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The Carolina Center of Cancer Nanotechnology Excellence: Past Accomplishments and Future Perspectives

R.L. JULIANO*, S. SUNNARBORG, J. DESIMONE, and Z. HAROON

University of North Carolina, Chapel Hill NC 27599, USA

SUMMARY

The Carolina Center of Cancer Nanotechnology Excellence (C-CCNE) is funded by the National Cancer Institute and is based at the University of North Carolina. The C-CCNE features interactions among physical and biological scientists in a series of projects and cores that work together to quickly harness innovations in nanotechnology for the early diagnosis and treatment of cancer. Two key focus areas of the C-CCNE are, first the selective delivery of drugs and imaging agents utilizing advanced nanoparticle technology, and second novel approaches to imaging and radiotherapy utilizing carbon nanotube based X-ray sources.

Keywords

Cancer; Nanotechnology; Nanomedicine; Nanoparticle; Carbon Nanotubes; Imaging; Therapy

INTRODUCTION: AN OVERVIEW OF THE C-CCNE

1. Formation of the C-CCNE

The Carolina Center of Cancer Nanotechnology Excellence (C-CCNE), as its name implies, seeks to utilize advanced nanotechnology for cancer research, diagnosis and treatment. The C-CCNE is part of the National Cancer Institute's Alliance for Nanotechnology in Cancer (<http://nano.cancer.gov/>) and is thus supported by funds from the NCI. The C-CCNE has completed five years of research and has recently been selected for a further five years of funding.

The period 2004–05 was an exciting time for scientists interested in the emerging discipline of nanomedicine. Inspired by the success of the National Nanotechnology Initiative (<http://www.nano.gov/>) in the physical sciences, the National Institutes of Health began several thrusts to bring nanotechnology to bear on biomedical research and ultimately on clinical practice. One of these emanated from the NIH Director's office and eventually led to the funding of several university-based Nanomedicine Development Centers, while several individual NIH Institutes also initiated their own nanotechnology programs. However, by far the largest effort came from the National Cancer Institute, which invested approximately \$150M in the Alliance for Nanotechnology in Cancer over a five-year period (1).

Well before the actual call for proposals, it became clear to some investigators in the academic community that a major new opportunity for funding research in nanomedicine was about to emerge. This issue was how to respond to this unique circumstance. At the

*corresponding author (arjay@med.unc.edu).

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University of North Carolina (UNC) we were fortunate to have outstanding nanotechnologists in our Chemistry and Physics departments and outstanding biomedical researchers in our Medical School, particularly in the area of cancer. However, up to that point there had been only modest interactions between our biomedical and physical scientists. To foster additional interdisciplinary activity, several UNC scientists (including RLJ and JD) organized a series of workshops where investigators from many fields could discuss their work in an informal setting. This effort was strongly supported by Dr. H.S. Earp the Director of the UNC Lineberger Comprehensive Cancer Center (LCCC). The cross-fertilization and collaboration that emerged from these workshops provided the intellectual basis that allowed UNC to pursue major funding in the field of nanomedicine.

When the competition for Centers of Cancer Nanotechnology Excellence was announced by the NCI in Dec. 2004 UNC was well prepared to participate. R.L. Juliano was chosen to coordinate the submission of the large and complex proposal required, and the staff of the LCCC, particularly Mike O' Malley, Mark Kramer and Wendy Sarratt, made key contributions. After scientific and administrative review, the NCI announced that UNC would be one of eight universities to receive a CCNE award. At almost \$4.5M total cost per year for 5 years this was one of the largest basic research grants ever awarded to our university. This first iteration of the C-CCNE was comprised of six research projects and four supporting cores and was led by R.L. Juliano as Principal Investigator and J. DeSimone as co-PI with Susan Sunnarborg as an associate director. Although primarily based at UNC Chapel Hill, the C-CCNE also involved investigators at NC State University, Duke University, University of Illinois Chicago and University of California San Francisco.

The individual projects of this first iteration of the C-CCNE dealt with several important themes in nanomedicine. Projects 1 and 2 were based on a novel strategy for nanoparticle fabrication termed PRINT (Particle Replication in Non Wetting Templates) that was developed in the DeSimone laboratory (2,3). Utilizing techniques adapted from the microelectronics industry, Project 1 researchers were able to produce nanoparticles of extraordinary uniformity with precise control of size and shape at dimensions ranging from tens of nanometers to microns (FIGURE 1). A variety of drugs or imaging agents could be incorporated in the PRINT particles while the particle surfaces could be readily modified with polyethylene glycol and/or various receptor-specific targeting ligands. In Project 2 various PRINT particles were examined for their cellular interactions, their blood clearance kinetics and biodistribution, and in the case of drug-loaded particles, for their effects on tumors in mouse models. The rapid evolution of the PRINT technology has clearly been one of the major accomplishments of the C-CCNE.

