# Ming Hsieh Institute for Research on Engineering Medicine for Cancer

# Strategic Plan

## April 5, 2011

## 1. Setting the Stage for the Hsieh Institute

41% of Americans born today will be diagnosed with cancer at some time in their life. Nearly 600,000 people will die this year from cancer in the United States. Cancer is the second leading global killer, accounting for 12% of all deaths, and the World Health Organization estimates that cancer will become the leading cause of death worldwide, as it already is in the United States. Despite the large investments in cancer research made in the U.S. over the last 50 years, we do not yet have the types of therapies and diagnostics that will dramatically alter cancer survival rates.

The Ming Hsieh Institute at the University of Southern California aims to turn this corner. Established in 2010 through a generous gift from Ming Hsieh (a USC graduate of the Viterbi School of Engineering and founder of Cogent Systems), the centerpiece of the Hsieh Institute will be integrated engineering, scientific and medical research that speeds discovery and creates the pathway by which research rapidly improves the lives of real cancer patients. By embarking on this new interdisciplinary direction, we aim to target and destroy malignant cancer cells before they cause systemic harm to cancer patients, and without the toxic effects normally associated with chemo therapeutic agents.

Nanomedicine represents the application of nanoscale science and engineering approaches for the improvement of medical care. Nanomedicine is the focus of the Hsieh Institute because it offers the potential to manipulate materials and therapeutic agents at the scale of molecules ($10^{-9}$ m), so that medications and diagnostics can be precisely delivered for the most challenging diseases, and personalized to the individual. The Institute intends to unlock the potential of nanoscale science and engineering within integrated programs of research, and to focus on cancer, because it today kills more Americans than any other disease.

The Hsieh Institute promises to make USC a national and international leader in translational cancer research that bridges basic science, engineered devices, synthesized molecules and materials, and medicine. Our aims are to:

- Attract exceptional new faculty, postdoctoral scholars and students to USC.
- Conduct research that is recognized for the innovations that arise from interdisciplinary collaboration.
- Test the therapies and diagnostics that arise from USC research in human subjects, and catalyze the translation of these inventions into medical practice for the benefit of cancer patients.
- Leverage the Hsieh Institute endowment toward additional funding, from competitive peer-reviewed grants, industry contracts, intellectual property income, and new gifts.

This document presents the initial scientific plan for the Hsieh Institute, addressing the launch of the institute and the first five years of activity, and reflects input received from the research community at USC (via survey, faculty retreat and faculty advisory task force), as well as an examination of nanomedicine research taking place elsewhere.

## 2. State of Knowledge on Nanomedicine for Cancer

While small particles have been in use for biomedical research and in-vitro diagnostics over the last fifty years, their potential for revolutionizing cancer care has only begun to be realized over the last decade. When the National Nanotechnology Initiative was begun in 2001, the National Institutes' of Health (NIH) investment in nanoscale science and engineering (NSE) was modest, even though it was anticipated that nanoscale technology might provide truly novel capabilities, less expensive alternatives to traditional medicine, and increased R&D productivity.

Two workshops[1], along with promising results from research[2], led to major increases in the NIH investment in nanomedicine, which was incorporated in the NIH Roadmap for Medical Research in 2004[3]; the nanoscale investment by NIH has more than doubled since 2005 (hextupled since 2001). Nanoscale science and engineering publications associated with medicine and biology have grown rapidly over the last decade, as reflected in publications within the Thompson ISI Web of Science database (Figure 1, showing results for keyword searches). Publications addressing cancer grew rapidly after the creation of the NIH Alliance for Cancer Nanotechnology in 2005, multiplying by a factor of six.

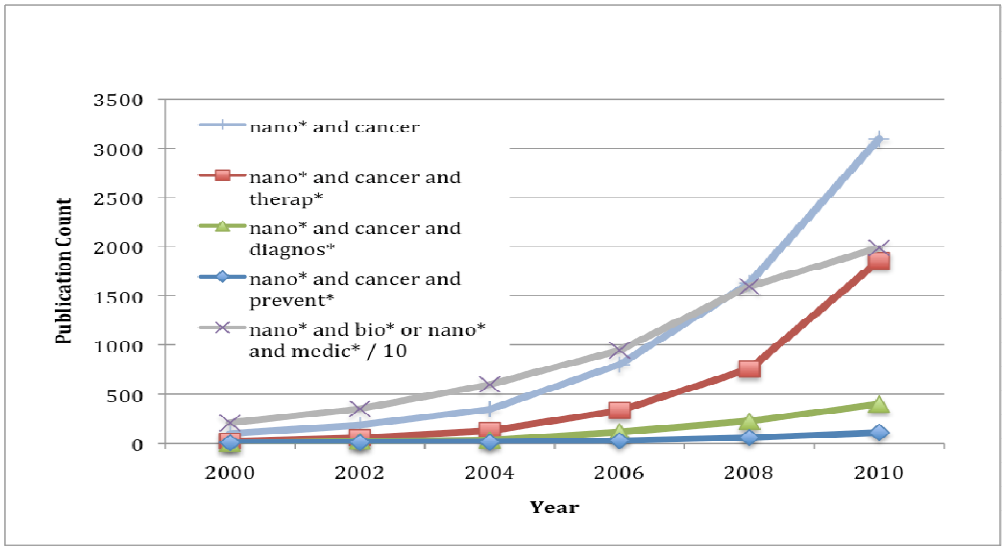


**Figure 1: Publication Counts for nano, cancer and bio research**

The growing attention to nanostructures in medicine/health is also reflected in the professional science/engineering communities, many of which have sessions devoted to the nanoscale impact on medicine/health, and have launched specialized journals:

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[1] Nanobiotechnology, Report of the National Nanotechnology Initiative Workshop, October 9-11, 2003; http://www.nano.gov/nni_nanobiotechnology_rpt.pdf; Nanoscience and Nanotechnology: Shaping Biomedical Research, Symposium Report, June 2000

[2] Nanomedicine: Nanotechnology for Health, European Technology Platform, Strategic Research Agenda for Nanomedicine, November 2006, ISBN 92-79-02203-2.

[3] http://nihroadmap.nih.gov/nanomedicine/

- The Institute of Nanotechnology, founded in the United Kingdom in 1994, began its nanomednet[4] in 2007.
- The American Academy of Nanomedicine was founded in 2005 and launched a journal - *Nanomedicine: Nanotechnology, Biology and Medicine*.
- The journals *International Journal of Nanomedicine,* and *Nanomedicine* were initiated in 2006
- *Open Nanomedicine Journal was initiated* in 2008.
- The journals Wiley Interdisciplinary Reviews: *Nanomedicine* and *Nano Biomedicine,* and *Nano BioMedicine and Engineering* were initiated in 2009;
- The journals *Journal of Nanotechnology in Engineering and Medicine* and *Nano LIFE* were initiated in 2010.

The direct medical cost for cancer in the U.S. for 2007 was about $90B.[5] The combined annual net income for the top 10 pharmaceutical companies is around $73 billion.[6] With these economic drivers, the growing success at incorporating nanomedicine into medical products has attracted the attention of governments and venture capital. Lux Research (investment firm[7]) assessed the public/private investment in nano-enabled technologies in 2008 (Figure 2), finding nearly $2 billion in total investment in healthcare and life science applications of nanotechnology.

