

Engineering a Change in Cancer Diagnosis and Therapy through Nanotechnology

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Abstract — The Office of Cancer Nanotechnology Research is the centerpiece of nanotechnology funding leadership at the National Cancer Institute of the National Institutes of Health. Its funding portfolio consists of premier academic institutions that engineer state of the art particles and devices to transform cancer diagnosis and treatment. Beyond its research centers, this Alliance for Nanotechnology in Cancer also funds transdisciplinary training programs for students and early career scientists and engineers. Another essential component of the Alliance is the Nanotechnology Characterization Laboratory where the standard protocols of preclinical analysis for newly derived nanoparticles are developed and performed. The guiding mission of the Alliance is to reach beyond basic research and development toward clinical testing as well as product commercialization. At the conclusion of the first Phase of the Alliance that spanned 2005-2010, several hundred patent disclosures had been filed and dozens of industrial partnerships and spin off companies had been formed. Now as the second Phase begins the OCNR and the Alliance look forward to improve on their successful record of technological innovation and developing commercial entities. Beyond the Alliance, the NIH provides funding opportunities for a vast array of research topics that can be applied to health nanotechnologies, many of which can be applied to an electrical engineering audience.

Index Terms – cancer nanotechnology, standardization, commercialization, funding opportunities

I. INTRODUCTION

In 2004, The Center for Strategic Scientific Initiatives (CSSI) was established at the National Cancer Institute (NCI) of the National Institutes of Health (NIH) to focus programs at the forefront of innovative cancer research concepts and technology. One of the pillars of the CSSI is the Office of Cancer Nanotechnology Research (OCNR). The OCNR manages a portfolio of grants structured to facilitate the convergence of the life sciences with engineering and physical science to develop nanotechnological research institutes and trainees that will radically change how we diagnose and treat cancer. To this end, the OCNR targeted funding initiatives to draw in researchers across the spectrum of science and engineering disciplines. These efforts spawned remarkably successful convergent partnerships and transdisciplinary collaborations between leaders in these fields, many of whom had not

previously worked together. Over its relatively short existence, the Alliance for Nanotechnology in Cancer has produced over 1300 publications, averaging an impact factor of 7.4, many of which resulted from collaborations with other granted institutions across the Alliance network. These works have led to hundreds of patents, dozens of spin-off companies, and several clinical trials [1].

Collectively, the nationwide network of researchers involved in the Alliance has engineered an array of particles and devices that continue to make strides toward improving cancer care [2]. Material properties (e.g. magnetic, optical, chemical) and physical characteristics (e.g. size, charge, surface area) of inorganic and organic nanoparticles are being exploited to enhance contrast for multiple imaging modalities and to enable targeting of cancerous tissue and cells for therapy. Multifunctional nanoparticle conjugates and platforms combine these capabilities to simultaneously target, image, and treat a tumor. In addition to the use of nanoparticles in the body, a series of devices have been engineered to make use of nanoscale material properties to enhance instrument function. Some of these devices are tailored to be used in the hands of a clinician to detect Raman scattering of nanoparticles or to administer focused X-rays from a carbon nanotube-based field emission. Still other devices have been built with microfluidics to analyze rare biomarkers of disease or characteristics of single cells making the continuous surveillance for cancer treatment outcomes possible.

II. ALLIANCE AWARDS

A. *Centers for Cancer Nanotechnology Excellence*

Multidisciplinary CCNE teams function as the primary engines for discovery and tool development for the application of nanotechnology to clinical oncology. Each of these Centers is focused on integrated technology solutions and the aggressive development of these solutions from preclinical to clinical application and commercialization. The CCNEs are designed to enable transdisciplinary team research by linking physical scientists, engineers and technologists working at the nanoscale with cancer biologists and clinical oncologists specializing in the diagnosis, prevention and treatment of cancer. They

typically operate five different projects and several facilitative cores that synergize into an integrated Center that functions at a higher level. The current phase of the Alliance is composed of nine CCNEs, funded through the U54 specialized center cooperative agreement mechanism [3], essentially a network of networks.