The work of O. Zhou and colleagues in C-CCNE Project 3 has provided a revolutionary new approach to imaging (4,5). While computer assisted tomography and other X-ray based imaging approaches clearly have made enormous progress in recent years, the conventional method of X-ray generation has not changed since the days of Roentgen. In the novel system developed in the Zhou laboratory, a field emission process utilizing carbon nanotubes (CNTs) replaces the heated wire used to generate electrons in conventional X-ray sources. In terms of imaging this provides two important advantages. First, since electron emission from the CNTs is controlled by gating a voltage, X-ray generation can be rapidly turned on or off. This allows the X-ray source to be synchronized with, for example, the cardiac cycle or the breathing cycle, thus reducing motion blurring and providing enhanced resolution. Perhaps more importantly, it is feasible to fabricate arrays of CNT X-ray sources that can be switched on or off in a directional manner, thus allowing the generation of tomographic images without moving either the patient or the x-ray source. This provides enormous advantages in terms of speed and convenience. The CNT X-ray technology can also be

applied to radiation therapy, including the exciting emerging area of microbeam irradiation of tumors (FIGURE 2).

The C-CCNE also supported productive projects in other areas. For example, a thrust led by J.M. Ramsey developed a prototype of a microfluidics flow cytometer that could be used for point of care diagnosis. The project led by W. Lin produced several families of metallic–organic hybrid nanoparticles that display great potential for MR image enhancement. A project involving M. Yousaf, K. Hahn and others explored the migratory and signaling properties of tumor cells using nanopatterned adhesive surfaces. The work of the six Projects was supported by four excellent Cores: an animal models core, a combinatorial library core to generate targeting ligands, a small animal imaging core, and a pharmacokinetics core. In addition to its research thrusts the C-CCNE supported a variety of educational and outreach activities including a monthly campus wide seminar series, an annual regional nanomedicine symposium, and public outreach at local museums and schools in North Carolina. An overview of the C-CCNE can be found at (<http://carolinaccne.org/>).

2. Impact of the C-CCNE

The advent of the C-CCNE on our campus has had multiple important impacts on research, economic development, and education. First, C-CCNE supported investigators have proven to be immensely productive in terms of research publications. During the period 2005–10 over 200 peer-reviewed articles were produced, including one or more in *Nature*, *Cell*, *PNAS*, *NEJM*, *JCI*, *Angew Chem*, *JACS*, *Langmuir*, *Rev Sci Instrum*, *NanoLetters* and other distinguished journals. Second, intellectual property developed during the initial phase of the C-CCNE led to the founding of highly successful spin-off companies that have had a significant economic impact on our area. This includes Liquidia Inc., which is commercializing applications of PRINT technology in several domains, and Xintek, which is developing CNT X-ray technology for medical and national security applications. As of 2010 Liquidia has raised approximately \$32M in venture funding and now employs about 50 people. Xintek has entered into a partnership with Siemens, forming a new company Xinray to produce CNT based X-ray sources. In aggregate, Xintek and Xinray now employ about a dozen people. The C-CCNE has also triggered important changes in the educational portfolio at UNC Chapel Hill. For example, it inspired the launching in 2006 of a graduate course in Nanomedicine, one of the first such courses in the country. In addition, graduate students and postdoctoral fellows associated with the C-CCNE have had truly interdisciplinary training experiences, for example, spending time with a physicist or chemist and also with an MD oncologist. Thus the C-CCNE has had several major positive impacts on academics at our university and on economic growth in our community. The success of our Carolina CCNE parallels the overall success of the Alliance, as recently described by the NCI nanotechnology leadership (6).

3. Emergence of the Second Phase of the C-CCNE

UNC Chapel Hill responded to the May 2009 announcement of the competition for a second phase of the CCNEs. Happily we were chosen as one of the 9 universities to receive an award from the NCI. One of the primary directions of the new C-CCNE was to have more translational research. We emphasized the bridging of basic and clinical sciences by building a dual leadership structure, in which J. DeSimone will lead the area of applied nanotechnology and J. Tepper will lead the area of clinical oncology. This setup was emphasized for each individual project ensuring direct collaboration between scientists and physicians. The new iteration of the C-CCNE is comprised of five projects in two nanotechnology focus areas (FIGURE 3):

Nanoparticle Based Delivery of siRNA and Chemotherapy

Project 1: PRINT Nanoparticles: “Calibration Quality” Nano-tools for Studying Particle Biodistribution,

