanotechnology with regards to biomedical applications involves developing standardized, accurate and reproducible methodologies for the characterization of the physical properties of a given nanomaterial. Ensemble (or bulk) characterization techniques are simple and fast, but do not directly reveal information about sample homogeneity. Single nanoparticle analysis techniques based on microscopic imaging reveal homogeneity, but are slow and labor intensive. Clearly, there is a strong correlation between measurable characteristics such as size, shape and chemical composition, and measurable properties of nanomaterials. Inaccuracy or a lack of comparability in such measurements can result in a misleading representation of the material and its properties. Considering the immediate need, the collaboration between the DeSimone (UNC-Chapel Hill, Department of Chemistry) and the Manalis (MIT, Departments of Biological and Mechanical Engineering) laboratories has been established to address the issue of applying suspended microchannel resonators to enhance the characterization of PRINT® nanoparticles.

The PRINT platform, developed in the laboratory of Joe DeSimone, uniquely leverages micro- and nano-fabrication techniques from the electronics industry to precisely control the size and shape of particles ranging in size from tens of nanometers to hundreds of microns. The PRINT technology is being utilized for numerous applications, one of which is engineered drug therapies (Acc Chem Res. 2008, 41, 1685-95). Since the PRINT process allows for the modification of size, shape, modulus/flexibility, chemical composition and surface functionality, it is vital to have instrumentation to monitor the effect of these modifications on the outcome of the final "formulated" nanoparticle.

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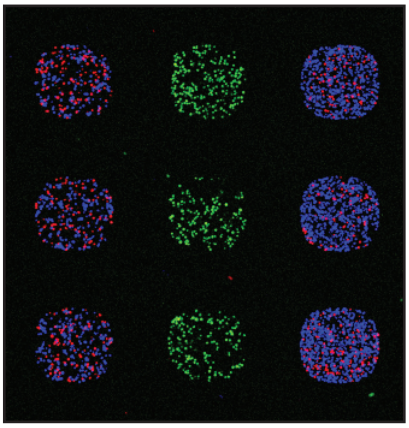
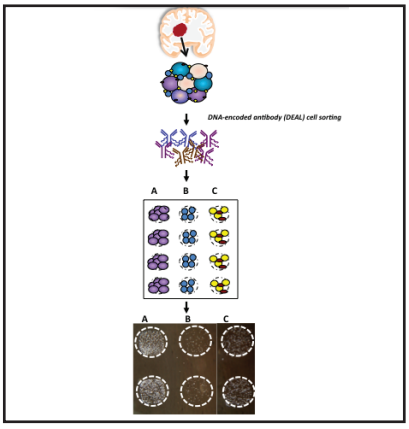
The miniaturization of mechanical resonators to the nanoscale has enabled mass to be resolved with a precision equivalent to a single gold atom when measured in vacuum (Nature Nanotechnology 2008, 3, 533 – 537; Nano Lettures 2008, 8, 4342-4346; Nano Lettures 2006, 6, 583-586). However, mass measurements in fluids have been over twelve orders of magnitude less sensitive (typically on the order of a nanogram), in part due to viscous damping from fluid that surrounds the resonator. In order to reduce this damping, the Manalis lab has developed the suspended microchannel resonator (SMR) which consists of a vacuum-packaged hollow cantilever. In addition to being able to resolve the mass of cells or particles with femtogram precision, the SMR can also measure mass density and charge (Nature 2007, 446, 1066-69).

The goal of this collaboration is to employ the suspended microchannel resonator technology to enhance the characterization of PRINT nanoparticles. Not only will this technology provide exquisitely accurate determination of the mass of manufactured nanoparticles, it will also provide precise measurements to determine the efficiency of numerous particle modifications. For example, this technology will be able to determine the efficiency of functionalization (targeting peptide or monoclonal antibody) of the surface of the nanoparticle. Also, this technology can be utilized to monitor particle degradation elicited by change in pH or other biologic factors. Mass sensing with resonating microchannels provides a powerful and attractive readout method for these PRINT nanoparticle biochemical assays since it has the ability to measure single particle masses with high resolution using inexpensive instrumentation.

The most current findings implicate physical attributes such as size, shape, hydrophilicity, and surface chemistry as key factors contributing to the fate of a nanomaterial in vitro and in vivo.





Glioblastoma biopsy are subject to cell sort using DNA-encoded antibody libraries (DEAL) approach. Each Column has an antibody to capture a specific cell type of interest. (Work from the laboratories of Drs. James Heath and Paul Mischel, performed by Shawn Sarkaria and Drs. Tiffany Huang and Gabe Kwong).