Some highlights of recent successes include several research breakthroughs and clinical advances, particularly from CCNEs that were funded in Phase I of the Alliance. The project led by Dr. Sam Gambhir at Stanford University has matured from its Phase I entity focused on therapeutic response to its Phase II incarnation CCNE-Translation. They have recently described the fate, toxicity, and biodistribution of silica-gold nanoparticles for their eventual use as surface enhanced Raman scattering (SERS) imaging particles potentially for colorectal cancer when coupled with an endoscopic device [4]. These particles showed little to no toxicity and, when rectally administered, no particles were detected in any other tissue after painstaking electron microscopic pathologic tissue sectioning [5]. The MIT-Harvard CCNE led by Dr. Robert Langer has also continued to build from its successes as a Phase I Center. A project led by Drs. Mounji G. Bawendi and Dai Fukumura has recently demonstrated a proof of principle multistage 'shrinking' nanoparticle that first hones to a tumor as a 100 nm gelatin particle due to the enhanced permeation and retention (EPR) effect of vascularized tumors [6]. The particles are gradually broken down via the function of local proteases to smaller components (such as 10 nm quantum dots in this study) which then deeply penetrate the dense tumor stroma. Such small particles would never have reached a tumor in the first place were it not for the larger carrier as 10 nm nanoparticles are readily cleared by the kidneys. Dr. Ralph Weissleder, also of the MIT-Harvard CCNE, has developed a small footprint micro-nuclear magnetic resonance (μ NMR) imaging device that can be used at a patient's bedside using a smart phone as the user interface [7]. Using magnetic nanoparticles to label a panel of biomarkers, this μ NMR instrument was shown to reliably diagnose cancers with greater accuracy and much faster processing time (one hour as compared to up to three days) than conventional methods. The collection of Centers for Cancer Nanotechnology Excellence continues to produce science that is closest to clinical relevance.

B. Cancer Nanotechnology Platform Partnerships

The CNPPs engage in directed, product-focused research that aims to translate cutting edge science and technology into the next generation of diagnostic and therapeutic tools. These platforms serve as the core technologies for a wide array of specific applications that will ultimately benefit cancer patients. CNPPs are designed to enable multidisciplinary team research and transformative discoveries in basic and preclinical cancer research. The proposed individual research projects are expected to address major barriers and fundamental questions in cancer biology, diagnosis, prevention and treatment of the disease using innovative nanotechnology solutions. To advance such new nanotechnology discoveries, the platform projects take

advantage of the collaborative environment of the Alliance network. The current phase of the Alliance is composed of twelve CNPPs funded through the U01 research project cooperative agreement mechanism.

Prior to the end of the first year of funding, several new CNPPs have already made remarkable progress in their respective technologies. The Platform directed by Drs. Cheryl Willman and C. Jeff Brinker at the University of New Mexico seek to develop stable nanoparticles that can carry a large volume and diverse payload and can target specific tumor antigens. They have created porous nanoparticle-supported lipid bilayers, called protocells, which are the first nanocarriers to be both targeted and able to deliver multiple drug components. The researchers administered doxorubicin in combination with siRNA cocktails or other chemotherapeutics against hepatocellular carcinoma cells, demonstrating a million-fold improvement versus comparable liposomes [8]. At the University of Utah, Dr. Mark Porter is leading another CNPP focusing on diagnostic devices using electromagnetic technologies. One recently published study involves using SERS for the early detection of pancreatic cancer [9], a historically late-diagnosis and therefore poor prognosis type of cancer. Conventional methods cannot detect the pancreatic cancer-specific glycoprotein Mucin 4 (Muc4) in patient sera. However, when gold nanoparticles are used in an antibody sandwich assay with a SERS readout, Muc4 was successfully detected in pancreatic cancer patient sera. This will hopefully translate into a diagnostic procedure that can distinguish patients exhibiting pancreatitis from those with early stage pancreatic cancer. These are only a few examples of the type of novel nanotechnology-based treatments being developed by the CNPPs [10].

C. Training

There is a recognized deficit of scientists with the interdisciplinary skill sets to be individually competent in the demands of nanobiomedical technology. To address this, the current Phase of the Alliance seeks not only to develop novel nanotechnologies, but also to facilitate the training of the next generation of nanobiomedical technology leaders. This is being approached through two funding mechanisms: the Cancer Nanotechnology Training Centers (CNTCs, funded through the R25 cancer education grant mechanism) to develop training programs and Pathway to Independence Awards (K99/R00) for individual investigators. CNTCs are designed to establish innovative research education programs supporting the development of a multidisciplinary nanotechnology workforce capable of pursuing cancer research and vice versa. CNTCs target graduate student and postdoctoral researchers with backgrounds in medicine, biology, and other health sciences as well as in the physical sciences, chemistry, and engineering in an effort to complement their respective fields to produce well-rounded biomedical nanotechnologists. The research education program is primarily focused on mentored laboratory-based training through participation in dedicated training research projects. The current phase of the Alliance funds six CNTCs. The primary purpose of the K99/R00 program is to increase

and maintain a strong pool of talented new investigators focused on research in cancer nanotechnology. The program is designed to facilitate a timely transition from being a mentored postdoctoral researcher to a stable independent researcher with independent grant support at an earlier stage than is the current norm. The current phase of the Alliance funds seven K99/R00 recipients, several of which are already transitioning to faculty appointments.