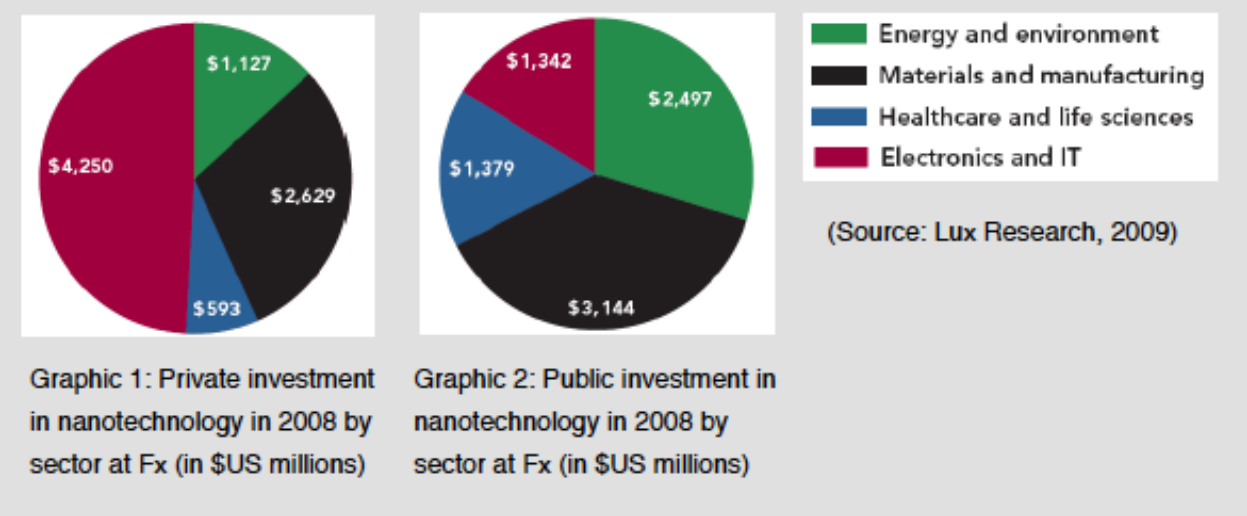


**Figure 2. Investments in Nanotechnology (source: Lux Research)**

One example of governmental investment is the European Technology Platform for Nanomedicine, led by industry in partnership with the European Commission[8]. It sponsors

[4] www.nano.org.uk/nanomednet/
[5] American Cancer Society: **Cancer Facts and Figures 2007.** 2007.
[6] "Nanotechnology Tools in Pharmaceutical R&D", CSSR Kumar, Materials Today 12, 24-30 (2009)
[7] http://www.luxresearchinc.com/; Lux is now (March 2011) offering a webinar in "Targeted Delivery State-of-the-Market: Growing Delivery Partnerships and Alliances:.
[8] http://www.etp-nanomedicine.eu/public

an annual meeting, the European Joint Conference for Nanomedicine (the most recent is CLINAM 2011, May 23th to 25th in 2011)[9].

## 2.1 NCI Alliance for Nanotechnology in Cancer (ANC)

Initiated in 2005 by the National Cancer Institute (NCI), the Alliance for Nanotechnology in Cancer (ANC)[10] integrates the capacities of the NCI Centers for Cancer Nanotechnology Excellence (CCNE), partnerships (Cancer Nanotechnology Platform Partnerships - CNPP), and consortia to increase the pace of technology development and clinical application in the fight against cancer. Its goals are to develop:

- Research tools to identify new biological targets
- Agents to monitor predictive molecular changes and prevent precancerous cells from becoming malignant
- Imaging agents and diagnostics to detect cancer in the earliest, most easily treatable, pre-symptomatic stage
- Multi-functional targeted devices to deliver multiple therapeutic agents directly to cancer
- Systems to provide real-time assessments of therapeutic and surgical efficacy
- Novel methods to manage symptoms that reduce quality of life

Through three workshops in 2009, the ANC has identified these promising research directions[11]:

- *In vitro* assay technology, particularly the identification and validation of additional cancer biomarkers, including markers of tumor metabolism, growth and dormancy as well as type and stage. The development of biomarkers other than proteins will be essential. Microfluidics will be a backbone technology.
- Collection and analysis of circulating tumor cells.
- Cancer nanotechnology prevention, including nanoparticle formulations of chemo preventives.
- Cancers having particularly poor outcomes, including brain, lung, pancreatic, and ovarian cancers.
- Greater focus on clinical translation in CCNEs, with at least one nanotechnology strategy in clinical trials by 2015 for each center.
- Multi-disciplinary training for a cadre of researchers who will be skilled in applying the tools of nanotechnology to critical problems in clinical oncology.

[9] http://www.etp-nanomedicine.eu/public/news-events/news/the-european-joint-conference-for-nanomedicine
[10] http://nano.cancer.gov/
[11] "The NCI Alliance for Nanotechnology in Cancer: Achievement and Path Forward", K Ptak, D Farrell, NJ Panaro, P Grodzinksi, and AD Barker, WIREs Nanomedicine and Nanotbiotechnology 2, 450 ( Sept/Oct 2010).

The ANC has also led to the Nanotechnology Characterization Laboratory (NCL) was recently created through a partnership of the NCI, National Institute of Standards (NIST) and the Food and Drug Administration (FDA) to support the research community. The NCL develops protocols for the characterization of nanostructures in biological applications, and provides services to characterize nanoparticles[12].

## 2.2 National Science Foundation (NSF)

Separately from the NIH effort, the NSF funded a series of four workshops that identified these opportunities for translational research:[13]

Diagnosis

- Point-of-care nano devices for early diagnosis and therapeutic response monitoring capable of using unprocessed bodily fluids with multiplexing and rapid analysis capabilities
- Diagnostic and post-therapy monitoring nano devices for the detection and interrogation of circulating tumor cells and circulating tumor initiating cells
- Nanotechnology-based techniques for intraoperative monitoring during surgery
- Nanotechnology tools to stratify patients for more personalized medicine

Theranostic (i.e., integrated therapy and diagnostic)

- Theranostic multifunctional nanoscale platforms capable of interrogating the tumor microenvironment, subsequently administering therapy, and providing a readout of therapeutic efficiency

Targeted Therapeutic

- Nanoparticle constructs capable of probing tumor microenvironments for tumor recognition and/or triggered drug release
- Nanoparticle-based drug formulations with significant improvement in targeting therapeutic windows as compared to free drug delivery

## 2.3 Challenges In Integrating Nanomedicine and Cancer Treatment

Nanomedicine is often described as highly interdisciplinary. That is certainly true for the application of nanostructures toward the understanding, diagnosis, treatment, and prevention of cancer:

[12] http://ncl.cancer.gov/working_application-process.asp

[13] "Applications: Nanobiosystems , Medicine, and Health", Chapter 12 in Nanotechnology Research Directions for Societal Needs in 2020, MC Roco, CA Mirkin and MC Hersam, Eds., Springer Science Policy Report (2010).

The physical science perspective includes:

- Creation of nanostructure core (platform) composition, size, shape, surfaces
- Measurement of any nanostructure novel properties
- Instrumentation sensitive with atomic precision to structure and properties.

The biological/pharmaceutical perspective includes:

- Adsorption, distribution, metabolism, excretion, including blood brain barrier
- Nanostructure effects on cellular chemistry and structure, including stem cells
- Energy transfer between nanostructure and cell – heat, cavitation, reactive oxygen
- Metastasized vice tumor cells
- Identification of biomarkers that are specific to the cancer cells
- Nanomedicine aspects of systems biology

The engineering perspective includes:

- Tailoring the nanostructure to incorporate multifunctional characteristics
- Scale-up to affordable manufacturing
- Stimulated response of nanoparticles to external stimuli that can penetrate body tissue (e.g., electric/magnetic field, radio frequency, microwave, ultrasound, Xray)
- Stimulated response of nanoparticles to ambient conditions – temperature, pH, other local chemistries
- Ability to measure single cell phenomena

The medical perspective includes:

- Availability of adequate quantities of approved human-use materials
- Mode of delivery – topical, oral, inhalation, intravenous or peritoneal infusion
- Ability to specifically target, locate, activate, and appraise nanoparticle effects
- Clinical evaluation

The commercialization perspective includes:

- Innovation to marketplace programs
- Intellectual property protection
- FDA approvals
- Market size

To accelerate the translation of discovery, including understanding the biological consequences, through the engineering of medical devices/systems, realizing successful clinical application, and entry into the marketplace, it will be necessary to devise a highly integrated effort that effectively incorporates all of these perspectives. **USC is unique among universities in having strong programs in all of these areas. The Hsieh Institute can provide a mechanism to forge an integrated program.**

## 3. Research on Nanomedicine at USC

Over the last five years, USC has made a major investment in scientific infrastructure and new faculty within its Biomedical Nanoscience Initiative (BNI). The vision of the BNI has been to take a revolutionary approach toward human disease through the integration of nanoscale science, engineering and medicine in order to detect disease at the earliest time, to treat with the greatest specificity, and to restore and regenerate function. The BNI has engaged faculty from the Viterbi School of Engineering and the Keck School of Medicine, as well as the College of Letters, Arts and Sciences and the School of Pharmacy, and has expanded our capability to characterize and fabricate materials and devices at the nano scale.

USC is also highly skilled at interdisciplinary research spanning engineering, science and medicine. For instance, the university recently launched the Health, Technology and Engineering (HTE) program to educate medical doctors in engineering principles, and to educate engineers in medical principles. Interdisciplinarity also pervades our many research centers, as described in the following section.