DEVELOPING OF MICROFLUIDICS INTEGRATED NANOELECTRONIC SENSORS AS A DIAGNOSTIC TOOL FOR PATHOLOGIC ANALYSIS OF CANCER TISSUES

By: Paul Mischel, MD
University of California,
Los Angeles (NSBCC)
Los Angeles, CA

Spectacular advances in genomics and molecular biology coupled with powerful new technologies for assaying molecular networks promise to transform the care of cancer patients. Moving from "one-size-fits-all" diagnoses and treatments to molecularly guided therapies will greatly improve the care of cancer patients. To achieve this goal, we need to develop a set of tools that will enable us to identify the right combination of targeted agents for each patient, based upon the tumor's molecular composition. These tools will most likely spring from the physical sciences and engineering and will need to connect in real ways with clinical biology. This is a vision that I strongly believe in, and that is why I become involved with the CCNE program.

I am a physician scientist, a pathologist, whose work focuses on glioblastoma, the most common malignant primary brain tumor of adults and one of the most lethal of all cancers. I graduated from medical school, trained as a pathologist and neuropathologist and then did my post-doctoral research fellowship with Dr. Louis F. Reichardt at the Howard Hughes Medical Institute at UCSF, receiving training in signal transduction and molecular neurobiology. I joined the faculty of UCLA and in the course diagnosing patients with brain tumors, it become clear to me that traditional pathological examination, the "gold standard" of cancer diagnostics, is not well-suited towards molecularly targeted approaches. The morphology-based distinctions that are used in traditional pathology fail to reveal the underlying molecular networks determining response to signal transduction inhibitors in the clinic.

As a result, I focused my laboratory towards developing an understanding of the molecular circuitry that determines sensitivity and resistance of malignant gliomas to kinase inhibitor therapy, and towards developing quantitative molecular approaches to help identify the individual patients most likely to benefit. This work involves integrating information from patients studied in rigorously designed and analyzed clinical trials with experimental observations in model systems to help guide cancer treatment. Along the way,

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I have collaborated with, and continue to collaborate with outstanding scientists, including Charles Sawyers, Ingo Mellinghoff, Tim Cloughesy, Web Cavenee and others. We have identified some of the molecular determinants of response to EGFR kinase inhibitors in glioblastoma patients and begun to identify potential combination strategies to overcome resistance (Mellinghoff et al., NEJM 2005). This work, funded by RO1 grants through the NINDS and the NCI, was highlighted in the NIH fact sheet for the public in 2005-2006 "Driving the Transformation Towards Predictive, Personalized and Preemptive Medicine." It has also led to a number of ongoing clinical trials. Building upon these studies, we have used systems biology approaches to identify and validate new pathway targets (Lu et al., JBC 2005; Horvath et al. PNAS 2006) and have begun to identify novel mechanisms of resistance to targeted pathway inhibitors (Cloughesy et al, PLoS Medicine, 2008). While we have made real progress, we are acutely aware that clinical responses to targeted agents for glioblastoma patients, like response to targeted agents for most cancer patients, remain infrequent and short lived.

This has led us to seriously reconsider where the current gaps in our knowledge lie. Glioblastomas, like other solid cancers, are heterogeneous; not only between patients, but the cells within a patient may differ in their suite of molecular alterations that drive response to therapy. If an agent, or combination targets most of the tumor cells, but leaves a fraction of actively proliferating cells behind, then clinical responses are likely to be infrequent and short-lived. Therefore, our next set of challenges include: 1) developing rational approaches to combine molecularly targeted agents for patients based on a mechanistic understanding of the molecular circuitry of each patient's tumor; 2) developing and testing new technologies that facilitate molecular analysis of key targetable signaling networks in patient samples, particularly those that are a heterogeneous mix of tumor cells.

Focusing on these goals, we are working closely with Jim Heath at CalTech, Hsian-Rong Tseng at UCLA and Lee Hood at the Institute for Systems Biology (and their groups) through the CCNE program, to address these clinical challenges with powerful new technologies. We are developing ex-vivo diagnostics that enable us to identify the molecular circuitry of complex heterogeneous tumors from clinical samples and using this information to identify the best combination of targeted agents that will promote response and anticipate and suppress resistance. We are studying patients in the clinic, and integrating these technologies into the molecularly-guided clinical trials.