D. Networking the Alliance

A driving philosophy behind the Alliance is the benefit of networked scientific collaboration. As stated in the training section, there is a dearth of specialized biomedical nanotechnologists. This lack of individual knowledge is compensated for by collaboration, but the fact persists that most collaborations supply instrumentation and expertise that do not reach into novel fields [11]. A goal of the Alliance has been to encourage collaboration outside of the normal comfort zone of the researchers and to facilitate this by building a close knit network where investigators leverage each others' diversity. One method the program office engineered to steer such value-added networking is by restricting a portion of the project funding to be devoted to "Challenge Projects." These projects compel inter-grant collaboration to conduct research not addressed in either parent grant. There is growing sentiment that such a network is paying dividends as reflected by the high publication rate of the program. Furthermore several researchers have noted that many projects are now being conducted exploring areas that they never would have thought to investigate.

Recognizing the benefit of the larger Alliance network model, the CNTCs have recently initiated an inter-CNTC Alliance network working group. This sub-network aims to compare, contrast, build, evaluate, and continually improve these training programs and the research they enable. From this unique network, the CNTCs expect to assimilate best practices in the field of biomedical nanotechnology training that may be translatable to many other disciplines.

III. NANOTECHNOLOGY CHARACTERIZATION LABORATORY

The NCI established the intramural Nanotechnology Characterization Laboratory (NCL) as a part of the Alliance at its NCI-Frederick facility to provide critical infrastructure support to this rapidly developing field. Working with the National Institute of Standards and Technology (NIST) and the U.S. Food and Drug Administration (FDA), the NCL is accelerating the translation of basic nanobiotechnology research into preclinical applications for academic, small business, and industry researchers. It also serves as an international resource and knowledge base for cancer researchers. As a result, NCL is speeding the development of nanotechnology-based products for cancer patients, reducing potential risks, and encouraging private sector investment in this area of technology development.

IV. COMMERCIALIZATION AND CLINICAL TRIALS

A central tenet for the Alliance is for its research projects to bridge the translational gap between basic research and

development toward clinical use and commercialization. Alliance investigators are involved in many commercialization efforts: disclosing and receiving nearly 300 patents as well as founding over 50 nanobiotechnology companies. Many of these companies got their start through the Small Business Innovation Research (SBIR) funding program on topics that support the mission of the Alliance. The basis for the program is to provide early-stage technology financing in order to promote innovation for developing and commercializing novel technologies and products to prevent, diagnose, and treat cancer. The success of the Alliance program hinges on how well it actually impacts the lives of cancer patients. Thus far, Alliance projects have led to several clinical trials, as well as a handful of IND and IDE applications. The goal for the second phase of the Alliance is for each center to enter clinical development by the end of the funding cycle [1].

Some recent examples of Alliance-founded small companies that have leveraged their SBIR successes into clinical study advancement are BIND Biosciences and Calando Pharmaceuticals. BIND Biosciences is a company spun off from the works of Drs. Langer and Omid Farokhzad from their Alliance Phase I MIT-Harvard CCNE. Founded in 2007, it received a Phase I SBIR contract. Recently, BIND has entered phase I clinical trials with their candidate BIND-014 to assess its safety, tolerability, and pharmacokinetic profile with an escalating dose. This particle is composed of a biocompatible polymer that carries the chemotherapeutic drug docetaxol and is specifically targeted to prostate tumors thanks to incorporated prostate-specific membrane antigen (PSMA) ligands [12]. Calando Pharmaceuticals, spun off from the work of Dr. Mark Davis of the Caltech-UCLA CCNE, received SBIR funding in 2006 to develop their targeted polymeric nanoparticles for therapeutic siRNA delivery. This particle, CALAA-01, is undergoing Phase I clinical studies to evaluate the drug's safety and has already been the first demonstration of *in vivo* delivery of siRNA in humans [13].