### 3.1 Research Centers

USC's BNI is supported by the work of the University's research centers, including:

- The USC **Norris Comprehensive Cancer Center** (**CCC)**, with nearly 200 members investigating the complex origins and progression of cancer, developing prevention strategies and searching for cures. USC Norris is part of the Keck School of Medicine and is designated by the National Cancer Institute as one of the nation's 40 comprehensive cancer centers. Biomarkers for cancer will be crucial for targeted delivery. The USC/Norris Comprehensive Cancer Center is part of a new consortium of researchers embarking upon an intensive quest to pinpoint breast-cancer biomarkers—unique proteins in the blood that may signal the presence of cancer at its earliest stages, when survival rates from treatment are highest. More generally, the CCC clinical research focuses on testing new therapies for cancer, optimizing existing treatments, discovering prevention methods and developing ways to improve the quality of life for both healthy individuals and those living with cancer.

- The NIH funded **Physical Sciences-Oncology Center (PS-OC)** is creating a predictive model of cancer that can be used to determine tumor steady state growth and drug response, particularly those involved in the hematological malignancies of acute myeloid leukemia and non-Hodgkin lymphoma. Multi-scale physical measurements will be unified with sophisticated modeling approaches to model the tumor's traits during its growth and after any distress, such as chemotherapeutic treatment. The PS-OC faculty also constitute a major component of an NCI Center for Cancer Nanotechnology Excellence focused on therapy response.

- The **Biomimetic Microelectronic Systems Center (BMES)** is a research center dedicated to the development of implantable microelectronic devices for the treatment of presently incurable diseases. Its strategy is to use microelectronic and biomedical technologies to create novel interventions for ophthalmic, neurological and other systemic disorders.

- The **Biomedical Simulations Resource (BMSR)** is dedicated to the advancement of the state-of-the-art in biomedical modeling and simulation through core and collaborative research projects, as well as the dissemination of this knowledge and related software .

- The **Center for Biomedical Informatics Sciences (CBIS)** combines biomedical informatics and biostatistical design to optimize service, training, and methodological developments in relation to study design, information management, and data analysis. CBIS supports research on cancer, molecular genetics, epigenetics, tumor micro environments, and clinical research on various cancers.

- The **Whittier Nanobiotechnology Initiative** is focused on accelerating research on both therapeutic and diagnostic uses of cutting-edge nanotechnologies to help eradicate serious diseases, including cancer, diabetes and cardiovascular.

From the perspective of research translation, USC is also home to the Alfred E. Mann Institute for Biomedical Engineering, the LA Basin Clinical and Translational Science Institute and the USC Stevens Institute for Innovation, a university-wide resource for USC innovators in the office of the Provost. Designed to harness and advance the creative thinking and breakthrough research at USC, the USC Stevens Institute was launched to develop a new model for interdisciplinary innovation.

### 3.2 Laboratory Infrastructure

USC's investments in infrastructure have supported the creation and expansion of core laboratories that support access to shared equipment. Examples include:

- The **Center for Electron Microscopy and Microanalysis** (CEMMA) that includes a suite of new scanning electron microscopes (SEM) and will soon be the home for a new transmission electron microscope (TEM), for material characterization.

- The **Keck Photonics Center** is a clean room facility, including: Compound Semiconductor Lab, with three types of metal-organic chemical vapor deposition (MOCVD) systems; the Optical Communications Laboratory, with extensive laser and optics resources; the Photonics Materials and Devices Laboratory, and the Advanced Interconnect and Network Technology lab with microdisk lasers.

- The **Chemistry Instrumentation Facility** includes: several high field NMR spectrometers (a 600, two-500 and three-400 MHz instruments) as well as FT-

Infrared, absorbance, emission and MALDI mass spectrometers. The facility will take delivery of a pulsed EPR spectrometer this year to compliment the scanning system in place currently. The facility also has Bruker single crystal and Rigaku powder X-ray diffractometers.

- The **Nano-BioPhysics Core Facility** includes: Biacore surface plasmon resonance instrument T100, light scattering equipment, both dynamic and multiangle devices from Wyatt, and an Atomic Force Microscope Nanoscope IIIa.

- **Molecular Imaging Center (MIC)** offers state-of-the-art imaging instrumentation for small animals. The MIC staff utilize pre-clinical versions of positron emission tomography (PET), computed tomography (CT, Xray) and ultrasound scanners (US) to provide information that can be directly translated to clinical settings. In addition supplemental data can be acquired using autoradiography, biodistribution and optical imaging (including quantum dot nanoparticle fluorescence)

- The **Cell and Tissue Imaging Facility** has a number of instruments for studying nano materials prepared in this program, including confocal microscopes, a 200 kV TEM (JEOL JEM 2100 LaB6), a JEOL JSM/6390LV SEM and a range of optical and fluorescence microscopes.

- **Proteomics Core Facility** enables researchers to answer pressing biological questions about the functions and roles of proteins in disease by combining proteomics with advanced mass spectrometry.

- **High Performance Computing Center** includes: high performance computer resources, recently ranked as the 2nd fastest computing cluster in an academic setting in the US. Primary resources include a Linux cluster supercomputer and Sun Fire 15K shared memory system.

### 3.3 Nanomedicine Research Projects

The BNI has catalyzed nanomedicine research at USC in four schools and some 20 academic departments, with involvement of more than 50 faculty (Table 1). Focus areas include:

<u>Targeted Theranostics</u>

A topic of specific NCI interest, theranostics combine diagnostics with targeted therapeutics, within these topics:

| | |
|---|---|
| NP creation/characterization | Wang, Zhou, Brutchey, Malmstadt, Cronin |
| External Activation | Vernier |
| Sensing | Zhou, Thompson |
| Pharmacy | Neamati, Hamm Alvarez, MacKay, Olenyuk |
| Medical | Uckun, Triche, Markland, Crandall, Chen |

## Table 1. Faculty with Demonstrated Interest in Nanomedicine

| Name | | School | Department |
|---|---|---|---|
| Timothy | Triche | CHLA | Pediatrics |
| Fatih | Uckun | CHLA | Pediatrics |
| Xiaojiang | Chen | College | Biological Sci |
| Richard | Brutchey | College | Chemistry |
| Theo | Hogen-Esch | College | Chemistry |
| Nicos | Petasis | College | Chemistry |
| Richard | Roberts | College | Chemistry |
| Mark | Thompson | College | Chemistry |
| Ken | Nealson | College | Earth |
| Mohamad | El-Naggar | College | Physics |
| Rajiv | Kalia | College | Physics |
| Michael | Kahn | Keck | BioChem/MolecBio |
| Joe | Landolph | Keck | BioChem/MolecBio |
| Frank | Markland | Keck | BioChem/MolecBio |
| Steve | Swenson | Keck | BioChem/MolecBio |
| David | Agus | Keck | Medicine |
| Amir | Goldkorn | Keck | Medicine |
| Cheng | Ji | Keck | Medicine |
| Heinz-Joseph | Lenz | Keck | Medicine Oncology |
| Tom | Chen | Keck | Neurological Surgery |
| Mark | Humayun | Keck | Opthalmology |
| Samuel | Yiu | Keck | Opthalmology |
| Rizwan | Masood | Keck | Otolaryngology |
| Uttam | Sinha | Keck | Otolaryngology |
| Alan | Epstein | Keck | Pathology |
| Florence | Hofman | Keck | Pathology |
| Arthur | Olch | Keck | Pediatics |
| Erlinda | Gordon | Keck | Pediatrics |
| Peter | Conti | Keck | Radiology |
| Zibo | Li | Keck | Radiology |
| Edward | Crandall | Keck | SOM |
| Peter | Jones | Keck | SOM |
| Peter | Laird | Keck | Surgery |
| Sarah | Hamm-Alveraz | Pharmacy | PPS |
| Andrew | MacKay | Pharmacy | PPS |
| Nouri | Neamati | Pharmacy | PPS |
| Bodgan | Olenyuk | Pharmacy | PPS |
| Wei-Chiang | Shen | Pharmacy | PPS |
| Walter | Wolf | Pharmacy | PPS |
| Jennica | Zaro | Pharmacy | PPS |
| Paul | Newton | Viterbi | AME |
| David | D'Argenio | Viterbi | BME |
| Ellis | Meng | Viterbi | BME |
| Kirk | Shung | Viterbi | BME |
| Noah | Malmstadt | Viterbi | CEMS |
| Priya | Vashista | Viterbi | CEMS |
| Pin | Wang | Viterbi | CEMS |
| Andrea | Armani | Viterbi | EE |
| Steve | Cronin | Viterbi | EE |
| Martin | Gundersen | Viterbi | EE |
| Michelle | Povinelli | Viterbi | EE |
| Tom | Vernier | Viterbi | EE |
| Chongwu | Zhou | Viterbi | EE |

| | |
|---|---|
| BioMarker | Laird (breast), Lenz (colorectal) |
| Imaging | Wolf, Conti |

Cancer Metastasis

Nanotechnology for detecting/treating metastasized cancer cells

| | |
|---|---|
| Cancer metastasis | Gordon |
| Dynamics of metastasizing cells | Newton |
| Detecting circulating cancer cells | Goldkorn |

Systems Biology/Single Cell

| | |
|---|---|
| Physical Sciences - Oncology | Agus, Hillis |
| Membrane modeling/simulation | Vashista, Kalia, Vernier |
| Nanoparticle toxicity in lung | Crandall |

More specifically, we highlight three examples of USC's current research on nanomedicine for cancer to demonstrate contributions we have already made and will make in the future.