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Our work together in the CCNE program is guided by the following principles:

1) ***Curing brain tumors will require that we study patients (and their tissue and fluids), including patients in clinical trials with targeted agents.*** Model systems are wonderful for learning biology, but we believe every person is an individual in ways that cannot be adequately modeled in mice or cell cultures. Thus, although we use these tools extensively (and they are critical for understanding biology), we must learn directly from our patients.

2) ***New technologies that can transform science must be co-developed to address specific clinical needs in highly interdisciplinary teams and used to study patients.*** We believe that our task at hand, ***elucidating the molecular circuitry of molecularly heterogeneous brain tumors*** requires a new suite of technologies. We also believe that the best tools are developed when they are designed to address specific challenges. Thus, we work actively with our technology partners Jim Heath, Hsian-Rong Tseng, Lee Hood and others through the CCNE to develop tools that address the questions of importance for the care of malignant glioma patients.

3) ***Molecular diagnostics must be linked to molecular therapeutics.*** To personalize the care for each cancer patient, we must develop ways to assay the molecular circuitry of their tumor and use it to guide therapy, including anticipating and preventing resistance.

4) ***We must develop tools to non-invasively monitor and guide therapy.*** Patients with cancer usually do not have a lot of time. We must know quickly whether or not a therapy, or combination of therapies is working. Structural imaging such as MRI is very useful and molecular imaging will be an important tool. However, serum diagnostics presents potentially the most powerful, rapid and cost-effective way to monitor therapy and is an area of active work for our group.

5) ***We must develop tools that can be widely used and provided to the community at large.*** This depends on developing tools and assays to study molecular circuitry of each patients disease and doing it in a way that is efficient and cost-effective so that it can be widely disseminated to all patients suffering from brain tumors (and other cancers).

Building Team Science

AN ELECTRICAL AND COMPUTER ENGINEER AT THE FOREFRONT OF CANCER NANOTECHNOLOGY RESEARCH

By: Sadik Esener, PhD
University of California, San Diego
(NANO-TUMOR)
San Diego, CA

Team science, a new way of conducting and managing research is believed to be a powerful approach to bring success in cancer nanotechnology research and ensure its expeditious translation into useful clinical applications. The recently funded CCNEs by NCI rely on multi-disciplinary teams operating in inter-disciplinary working environments. While the participation of clinicians, oncologists, engineers, biologists, physicists and chemists to such a team is natural, finding researchers with enough "bandwidth" that can effectively lead and manage such teams is challenging. Indeed, as we transition from a single PI driven research era, where researchers were trained to be highly specialized and focused, identifying team science leaders with the necessary vision, character traits, management skills and a broad technical background has been a challenge.

At UCSD, Dennis Carson, the director of the UCSD's Moores Cancer Center, had shared the strong belief that the time was ripe for cancer research to adopt a team science type of management approach with a strong engineering component to take advantage of opportunities provided by new developments in high tech and especially in nanotechnology. In 2005, when he decided to respond to an RFA put forward by NCI to develop cancer nanotechnology, he knew that there was significant talent and interested faculty at UCSD to carry out such a large scale multi-disciplinary effort. However, he needed to identify a director at UCSD who could lead this diverse talent to success. In consultation with Dr. Roger Tsien, UCSD's leading biochemist in the field of nanotechnology and Dr. Andrew Kummel, a chemist and materials scientist very familiar with the engineering faculty, they quickly reached a bold and unusual decision. Their choice to lead the effort was Dr. Sadik Esener, a professor of Electrical and Computer Engineering and of Materials Sciences at the Jacobs School of Engineering with a strong expertise in electronics and photonics but surprisingly little involvement with cancer or nanoparticle research at UCSD. However, Esener had the key attributes required for successful leadership of the new center: (a) respect of his colleagues and proven success in running large scientific projects, (b) multiple successes in commercializing medically related chip-based technologies, (c) the ability to work with scientist of different backgrounds and personalities on their ideas, and (d) the speed in learning new fields of science.

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Of Turkish origin, Esener grew up in France, earned his B.S. from the technical University of Istanbul, and his M.S. from the University of Michigan in electrical engineering. Esener considered becoming a medical doctor and registered for medical school back in Strasbourg, but he lasted one week when he started working at the morgue. In 1983, he arrived in San Diego and went on to earn his Ph.D. in 1987 in Applied Physics and Electrical Engineering working on how to integrate electronics and photonics on a single chip to enhance computer performance. Esener remained at UCSD as a faculty and became an internationally renowned expert in optical interconnects and communication, and in the field of optical data storage pioneering multilayer high capacity optical data storage for future generation DVDs.