Project 2: Ras pathway siRNA for Lung Cancer Treatment

Project 3: Translational Nanosystems for Improved Lung Cancer Treatment with Small Molecules

Carbon Nanotube Based Radiation Therapy and Early Detection

Project 4: Compact Micro Beam Radiation Therapy System for Brain Cancer Treatment

Project 5: Stationary Digital Breast Tomosynthesis System for Early Breast Cancer Detection

FUTURE PERSPECTIVES

Successful application of nanotechnology to cancer requires an interactive and diverse team with innovative and creative solutions. The innovation and goals proposed in new CCNE are challenging but mirror the strength of our researchers and partnerships, especially since our focus is to translate these nanotechnologies to cancer disease management. One of the difficulties in harnessing the full potential of nanotechnology is its multidisciplinary nature. At UNC-Chapel Hill and its Lineberger Comprehensive Cancer Center (LCCC), we understand the role of effective communication, and have created a synergy between chemists, physicists, biologists and clinicians that fosters collaborative pursuits and a commitment to bringing these transformative technologies to actual applications that benefit patients.

One of the focus areas of the new C-CCNE is nanoparticle-based therapy. We propose developing methods for targeted delivery of biological, chemo- and radiotherapies against lung and brain cancer utilizing innovative nanotechnologies developed here at UNC-Chapel Hill. The proposed nanoparticle science is primarily focused on targeted delivery of biological (siRNA) and chemotherapy to cancer cells. A key basic science question we will address is the implications of nanoparticle size, shape and modulus in accessing various tissues in the body. This question can effectively be answered by the UNC-developed PRINT technology, which features exquisite control over particle properties and will result in the establishment of *in vivo* maps for nanoparticle delivery. Two additional nanoparticle-based projects, with four distinct types of nanoparticles that are capable of carrying multiple payloads, will deliver biological and chemotherapy in a targeted fashion to lung cancer. We will establish the first direct comparison of efficacy and toxicity of these various approaches against the equivalent of clinical standard of care in sophisticated murine lung cancer models. The other major focus of the new C-CCNE care in sophisticated murine lung cancer models. The other major focus of the new C-CCNE involves CNT based radiotherapy and imaging. A highly innovative thrust will be the development of compact micro-beam radiation systems, thus translating a technology that currently requires use of a mile-long atomic particle accelerator to a form that can be readily deployed in hospitals and clinics.

From a broader perspective, the precision and uniformity associated with nanomanufacturing of integrated circuits by the microelectronics industry is poised to play an important role for making new generation therapeutics and vaccines. In 1965, Gordon Moore, co-founder of Intel, described the trend that the number of components in integrated circuits had doubled every year since 1958. This trend has continued to today, enabled by advances in photolithography which has taken the minimum feature size of transistors down from about 10 microns in 1970 to 0.045 microns (45 nm) today. In biological terms, this corresponds to going from the size of a red blood cell to the size of a single virus particle! As such, this top-down nano-fabrication technology from the semiconductor industry is, for

the first time, in the size range to be relevant for the design of medicines and vaccines. This opportunity to truly design and synthesize nanoparticles with molecular engineering principles using a top-down nano-fabrication techniques will allow the fabrication of precisely defined micro- and nanoparticles in a continuous manner with control over chemical composition, size, shape, deformability and surface chemistry. Such precision particles will be of immense benefit as vaccines (influenza, H1N1, pneumo), targeted chemotherapy agents, anti-bacterials, and even as an entirely new class of inhalation therapeutics.

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BULLET POINTS

- The C-CCNE is administered by the Lineberger Comprehensive Cancer Center of the University of North Carolina.
- The C-CCNE is supported by a grant from the National Cancer Institute.
- A major emphasis of the current C-CCNE is advanced nanoparticle technology for delivery of drugs and imaging agents to tumors, particularly emphasizing the PRINT technology for nanoparticle fabrication.
- Another major emphasis of the current C-CCNE is X-ray imaging and radiotherapy utilizing CNT-based X-ray sources.
- Over its first five years of funding the C-CCNE has been highly productive in terms of research publications, generation of IP, launching start-up companies, and interdisciplinary training of students and postdoctoral fellows. The C-CCNE is now entering its next five-year funding cycle.

Figure 1.
(A) SEM of 3 micron hex nut PRINT particle on the surface of a HeLa cell at early time in uptake process.

Figure 2.
Microbeam Radiation Therapy: Microbeam radiation generated using a CNT x-ray source.

Figure 3.
Organizational structure of the second iteration of the Carolina Center of Cancer Nanotechnology Excellence.