Bionanosensors for Early and Accurate Cancer Detection at Point of Care
(Thompson, Zhou, Roberts, Kartalov, Cote, Datar, Tigli)

USC is developing a sensor platform that will enable multiple cancer biomarkers to be monitored in serum, with high precision, on a small blood sample, typically only a few drops. This technology is scalable to measure up to 100 biomarkers simultaneously on the same small blood sample. The core of this nano biosensing platform is a nanowire based field-effect transistor. To make the sensor responsive to the target biomarker, the nanowire is coated with antibodies or aptamers for the biomarker. Our plan is develop antibody mimics for a wide range of cancer biomarkers and implement them in devices. We have recently demonstrated the detection of five different biomarkers for ovarian cancer, at levels 10-100 times lower than the physiological levels of each biomarker.

Our goal is to make multiplexed sensor arrays. These arrays could have over 100 independent sensors on an area of a few $mm^2$, allowing the simultaneous measurement of 100 different biomarkers, when coupled with microfluidic delivery. Even though we are using nano wires for sensing, there are no complicated or expensive fabrication steps. The nano wires and electrode arrays are deposited using simple, low resolution lithographic techniques, and the electronics needed to probe the devices is fairly simple. Thus, we see this as a technology that has the potential to be adopted for early and accurate diagnosis of cancer at the point of care, inside clinics.

Nanotechnology for Radiation Dose Reduction in Cancer Therapy
(Sinha)

Radiation therapy (RT) constitutes one of the most important treatment modalities for cancer. Permanent collateral damage to the normal tissues, acute and chronic toxicities leading to death and immune depletion are among the most serious complications related to radiation therapy. These limitations of current radiation methods pose a desperate need for approaches that reduce ionizing radiation while still eradicating cancer.

By inhibiting a gene, called sphingosine kinase, the dose of radiation can be reduced by 8-10 fold without loss in clinical efficacy. This unique approach of gene delivery is based on a synergistic combination of radioactive gold nanorods (rGNR), small interfering RNA (siRNA) (together called nanoplex), and micro-electromechanical system (MEMS)-based mini-pump. In animal tests these nanoplexes have sensitized tumor tissue to radiation therapy, allowing potent radiation therapy of cancer at low, non-toxic dosages.

Theranostics and Drug Delivery: Center for Biomolecular Engineering of Nanomedicines
(MacKay, Chen, Conti, Epstein, Li, Markland, Swenson)

USC is developing genetic engineering approaches to biosynthesize protein polymers that self-assemble into biocompatible, monodisperse nanoparticles from 10 to 100 nm in diameter. The peptides used to generate these small particles are exceptionally versatile. As gene products, they can be fused directly to many different proteins and peptides to provide multivalency, drug entrapment, controllable release and reversible self-assembly. As such, they are an emerging platform of nanoparticles that can leverage the expertise of a significant number of investigators across the university.

Currently USC is performing preclinical studies in mice to determine if peptide/proteins can be enhanced through genetically engineered nanotechnology. We now explore four classes of therapeutic biopharmaceuticals: (i) small peptides as ligands for tissue-specific receptors; (ii) viral-derived protein fragments; (iii) ADAM-derived disintegrin proteins; and (iii) therapeutic antibody fragments. Nanoparticles composed of protein polymers can also be loaded with small-molecule therapeutics, diagnostic agents, or both. With PET (positive emission tomography) imaging labels, we are exploring a "theranostic" approach that individualizes rational selection of targeted nanomedicine.

## 4. USC's Opportunity for Leadership in Nanomedicine for Cancer

The Ming Hsieh Institute has positioned USC to greatly expand its biomedical nanoscience initiative, taking a major leap in the use of nanomedicine, with the goal of increasing survival rates and reducing adverse effects of cancer and cancer therapies. However, USC will need to be extraordinarily creative to surpass the teams of faculty already working on nanomedicine for cancer around the world. Beyond our specific expertise in nanomedicine, we hope to do this by integrating the following elements:

- Computational science, capturing USC's vast talent pool in computer science, high performance computing, simulation and mathematical modeling of biological systems.
- Epidemiology and our understanding of the statistical prevalence of cancer based on genetics, exposure, biomarkers and other predictive factors, so that cancer care can be personalized for each individual cancer patient.

The integration of these skills with traditional engineering, science and medicine will give USC the edge to make discoveries that are not possible elsewhere.

Our approach will center on these principles:

- Teamed research, in which medical doctors work with scientists and engineers on every project, and researchers having the opportunity to interact with real patients and their families.

- Integration of modeling, simulation and information technologies, so that we can better predict, and precisely target, therapies and diagnostics.

- A focus on promising new technologies, including:
    - Theranostics that use multifunctional nanoparticles to image the tumor, provide targeted treatment and assess in real-time the therapeutic action.
    - External activation of nanoparticles as a mechanism for non-invasive local delivery of drug and/or tumor ablation.
    - Nanoparticles, including their synthesis, genetic engineering, surface engineering and characterization that can be readily tailored for multifunctionality toward specific clinical applications.
    - Biomarkers that can be exploited to attach nanoparticles to specific cancer cells.
    - Nanoparticle delivery of DNA/RNA based therapies.

- Selection of research investments by rigorous peer review, supporting seed work that will be highly competitive for funding by the NIH and other granting agencies, and has strong potential for dramatically improving outcomes for cancer patients.

- Concentration on the types of cancer where nanomedicine is likely to have the largest impact, such as brain, lung, pancreatic, and ovarian.

- Creation of pathways to speed the translation of research into clinical trials and eventual adoption into medical practice.

- Teaming with industrial partners to facilitate adoption of the USC breakthroughs.

The Hsieh Institute will address challenges that have slowed progress in the past: the

different perspectives (language and culture) amongst scientists, engineers and clinicians; the difficulties associated with inter-departmental/school collaborations; and the absence of a ready mechanism to synthesize, tailor, and characterize nanoparticles for specific clinical trials.

### 4.1 Mechanisms to Accelerate Impact

To achieve these ends, the Hsieh Institute, working closely with the Keck School of Medicine and the Viterbi School of Engineering, will catalyze interdisciplinary collaborations that provide a direct link between research on nanomedicine and real cancer patients. We will do this through the following investments:

- Recruitment of transformative faculty to expand USC expertise, for instance:
    - Nanoparticle creation and modification with chemistry or related disciplines.
    - Advanced therapeutics, within the Norris Cancer Center

- A concierge service provided by an individual with detailed knowledge of the disciplines and capabilities throughout the university, whose job would be to broker collaborations amongst the faculty, especially toward translation from science/engineering into clinical trial. He/she would also reach out beyond the University to gain the necessary expertise/capability when not present here.

- Pilot grant program to seed interdisciplinary research, requiring each funded project to include both clinical and scientific/engineering co-investigators, as well as a plan toward securing follow-on external funding and eventual clinical trials. Funding will go toward two types of projects:

    - Early stage work in which a clinical perspective informs and guides basic research toward nanomedicine solutions.
    - Translational projects, in which already developed nanomedicine approaches are married with clinical patient populations for human testing.