Esener had previous management experience running two large DARPA funded multi-disciplinary consortia between industry and university. Esener was also the director of the Center for Heterogeneously Integrated Photonic Systems (CHIPS), a multi institutional DARPA funded center based on Esener's vision to combine microfluidics, nanophotonics and light tweezers technologies to develop highly sensitive biochemical sensor chips with high specificity. Esener was a co-founder in five successful start-ups in the San Diego area. Two of the companies Nanogen Inc. (NGEN: NASDAQ) and Genoptix Inc. (GXDX :NASDAQ) were in the medical diagnostics market which indicated that Esener knew the barrier to success in commercializing medical technology. Nanogen used electrophoresis and CMOS electronics for SNP detection, an important tool to assess genetic disposition of individuals to certain types of cancer. As early as 1995, together with Michael Heller then at Nanogen, Esener co-authored the first patent on DNA assisted assembly techniques to heterogeneously integrate nano and micro devices. Genoptix used optophoresis, a technique developed by Esener and former graduate students Osman Kibar and Mark Wang, to determine drug dose response on leukemic cells using the interaction of optical forces with proteins being expressed. At Genoptix, Esener was interacting with oncologists and chemists and had rapidly developed an understanding of the limitations of conventional cancer therapies. Clearly, Esener was on his way to combine nanotechnology with electronic, optical and biological principles to open new engineering capabilities with potential impact to cancer research.

When Carson contacted Esener by phone to ask him if he would agree to serve as the PI, Esener recalls he first thought there must be some confusion. However, Carson was certain that Esener was the right choice. "Clearly, the success of team science depends on leaders like Esener who excel at boundary-crossing activities. Esener had demonstrated the ability, the scientific inclination and curiosity, and willingness to work in an interdisciplinary environment,

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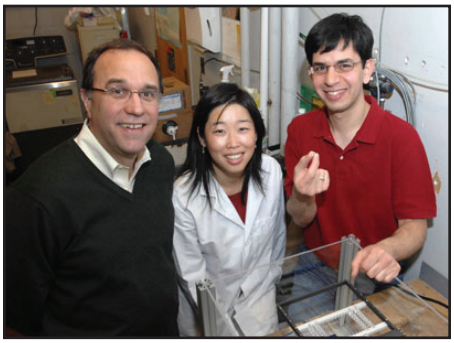
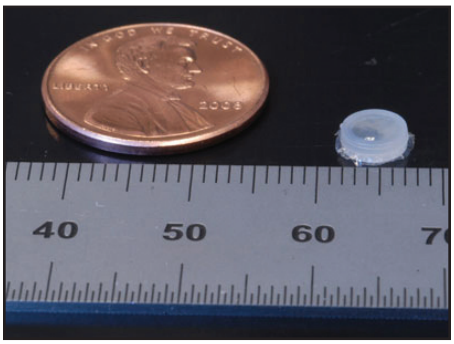
and to collaborate with different types of organizations with widely different cultures." Andrew Kummel adds that "we saw his personable visionary consensus builder humble nature and willingness to working with ideas others than his as a great asset. At the same time he was a well respected eminent scientist who had proven success in more than one field of research: this made him an ideal leader."

During the planning stages of the grant, Esener quickly gained the confidence of his new collaborators at the UCSD cancer center. Robert Mattrey, an internationally renowned expert in Ultrasound Imaging and co-chair of the Department of Radiology at UCSD school of Medicine comments "Esener has a remarkable ability to rapidly learn new evolving fields, understand the research issues involved, and develop a visionary research plan to address them. This requires a general knowledge of medical engineering and related commercial products and markets, including knowledge of cancer and conventional detection and treatment techniques, knowledge of evolving nanotechnology, drug delivery, and imaging and radiation therapy. Esener was able to acquire and master this knowledge in no time with his strong background in physics and chemistry and his exceptional intuitive sense of engineering."

"Nothing comes close to the fulfillment one feels as a researcher to know that you are wrestling with a problem that if resolved would eliminate so much pain and suffering in the world. Although, I had some doubts before I accepted this position that entails tremendous responsibility, I am now so grateful to have been given this remarkable opportunity to bring a new perspective to this disease as a result of NCI's bold undertaking and Dennis' courageous decision. I cannot imagine how I could have been involved with leading edge cancer research without this center and the team science approach," Esener concludes.