V. FUNDING OPPORTUNITIES

While the NCI Alliance has been a primary driver for advancing nanotechnology engineering and implementation in cancer biology, NIH-wide funding for health science research involving nanotechnology approaches \$300 million annually. Reflecting this broad interest, there are a variety of funding initiatives that either have a direct nano-component or can be related to the nanotechnology field. These encompass a wide variety of funding mechanisms including: mentored researcher (K99/R00 Pathway to Independence Award), exploratory/developmental research (R21 mechanism - applications that focus on novel or exploratory approaches that are risky but have potentially a high impact as well as proposed discovery research that may lead to new areas of biomedical investigations), research project (R01 mechanism - discrete, specified research projects to be performed by the named investigator), and small business development (Small Business Innovation Research [SBIR - funding to a small business concern toward product commercialization] and Small Business Technology

Transfer [STTR – similar to SBIR, but requiring a formal collaborative relationship between academia or another non-profit research institution and a small business concern]) mechanisms [3,10].

A number of these program announcements are particularly relevant to the IEEE-Nano audience, including: Bioengineering Research Partnerships (R01, PAR-10-234) – for a multi-disciplinary research team, that applies an integrative, systems approach to develop knowledge and/or methods to prevent, detect, diagnose, or treat disease or to understand health and behavior (It is expected that a BRP will have a well-defined goal or deliverable that will be achieved in a 5-10 year timeframe based on objective milestones specified in the initial application); Exploratory/Developmental Bioengineering Research Grants (R21, PA-10-010) – for hypothesis-driven, discovery-driven, developmental, or design-directed research to explore approaches and concepts for new technologies, techniques or methods; Nanoscience and Nanotechnology in Biology and Medicine (R21, PA-11-149; R01, PA-11-148) - to provide support for cutting-edge nanoscience and nanotechnology research and/or tools that can lead to biomedical breakthroughs and new investigations into the diagnosis, treatment and management of an array of diseases and traumatic injuries; Image Guided Drug Delivery in Cancer (R01, PA-09-253) – for research toward the development of integrated imaging-based platforms for multifunctional and multiplexed drug delivery systems in cancer; and Image-Guided Cancer Interventions for small businesses (SBIR R43/R44, PAR-10-079 or STTR R41/R42, PAR-10-080) - Support for the development and optimization of fully integrated cancer imaging, monitoring, and therapy systems and their validation (the development of multiple prototype integrated image-guided intervention [IGI] systems as required for multisite clinical evaluations) through partnerships among small business, large business, and academic clinical centers, as well as small business joint ventures, in order to reach the research goals. These and other funding mechanisms will be discussed in this talk.

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Dorothy Farrell received her doctorate in Physics from Carnegie Mellon University where her thesis project focused on the synthesis and characterization of self-assembled arrays of magnetic nanoparticles. She then spent two years at University College London, where she worked on the preparation of nanoparticle-antibody conjugates for use in cancer therapy. She returned to the United States to work at the Naval Research Laboratory, before joining the National Cancer Institute's Office of Cancer Nanotechnology Research in 2008.

Sara S. Hook looks after projects which use nanotechnology to enhance the understanding of cancer biology and use nanotechnologies for the delivery of genetic therapies; she participates in NCI-wide activities in research development for specific cancer types. Prior to joining the OCNR she did postdoctoral work at the Fred Hutchinson Cancer Research Center and at the University of Virginia. She holds a Ph.D. in Pharmacology from the Duke University Program in Cellular and Molecular Biology.

Nicholas J. Panaro is currently Senior Scientist at the Nanotechnology Characterization Laboratory, Advanced Technology Program.

Krzysztof Ptak acts as liaison between the program office and the bioinformatics community. He also coordinates communication between the program office and grantees. Prior to joining OCNR, he held research positions at Northwestern University and then at the National Institute of Neurological Disorders and Stroke, NIH. Dr. Ptak's experimental science focus was on the neurobiology of respiration and related specifically to the pathology of Sudden Infant Death Syndrome. Dr. Ptak earned his Ph.D.s in Neuroscience from the Paul Cezanne University in Marseilles and the Jagiellonian University in Krakow.

Piotr Grodzinski directs the operation of the OCNR and works closely with the extramural community to develop strategies for the use of nanotechnology in cancer. Previously, he built a large microfluidics program at Motorola Corporate Research & Development in Arizona. After his tenure at Motorola, Dr. Grodzinski joined the

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