    Following a model created in the Norris Comprehensive Cancer Center, awards would depend in part by an in person panel review, in which the work would be critiqued on the spot by experts. Each recipient of a pilot award would also receive support from USC Stevens or the DC Office of Research Advancement toward translation into medical uses or additional external funding.

- Cost-share funding that is leveraged against external peer reviewed grants.

- Support for interdisciplinary postdoctoral scholars that bridge research groups for a period of two years.

- Organization of collaborative events and tools, including an annual symposium that links USC researchers with industrial partners.

- Investment in critical shared equipment labs:
    - Facility to provide custom nanostructure synthesis and functionalization
    - Up-graded micro/nano fabrication facility capable of handling biologically pertinent materials.
    - Support for hiring key staff positions for initiating and conducting research within shared laboratories.

Beyond these efforts, the Hsieh Institute will engage the various USC industrial outreach efforts – the Stevens Institute for Innovation, the Alfred Mann Institute for Biomedical Engineering, and the LAB CTSI to facilitate the transition of successful clinical tests into medical practice.

### 4.2 Organization of the Hsieh Institute

The Hsieh Institute is a multi-school Organized Research Unit (ORU) of the University. It is governed by a Steering Committee, chaired and appointed by the President of USC, and including the Deans of the Viterbi School of Engineering and the Keck School of Medicine. The Hsieh Institute reports to the Vice President of Research. The Steering Committee must approve the strategic plan for the Institute and approve the fiscal year budget.

The Institute's research and educational activities are guided by a Scientific Committee, to be led by a faculty director who is appointed by the Provost of USC, in consultation with the Deans of Engineering and Medicine, and reporting to the Vice President of Research. The director should possess exceptional leadership skills, expertise in nanomedicine, and training in oncology (or, alternately, significant accomplishments in cancer applications of nanomedicine). Initially, an interim faculty director will be selected from within USC. However, our goal is to conduct a national search for a director of exceptionally high stature, to be appointed in 2013. The director will be responsible for the overall scientific leadership of the institute, for creating a research environment that catalyzes outstanding translational research, and for unifying university talent working on nanomedicine for cancer.

The Scientific Committee is charged with identifying promising research directions, recommending funding priorities to the Steering Committee, evaluating potential candidates for faculty positions and fellowships, and monitoring peer review of proposed work. The scientific committee, currently composed of nine members, will draw from the university's top research talent in the Viterbi School of Engineering, Keck School of Medicine, School of Pharmacy and the College of Letters, Arts and Sciences. Each member will be selected based on his or her scientific knowledge as it contributes to nanomedicine.

The scientific committee will also identify topics for translational teams, each of which will have the aim to integrate and stimulate research across the university within areas that engage clinicians, scientists and engineers within a group of 8-10 faculty. These teams will provide the venue for rapid and efficient communication about the needs and interests of

the cancer therapy community, and to stimulate creation of new research directions. The Director is charged with formation and organization of these teams, and ensuring that the teams make rapid progress toward the Institute's goals.

In addition, the Institute will establish an industrial advisory committee, drawing from scientific talent within companies that have the ability to further develop inventions originating from the Hsieh Institute, and for supporting research at USC.

The activities listed in Section 4.1 are representative of the potential funding priorities for the Institute. Actual expenditures in any year will depend on available funds and research priorities. Specific activities for each year will be specified in addenda.

The Institute will initially operate as a virtual Institute, linking laboratories from throughout the university. However, the Institute will eventually be anchored by a planned molecular science focused building on the University Park Campus along with the Norris Cancer Center. The director for the Hsieh Institute will in the future be based in one of these locations.

## 5. Key Milestones for the Hsieh Institute

Endowment income from the Ming Hsieh gift will fund the activities of the institute, beginning in July of 2011. Our aim is to achieve the following milestones:

- Support for Initial Interdisciplinary Pilot Research (July, 2011)
- Launch of the Institute website and first symposium (Fall, 2011)
- Initiation of translational research teams (Fall, 2011)
- Appointment of an interim director, recruited from inside USC (Fall, 2011)
- Interdisciplinary training program for postdoctoral scholars and PhD students (July, 2012)
- Hiring of transformational faculty (July, 2012)
- Competitive NIH funding (RO1 or program project), seeded from Hsieh Institute Pilot Funds (July, 2012)
- Clinical Trials Based on Inventions from the Ming Hsieh Institute (July, 2013)
- Appointment of permanent director, through national/international search (by Fall, 2013)
- Licensed Technology from the Ming Hsieh Institute (July, 2015)

From a funding perspective, our goal is to multiply annual endowment income from the Hsieh gift by a factor of five within five years, in the form of externally funded grants and contracts, licensing income and new donations. We aim to have a measurable impact on survival rates for targeted cancers within ten years.

## 6. Members of the Hsieh Institute Task Force

The following people participated in the development of this plan:

| | |
|---|---|
| David Agus | Keck School of Medicine |
| Ed Crandall | Keck School of Medicine |
| David D'Argenio | Viterbi School of Engineering |
| Sarah Hamm-Alvarez | School of Pharmacy |
| Thieo Hogen-Esch | College of Letters, Arts and Sciences |
| Peter Jones | Keck School of Medicine |
| James Murday | Office of Research Advancement |
| Nicos Petasis | College of Letters, Arts and Sciences |
| Mark Thompson | College of Letters, Arts and Sciences |
| Pin Wang | Viterbi School of Engineering |
| Chongwu Zhou | Viterbi School of Engineering |

Randolph Hall, Vice President of Research, chaired the task force.

## Appendix A: Recent Review Articles on Nanomedicine for Cancer

**Overview - nanomedicine**

a. "Nanomedicine" BYS Kim, JT Rutka, WCW Chan, New England Journal of Medicine, 2434-2443 (2010)
b. "Nanomedicine – Nanoscale Drugs and Delivery Systems", Journal of Nanoscience and Nanotechnology, 10(12), 7906-7918 (2010)
c. "Translational Nanomedicine: Status, Assessment and Opportunities", JS Murday, RW Siegel, J Stein, and JF Wright, Nanomedicine: Nanotechnology, Biology, and Medicine 5(3), 251-273 (2009)
d. "Nanomedicine – Challenge and Perspectives", K Riehemann, SW Schneider, TA Luger, B Godin, M Ferrari, H Fuchs, Angew. Chem. Inst. Ed. 48, 872-897 (2009)
e. "Nanotechnology Tools in Pharmaceutical R&D", CSSR Kumar, Materials Today 12,24-30 (2009)

**Overview – nanotechnology in cancer**

a. "The NCI Alliance for Nanotechnology in Cancer: Achievement and Path Forward", K Ptak, D Farrell, NJ Panaro, P Grodzinski and AD Barker, WIREs Nanomedicine and Nanobiotechnology 2, 450-460 (Sep/Oct 2010)
b. "Delivering Nanomedicine to Solid Tumors", RK Jain and T Styllanopoulos, Nature Reviews: Clinical Oncology 7, 653-664 (2010)
c. "Emerging Nanomedicines for Early Cancer Detection and Improved Treatment: Current Perspective and Future Promise", DJ Bharali, SA Mousa, Pharmacology &Therapeutics 128, 324-335 (2010)
d. " Engineering Nanocomposite Materials for Cancer Therapy", C Minelli, SB Lowe, MM Stevens, Small 6(21), 2336-2357 (2010)

**Nanoparticles - generic**

a. "Nanoparticulate Drug Delivery Systems for Cancer Chemotherapy", RN Saha, S Vasanthakuimar, G Bende, M Snehalatha, Molecular Membrane Biology 27(7), 215-231 (2010)

Nanoparticles – Opportunities and Challenges", JM Rosenholm, C Sahlgren, M Linden, Nanoscale 2(10), 1870-1883 (2010)

b. "Nanoparticles: Functionalization and Multifunctional Applications in Biomedical Sciences", R Subbiah, M Veerapendian, KS Yun, Current Medicinal Chemistry 17(36), 4559-4577 (2010)
c. "Receptor-targeted Nanocarriers for Therapeutic Delivery to Cancer", B Yu, HC Tai, WM Xue, LJ Lee, RJ Lee, Molecular Membrane Biology 27(7), 286-298 (2010)