IMPLANTABLE DEVICE OFFERS CONTINUOUS CANCER MONITORING, NEW DEVICE COULD TRACK TUMOR'S GROWTH

By: Anne Trafton, News Office (May 2009)
Massachusetts Institute of Technology and Harvard University (MIT-Harvard CCNE)
Cambridge, MA

Surgical removal of a tissue sample is now the standard for diagnosing cancer. Such procedures, known as biopsies, are accurate but only offer a snapshot of the tumor at a single moment in time.

Monitoring a tumor for weeks or months after the biopsy, tracking its growth and how it responds to treatment, would be much more valuable, says Michael Cima, MIT professor of materials science and engineering, who has developed the first implantable device that can do just that.

Cima and his colleagues recently reported that their device successfully tracked a tumor marker in mice for one month. The work is described in a paper published online in the journal Biosensors & Bioelectronics in April.

Such implants could one day provide up-to-the-minute information about what a tumor is doing — whether it is growing or shrinking, how it's responding to treatment, and whether it has metastasized or is about to do so.

"What this does is basically take the lab and put it in the patient," said Cima, who is also an investigator at the David H. Koch Institute for Integrative Cancer Research at MIT.

The devices, which could be implanted at the time of biopsy, could also be tailored to monitor chemotherapy agents, allowing doctors to determine whether cancer drugs are reaching the tumors. They can also be designed to measure pH (acidity) or oxygen levels, which reveal tumor metabolism and how it is responding to therapy.

With current tools for detecting whether a tumor has spread, such as biopsy, by the time you have test results it's too late to prevent metastasis, said Cima.

"This is one of the tools we're going to need if we're going to turn cancer from a death sentence to a manageable disease," he said.

In the Biosensors & Bioelectronics study, human tumors were transplanted into the mice, and the researchers then used the implants to track levels of human chorionic gonadotropin, a hormone produced by human tumor cells.

The cylindrical, 5-millimeter implant contains magnetic nanoparticles coated with antibodies specific to the target molecules. Target molecules enter the implant through a semipermeable membrane, bind to the particles and cause them to clump together. That clumping can be detected by MRI (magnetic resonance imaging).

The device is made of a polymer called polyethylene, which is commonly used in orthopedic implants. The semipermeable membrane, which allows target molecules to enter but keeps the magnetic nanoparticles trapped inside, is made of polycarbonate, a compound used in many plastics.

Cima said he believes an implant to test for pH levels could be commercially available in a few years, followed by devices to test for complex chemicals such as hormones and drugs.

Lead author of the paper is Karen Daniel, a recent MIT PhD recipient. Other authors are recent PhD recipients Grace Kim and Christophoros Vassiliou; Marilyn Galindo, research affiliate in the Harvard-MIT Division of Health Sciences and Technology; Alexander Guimares, a radiologist at Massachusetts General Hospital; Ralph Weissleder, a professor of radiology at Harvard Medical School; Al Charest, visiting assistant professor of biology at MIT; and Institute Professor Robert Langer.

The research was funded by the National Cancer Institute Centers of Cancer Nanotechnology Excellence and the National Science Foundation.

Nanotechnology Highlights

INSTITUTE FOR BIONANOTECHNOLOGY

By: Samuel I. Stupp, PhD
Northwestern University
(NU-CCNE) Evanston, IL

Sam Stupp's scientific background combines the fields of materials science and chemistry, and his work is focused on the use of self-assembly to create highly functional organic and hybrid materials. His combined background allowed him to initiate in the 80s pioneering work in materials chemistry. This was the time when synthetic chemistry started to make inroads into molecular design of materials properties and functions, not only in polymers but also in materials at large. In the 90s Stupp's laboratory introduced the use of self-assembly as a strategy to create bulk materials composed of nanostructures (*Science* 1993,1997). This occurred before the popularization of the term nanotechnology and offered a supramolecular chemistry approach to create functional nanostructures. Influenced by very early interests in the field of biomaterials for use in medicine, primarily materials for bone repair, Stupp developed over the past ten years a very broad platform of self-assembling bioactive materials for regenerative medicine. The vision in this platform was to develop one-dimensional nanostructures that emulate the architecture of fibers in extracellular matrices designed with chemical structures that would allow them to signal cells through receptors and also serve as delivery vehicles for proteins, drugs, and nucleic acids. The platform has been tested in many animal models and shown to be adaptable by design to promote widely different regenerative processes. Examples include axon regeneration after spinal cord injury with recovery of some function, regeneration of bone and cartilage, restoration of heart function after infarct using nanostructures that promote angiogenesis, among others.