"Cationic Nanoparticles for Cancer Therapy", E Bilensoy, Expert Opinion on Drug Delivery 7(7), 795-809 (2010)

d. "Bioavailability and Delivery of Nutraceuticals Using Nanotechnology", QR Huang, HL Yu, QM Ru, Journal of Food Science 75(1), R50-R57 (2010)
e. "Nanoparticulate Drug Delivery Systems for Cancer Chemotherapy", RN Saha, S Vasanthakumar, G Bende, M Snehalatha, Molecular Membrane Biology 27(7), 215-231 (2010)

f. "Concise Review: Nanoparticles and Cellular Carriers – Allies in Cancer Imaging and Cellular Gene Therapy", C Tang, PJ Russell, R Martiniello-Wilks, JEL Rasko,A Khatri, Stem Cells 28(9), 1686-1702 (2010)
g. "Macromolecular Drug Delivery: Basic Principles and Therapeutic Applications", Molecular Biotechnology 43(1), 89-94 (2009)

**Nanoparticles - membrane penetration**

a. "Current Approaches for Drug Delivery to Central Nervous System", S Hossain, T Akaika, EH Chowdhury, Current Drug Delivery 7(5), 238-397 (2010)
b. "Strategies for the Intracellular Delivery of Nanoparticles", LYT Chou, K Ming, WCW Chan, Chemical Society Reviews 40(1) 233-245 (2011)

**Nanoparticles – micellar**

a. Micelle is an aggregate of surfactant molecules dispersed in a liquid colloid
   A vesicle has at least one phospholipid bilayer. If there is only one phospholipid bilayer, they are called *unilamellar* vesicles; otherwise they are called *multilamellar*.
   Liposome is an artificially prepared vesicle made of a lipid bilayer
b. "Micellar Nanocarrier: Pharmaceutical Perspectives", VP Torchilin, Pharmaceutical Research 24(1) 1-16 (2007)
c. "pH-R"Polymeric Micelles as Drug Stabilizers: the Camptothein and Simvastatin Cases", C Alvarez-Lorenzo, A Concheiro, Journal of Drug Delivery Science and Technology 20(4), 249-257 (2010)
d. "Cancer Chemotherapy with Lipid-based Nanocarriers", DH Liu,N Zhang, Critical Reviews in Therapeutic Drug Carrier Systems 27(5) 371-417 (2010)
e. "Advances in Polymeric Micelles for Drug Delivery and Tumor Targeting", U Kedar, P Phutane, S Shidhaye, V Kadam, Nanomedicine-Nanotechnology, Biology and Medicine 6(6), 713-729 (2010)
f. "Polyester-based Micelles and Nanoparticles for the Parenteral Delivery of Taxanes", G Gaucher, RH Marchessault, JC Lemux, Journal of Controlled Release 143(1), 2-12 (2010)

**Nanoparticles – polymer**

a. "Strategies in the Design of Nanoparticles for Therapeutic Applications", RA Petros, JM DeSimone, Nature Reviews Drug Discovery 9(8), 615-627 (2010)
b. "Drug Delivery Using Mulifuncional Dendrimers and Hyperbranched Polymers", CM Paleos, D Tsiourvas, Z Sideratou, LA Tziveleka, Expert Opinion on Drug Delivery 7(12), 1387-1398 (2010)
c. "Dendrimers as Multi-purpose Nanodevices for Oncology Drug Delivery and Diagnostic Imaging", Tomalia DA, Reyna LA, Svenson S, Biochemical Society Transactions 35, 61-67 (2007)
d. "Polyester-based Micelles and Nanoparticles for the Parenteral Delivery of Taxanes", G Gaucher, RH Marchessault, JC Lemux, Journal of Controlled Release 143(1), 2-12 (2010)
e. "Improving the Efficacy of Combined Modality Anticancer Therapy using HPMA Copolymer-based Nanomedicine Formulations",T Lammers, Advanced Drug Delivery Reviews 62(2) 203-230 (2010)

f. "Precise Engineering of Targeted Nanoparticles by using Self-assembled Biointegrated Block Copolymers", Gu F, Zhang L, Teply BA, Mann N, Wang A, Radovic-Moreno AF, Langer R, Farokhzad OC: PNAS 2008, 105:2586-2591.
g. "Emerging Nanomedicine Opportunites with Perfluorocarbon Nanoparticles", Winter PM, Cai K, Caruthers SD, Wickline SA, Lanza GM: Expert Rev Med Devices 2007, 4:137-145.

**Nanoparticles - magnetic**

a. "Magnetic Nanoparticles: Biomedical Applications and Challenges", N Tran and TJ Webster, Journal of Materials Chemistry 20, 8760-8767 (2010)
b. "Synthesis and Applications of Magnetic Nanoparticles for Biorecognition and Point of case Medical Diagnostics", A Sandhu, H Handa, M Abe, Nanotechnology 21(44), #442001 (2010)
c. "Synthesis and Applications of Magnetic Nanoparticles for Biorecognition and Point-of-care Medical Diagnostics", A Sandhu, H Handa, M Abe, Nanotechnology 21(44), #442001 (2010)
d. "Recent Advances in Surfac Engineering of Superparamagnetic Iron Oxide Nanoparticles for Biomedical Applications", M Mahmourid, A Simchi, M Imani, Journal of the Iranian Chemical Society 6, S1-S27 (2010)

**Nanoparticles - gold**

a. "Gold Nanostructures: a Class of Mutifunctional Materials for Biomedical Applications", CM Cobley, J Chen, EC Cho, LV Wang, Y Xia, Chemical Society Reviews 40(1) 44-556 (2011).
b. "Gold Nanoparticle Platforms as Drug and Biomacromolecule Delivery Systems", B Duncan, C Kim, VM Rotello, Journal of Controlled Release 148(1), 122-127 (2010)
c. "Controlled synthesis and Bioconjugation of Core-Shell Structured Gold Nanoparticles", Chinese Journal of Inorganic Chemistry 26(10), 1768-1775 (2010)
d. "Porous Hollow Gold Nanoparticles for Cancer SERS Imaging", Cw Huang, YW Hao, J Nyagilo, DP Dave, LF Xu, XK Sun, Journal of Nano Research 10, 137-148 (2010)

**Nanoparticles – mesoporous silica**

a. "Shell-by-shell Synthesis of Multi-shelled Mesoporous Silica Nanospheres for Optical Imaging and Drug Delivery", CC Huang, W Huang, CS Yeh, Biomaterials 32(2), 556-564 (2011)
b. "Mesoporous Silica Nanoparticles: Structural Design and Applications", II Slowing, JL Vivero-Escoto, BG Trewyn, VSY Lin, Journal of Materials Chemistry 20(37), 7924-7937 (2010)
c. "Towards Multifunctional, Targeted Drug Delivery Systems Using Mesoporous Silica
d. "Inorganic Nanomedicine – Part 2", BS Sekhon, SR Kamboj, Nanomedicine-Nanotechnology, Biology and Medicine 6(5), 612-618 (2010)

**Nanoparticles – carbon**

a. "DNA and Carbon Nanotubes as Medicine", W cheung, F Pontoriero, O Taratual, AM Chen, HX He, Advanced Drug Delivery Reviews 62(6), 633-649 (2010)
b. "Toxicity Issues in the Application of Carbon Nanotubes to Biological Systems", CP

Firme, PR Bandaru, Nanomedicine-Nanotechnology, Biology and Medicine 6(2), 245-256 (2010)

c. "Advancement in Carbon Nanotubes: Basics, Biomedical Applications, and Toxicity", S Beg, M Rizwan, AM Sheikh, MS Hasnain, K Anwer, K Kohli, Journal of Pharmacy and Pharacology 63(2), 141-163 (2011)

**Nanoparticles – detection/imaging**

a. "Porous Hollow Gold Nanoparticles for Cancer SERS Imaging", Cw Huang, YW Hao, J Nyagilo, DP Dave, LF Xu, XK Sun, Journal of Nano Research 10, 137-148 (2010)
b. "Functional Nanoprobes for Ultrasensitive Detection of Biomolecules", SP Song, Y Qin, Y He, Q Huang, CH Fan, HY Chen, Chemical Society Review 39(11), 4234-4243 (2010)

**Nanoparticles - responsive**

a. "Tumor Ablation and Nanotechnology", RL Manthe, SP Foy, N Krishnamurth, B Sharma, V Labhasetwar, Molecular Pharmaceutics 7(6), 1880-1898 (2010)
b. "Responsive Nanoparticles for Drug Delivery", WW Gao, JM han, OC Farokhzad, Molecular Pharmaceutics 7(6), 1913-1920 (2010)
c. "Magnetic Mesoporous Silica Spheres for Hyperthermia Therapy", FM Martin-Saavedra, E Ruiz-Hernandez, A Bore, D Arcos, M Vallet-REgi, N Vilaboa, Acta Biomaterialia 6(12), 4522-4531 (2010)
d. "Photo-driven Nano-impellers and Nanovalves for on-command Drug Release", YA Lau, DP Ferris, JI Zink, Nanoscale Imaging, Sensing, and Actuation for Biomedical Applications VII, Proc of SPIE, 7574 (2010)
e. "Design and Synthesis of New Gold Nanoparticles for Enhanced Photoacoustic Response", CW Wei, C Poe, CM Chen, YH Lee, CRC Wang, PC Li, Photons Plus Ultrasound: imaging and Sensing 2010, Proc of SPIE 7564 (2010)
f. "Light-sensitive Lipid-based Nanoparticles for Drug Delivery: Design Principles and Future Considerations for Biological Applications', A Yavlovich, B Smith, K Gupta, R Blumental, A Puri, Molecular Membrane Biology 27(7), 364-381 (2010)
g. "Enzyme-triggered Nanomedicine: Drug Release Strategies in Cancer Therapy", TL Andersen, DH Thompson, T Kaasgaard, Molecular Membrane Biology 27(7), 353-363 (2010)
h. "Hydrogel Nanocomposites: a Review of Applications as Remote Controlled Biomaterials", NS Satarkar, D Biswal, JZ Hilt, Soft Matter 6(11), 2364-2371 (2010)

**Theranostics**

a. "Imaging and Drug Delivery using Theranostic Nanoparticles", SM Janib, AS Moses, JA MacKay, Adv Drug Delivery Review 62, 1052-1063 (2010)
b. "Imaging Beyond the Diagnosis: Image-Guided Enzyme/Prodrug Cancer Therapy",XY Tong, XS Chen, C Li, Acta Biochimica Biophysica Sinica 43(1), 4-12 (2011)
c. "Quantum Dots Synthesis and Biological Applications as Imaging and Drug Delivery Systems", O Obonyo, E Fisher, M Edwards, D Douroumis, Critical Reviews in Biotechnology 30(4) 283-301 (2010)
d. "Imaging Beyond the Diagnosis: Image-guided Enzyme/Prodrug Cancer Therapy", XY Tong, XS chen, C Li, Acta Biochmica et BioPhysica Sinica 43(1) 4-12 (2011)

**Biomarkers**

a. "Nanocytology: A Novel Class of Biomarkers for Cancer Management", L Wilson, S Cross, J Gimzewski, JY Roa, IDRUGS 13(12), 847-851 (2010)
b. "Measurement of Biomarker Proteins for Point-of-care Early Detection and Monitoring of Cancer", JF Rusling, CV Kumar, JS Gutking, V Patel, Analyst 135(10), 2396-2511 (2010)
c. "Targeting Cancer Cells with Nucleic Acid Aptamers", L Cerchia, V de Franciscis, Trends in Biotechnology 28(10) 517-525 (2010)
d. "Aptamers Selected by Cell-SELEX for Application in Cancer Studies", YF Zhang, Y che, D Han, I Ocsoy, WH Tan, Bioanalysis 2(5), 907-918 (2010)
e. "Aptamer Applications for Targeted Cancer Therapy", AS Barbas, J Mi, BM Clary, RR White, Future Oncology 6(7), 1117-1126 (2010)
f. "Emerging Strategies for EphA2 Receptor Targeting for Cancer Therapeutics", M Tandon, SV Vemula, SK Mittal, Expert Opinion on Therapeutic Targets 15(1), 31-51 (2011)
g. "Understanding Wild-type and Mutant p53 Activities in Human Cancer: new Landmarks on the way to Targeted Therapies", IGoldstein, V Marcel, M Olivier, M Oren, V Rotter, P Hainaut, Cancer Gene Therapy 18(1) 2-11 (2011)

**RNA/DNA**

a. "Nanoparticles as Non-Viral Gene Delivery Vectors", CS Katragadda, PK choudhury, PN Murthy, Indian Journal of Phermaceutical Eduction and Research 44(2), 109-120 (2010)
b. "RNA Interference in the Clinic: Challenges and Future Directions", CV Pecot, CA Calin , RL Coleman, G Lopez-Berestein, AD Sood, Nature Reviews Cancer 11(1) 59-67 (2011)
c. "Metabolic Limitations of the Usae of Nucleoside Analogs in Cancer Therapy may be Overcome by Application of Nanoparticles as Drug Carriers: A Review", L Hajdo, AB Szulc, B Klajnert, M Bryszewska, Drug Development Research 71(7), 383-394 (2010)

**Single Cell**

a. "Single Cell Analysis: the new Frontier in 'omics'", DJ Wang, S Bodovitz, Trends in Biotechnology 28(6), 281-290 (2010)
b. "Electrical Cell-Substrate Impedance Sensing as a Non-invasive Tool for Cancer Cell Study", Analyst 36(2), 237-245 (2011)

**Systems Biology**

a. "Multifunctional Nanoscale Platforms for Targeting of the Cancer Cell Immortality Spectrum", V Soundararajan, K Warnock, R Sasisekharan, Macromolecular Rapid Communications 31(2), 202-216 (2010)

**Stem Cell**

a. "Applications of Naonmaterials in Cell Stem Therapies and the Onset of Nanomedicine", C Iancu, IR Llie, CE Georgescu, R llie, AR Biris, T Mocan, LC Mocan, F Zaharie, D Todea-Iancu, S Susman, DR Ciuca, AS Biris, Particulate Science and Technology 27(6), 562-574 (2009)

## Appendix B: ANC Funded Large-scale Efforts

**CCNE**

- **James Heath** **CalTech**

Develop and validate tools for early detection, diagnosis and therapy of melanoma, glioblastoma and ovarian cancers through in vitro diagnostics, in vivo molecular imaging and targeted therapies, including adoptive T cell immunotherapies and siRNA delivery.

- **Weissleder/Langer** **Harvard/MIT**

Develop and translate to the clinic a diversified portfolio of nanoscale devices for targeted drug and siRNA delivery, diagnostics, non-invasive imaging and molecular sensing for better diagnosis and treatment of melanoma, prostate and colon cancer.

- **Chad Mirkin** **Northwestern**

Develop novel nanoscale technologies including highly innovative "nanoflares" for the detection of circulating cancer stem cells and the development of model matrices to clarify cancer biology processes. These technologies have potential clinical use for brain, pancreatic and breast cancer detection, diagnosis and treatment.

- **Sanjiv (Sam) Gambhir** **Stanford**

Design and implement novel in vitro diagnostic devices and verify their performance using in vivo imaging to monitor lung cancer therapy and for earlier detection of ovarian cancer. (colon)

- **Joseph DeSimone** **UNC**

Develop innovative and significant core technologies, PRINT (Particle Replication on Non-Wetting Templates) nanoparticles and carbon-nanotube-based x-ray sources for cancer therapy and early detection of lung, brain and breast cancer.

- **Ian Baker** **Dartmouth**

Develop and use novel antibody-targeted magnetic iron/ iron oxide nanoparticles, which can be excited by alternate magnetic fields to induce localized hyperthermia in breast and ovarian cancer cells.

- **Peter Searson** **Johns Hopkins**

Develop and integrate nanotechnology-based in vitro assays, targeted chemotherapy and immunotherapy for diagnosis, therapy and post-therapy monitoring of lung and pancreatic cancer.

- **Mauro Ferrari** **UT Health Science**

Develop and apply nano platforms for new therapeutics, methodologies for reliable monitoring of therapeutic efficacy, early detection approaches from biological fluids and advances in imaging, and cancer-prevention protocols for ovarian and pancreatic cancers.

- **Vladimir Torchilin** **Northeastern**

Develop and characterize nano preparations that will be tested in vitro and in vivo for their ability to kill tumor cells, with a particular focus on lung, ovarian and pancreatic cancer.