Stupp's appointment at Northwestern's Feinberg School of Medicine and the creation of the Institute for BioNanotechnology in the medical campus were critical steps in establishing strong collaborations with faculty that led to the development of *in vivo* models for this nanotechnology platform. It is this same environment that was key in the initiation of a cancer research program in Stupp's laboratory. The co-localization of the BioNanotechnology Institute and the Cancer Center in the same building was an important factor in Stupp's decision to initiate a research program on cancer therapies. The platform developed for regenerative medicine is about bioactive nanostructures in which signals can be easily multiplexed and the nanostructures can simultaneously serve as delivery vehicles. Therefore it was clear a few years ago that this platform could become a novel way to signal for cell destruction, for example apoptosis, perhaps even without

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the use of cytotoxic drugs. Furthermore the technology is both biodegradable and thus leaves no trace behind, and its signals could easily include targeting information for specific cells. The enabling opportunity to start research on these new ideas was without a doubt the creation of the CCNE at Northwestern. This became the opportunity for the Stupp laboratory to connect with faculty having expertise on cancer biology and familiar with the animal models that could be used to test the platform. Four years ago Stupp was able to first connect with Hamid and Vimla Band in the context of the CCNE to initiate *in vitro* work with cancer cells. More recently Stupp's CCNE involvement led him to collaborate with Vince Cryns at Northwestern's Cancer Center to initiate *in vivo* research on the use of the novel therapy for breast cancer. The collaboration between Cryns and Stupp, enabled by CCNE, is now rapidly expanding and new graduate students and postdocs from different parts of the country have joined the effort attracted by strong interests in novel technology for cancer therapies.

Alliance Activities and Classifieds

courses

COURSES

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

S-CCNE, St. Louis, MO
Fall 2009 Course
Jointly offered by Washington University and University of Illinois, Urbana-Champaign
Now available on-line at
http://courses.wustl.edu

Course details:
School: Arts and Sciences
Department: Biology and biomedical sciences
Course: 5145
Title: Nanomedicine Applications
Credit: 1 Unit
Offered: Annually
Description: 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.

Fourth Annual NCI Alliance for Nanotechnology in Cancer Investigators' Meeting
October 20-22, 2009
Manhattan Beach, California

For more information, visit www.capconcorp.com/meeting/nano2009/default.asp

job opportunities

JOB OPPORTUNITIES

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/

C-CCNE, Chapel Hill, NC
The Center for Nanotechnology in Drug Delivery announces an appointment in the Division of Molecular Pharmaceutics in the UNC Eshelman School of Pharmacy in Cooperation with the Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill
The Division Molecular Pharmaceutics in the UNC Eshelman School of Pharmacy in cooperation with the Lineberger Comprehensive Cancer Center are seeking to fill a 12-month tenure-track position at the rank of Assistant or Associate Professor. The ideal candidate will have expertise in nanomedicine, nanotechnology and cancer drug delivery.

The qualified candidate must have a Ph.D. degree in an Engineering discipline, Pharmaceutical Sciences, Chemistry, or a closely related discipline.

Visit jobs.unc.edu/1001675 for more information. Applications should include a cover letter, CV, detailed statement of research program and interests, and the names and contact information of four references.

Interested candidates should apply directly to the search committee chair:
Dr. Michael Jay, Ph.D., at mjay@unc.edu
If you have any questions about the position or require assistance, please contact Holly Maguire 919-843-6142, hmaguire@email.unc.edu

The University of North Carolina at Chapel Hill is an equal opportunity employer.

MD Anderson-CNPP, Houston, TX
Postdoctoral Fellow in the Department of Diagnostic Imaging, The University of Texas M. D. Anderson Cancer Center
The Alliance for Nanohealth at Houston invites applications for postdoctoral fellows in nanotechnology and imaging sciences. Specific research topic includes development of multi-stage nanostructures for cancer diagnosis and therapy, and nanodevices for imaging treatment responses. Candidates should posses a PhD degree in material science or biomedical engineering. Experiences in animal imaging are required. \Send resume and names of 3 references to: Dr. Chun Li, Department of Experimental Diagnostic Imaging, Box 59, U. T. M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas, 77030; e-mail: cli@mdanderson.org. The University of Texas M. D. Anderson Cancer Center is an equal opportunity employer. Smoke-free and drug-free environment.

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, Lynn Coulter (Washington U. S-CCNE) and Diane Clark Robinson (NSBCC-CCNE), with coordination from NCI co-chair, Krzysztof Ptak, Ph.D.

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

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