**CNPP**

- **Mansoor Amiji** **Northeastern**

Combinatorial-designed Nano-platforms to Overcome Turmor Resistance

- **Alexander Kabanov** **University of Nebraska Medical Center**

High Capacity Nanocarriers for Cancer Therapeutics

- **Marc Porter** **Univ Utah**
  Magnetoresistive Sensor Platform for Parallel Cancer Marker Detection
- **Julia Ljubimova** **Cedars-Sinai Med Ctr**
  Nanoconjugate Based on Polymalic Acid for Brain Tumor Treatment
- **Wenbin Lin** **Univ North Carolina**
  Nanoscale Metal-Organic Frameworks for Imaging and Therapy of Pancreatic Cancer
- **Cheryl Willman** **Univ New Mexico**
  Peptide Directed Protocells and Virus-like Particles: New Nanoparticle Platforms for Targeted Cellular Delivery of Multicomponent Cargo
- **Naomi Halas** **Rice**
  Preclinical Platform for Theranostic Nanoparticles in Pancreatic Cancer
- **Peixuan Guo** **Univ Cincinnati**
  RNA Nanotechnology in Cancer Therapy
- **Fatih Uckun** **Children's Hospital LA**
  Targeting SKY Kinase in B-Lineage ALL with CD-19 Specific C-61 Nanoparticles
- **Lily Yang** **Emory**
  Theranostic Nanoparticles for Targeted Treatment of Pancreatic Cancer
- **Thomas O'Hailoran** **Northwestern**
  Tumor Targeted Nanobins for the Treatment of Metastatic Breast and Ovarian Cancer

# Appendix C: Nanotechnology Characterization Laboratory Assay Cascade Protocol

| **Physicochemical Characterization** | **Method ID** |
|---|---|
| Size, Size Distribution | |
| Measuring the Size of Nanoparticles in Aqueous Media Using Batch-Mode DLS | NIST-NCL PCC-1 |
| Size Measurement of Nanoparticles Using Atomic Force Microscopy | NIST-NCL PCC-6 |
| Measuring the Size of Nanoparticles Using Transmission Electron Microscopy | NIST-NCL PCC-7 |
| Analysis of Gold Nanoparticles by Electrospray Differential Mobility Analysis | NIST-NCL PCC-10 |
| Topology | |
| Molecular Weight | |
| Aggregation | |
| Purity | |
| | |
| Chemical Composition | |
| Measuring Free Gadolinium in Gadolinium-Containing Nanoparticles | PCC-3 |
| Determination of Gold in Rat Tissue with Inductively Coupled Plasma-Mass Spectrometry | NIST-NCL PCC-8 |
| Determination of Gold in Rat Blood with Inductively Coupled Plasma-Mass Spectrometry | NIST-NCL PCC-9 |
| Method for Determination of the Mass Fraction of Particle-Bound Gold in Suspensions of Gold Nanoparticles | NIST-NCL PCC-11 |
| Quantification of Free and Chelated Gadolinium Species in Nanoemulsion-Based Magnetic Resonance Imaging Contrast Agent Formulations using Hyphenated Chromatograph Methods | NIST-NCL PCC-14 |
| Surface Characteristics | |
| Functionality | |
| Zeta Potential | |
| Measuring Zeta Potential of Nanoparticles | PCC-2 |
| Measuring the Electrolytic Conductivity of Nanoparticle Suspensions | NIST-NCL PCC12 |
| Measuring the pH of Nanoparticle Suspensions | NIST-NCL PCC-13 |
| Stability | |
| Solubility | |

| In Vitro Characterization | Method ID |
|---|---|
| Sterility | |
| Detection of Endotoxin Contamination by End Point Chromogenic LAL Assay | STE-1 |
| Detection of Microbial Contamination | STE-2 |
| Detection of Mycoplasma Contamination | STE-3 |
| Targeting | |
| Cell Binding/Internalization | |
| In Vitro Immunology | |
| Blood Contact Properties | |
| Analysis of Hemolytic Properties of Nanoparticles | ITA-1 |
| Analysis of Platelet Aggregation | ITA-2 |
| Analysis of Nanoparticle Interaction with Plasma Proteins by 2D PAGE | ITA-4 |
| Qualitative Analysis of Total Complement Activation by Western Blot | ITA-5.1 |
| Quantitative Analysis of Complement Activation | ITA-5.2 |
| Coagulation Assay | ITA-12 |
| Cell-Based Assays | |
| Mouse Granulocyte Macrophage Colony-Forming Unit Assay | ITA-3 |
| Leukocyte Proliferation Assay | ITA-6 |
| Macrophage/Neutrophil Function (4 categories): | |
| Detection of Nitric Oxide Production by RAW 264.7 Macrophage Cell Line | ITA-7 |
| Chemotaxis Assay | ITA-8 |

| | |
|---|---|
| Phagocytosis Assay | ITA-9 |
| Cytokine Induction (6 assays): TNFα, IL-1β, IL-6, IL-8, IL-10, IL-12 | ITA-10 |
| Measurement of Nanoparticle Effects on Cytotoxic Activity of NK Cells by Label-Free RT-CES System | ITA-11 |
| Nanoparticle Effects on Maturation of Monocyte Derived Dendritic Cells In Vitro | ITA-14 |

| In Vitro Characterization | Method ID |
|---|---|
| Toxicity | |
| Oxidative Stress | |
| Hep G2 Hepatocyte Glutathione Assay | GTA-3 |
| Hep G2 Hepatocyte Lipid Peroxidation Assay | GTA-4 |
| Hepatocyte Primary ROS Assay | GTA-7 |
| Cytotoxicity (necrosis | |
| LLC-PK1 Kidney Cytotoxicity Assay (MTT and LDH Release) | GTA-1 |
| Hep G2 Hepatocarcinoma Cytotoxicity Assay (MTT and LDH Release) | GTA-2 |
| Cytotoxicity (apoptosis) | |
| LLC-PK1 Kidney Apoptosis Assay (Caspase 3 Activation) | GTA-5 |
| Hep G2 Hepatocarcinoma Apoptosis Assay (Caspase 3 Activation) | GTA-6 |
| Hep G2 Hepatocarcinoma Homogeneous Apoptosis Assay (Caspase 3/7 Activation) | GTA-14 |
| Autophagy | |
| Autophagic Dysfunction Assay: Qualitative Analysis of MAP LC3I to LC3-II Conversion by Western Blot | GTA-11 |
| Autophagic Dysfunction in LLC-PK1 Cells | GTA-12 |

In Vivo Characterization

Efficacy
- Therapeutic
- Imaging

Disposition study
- Tissue Distribution
- Clearance
- Half-live
- Systemic exposure (plasma AUC)

Single and Repeat-Dose Toxicity

Immunotoxicity

## Appendix D: Important Nanoparticle Characteristics for Cancer Applications

1. Core or "platform" material(s) prominent in the literature
    - polymer (synthetic, protein polymer)
    - dendritic
    - micelle (vesicle, liposome)
    - magnetic
    - gold
    - silica
    - carbon (CNT, fullerene,..)

2. Core or "platform" – important physical/chemical properties
    - size
    - shape
    - deformability
    - "porosity" (cargo capacity)
    - surface
        - charge
        - hydrophilicity
    - sensitivity to external probes – magnetic/electric field, EM wave, sound,...

3. Multifunctionality – tailoring the NP by surface modification/"shells"to accomplish
    - Solubility
    - Biological properties
        - ADME (adsorption, distribution, metabolism, excretion)
            - Enhanced permeability and retention (EPR)
            - Lifetime in circulation
            - Membrane penetration
                - Blood Brain
                - Renal
                - Extravascation
                - Cell
            - Opsonization (avoidance)
        - Toxicity
        - Immunogenicity
    - Targeting to specific sites
        - Chemical
            - Cell membrane protein
            - Organelle (nucleus, cytosol, mitochondria, peroxisome, endosome)
            - Cytoskelton, extracellular matrix
        - Physical
            - Vasculator leakage

Therapeutic action – apoptosis, thermal necrosis, interfere reproduction,
- angiogenesis
- chemical (drug) release
- hyperthermia
- reactive oxygen species (ROS) inducing
- photodynamic
- cavitating bubble
- high electric field pulse
- local high energy radiation
- RNA/DNA intervention

Trigger to induce latent therapeutic action
- Internal trigger
  - Temperature
  - pH
  - enzymatic
  - other chemical ambient
- External trigger
  - RF
  - MW
  - NIR
  - Ultra sound (HIFU)
  - Ionizing radiation for secondary electrons

Imaging for location and local properties
- Contrast agent
  - MRI (magnetic),
  - PET
  - Ultrasound (mechanical)
  - CT (heavy element)
- Molecular Diagnostic
  - Fluoresce
  - SERS

4. Medical Mode of administration
- Topical
- Inhalation
- Oral
- Intravenous injection
- Intraperitoneal injection