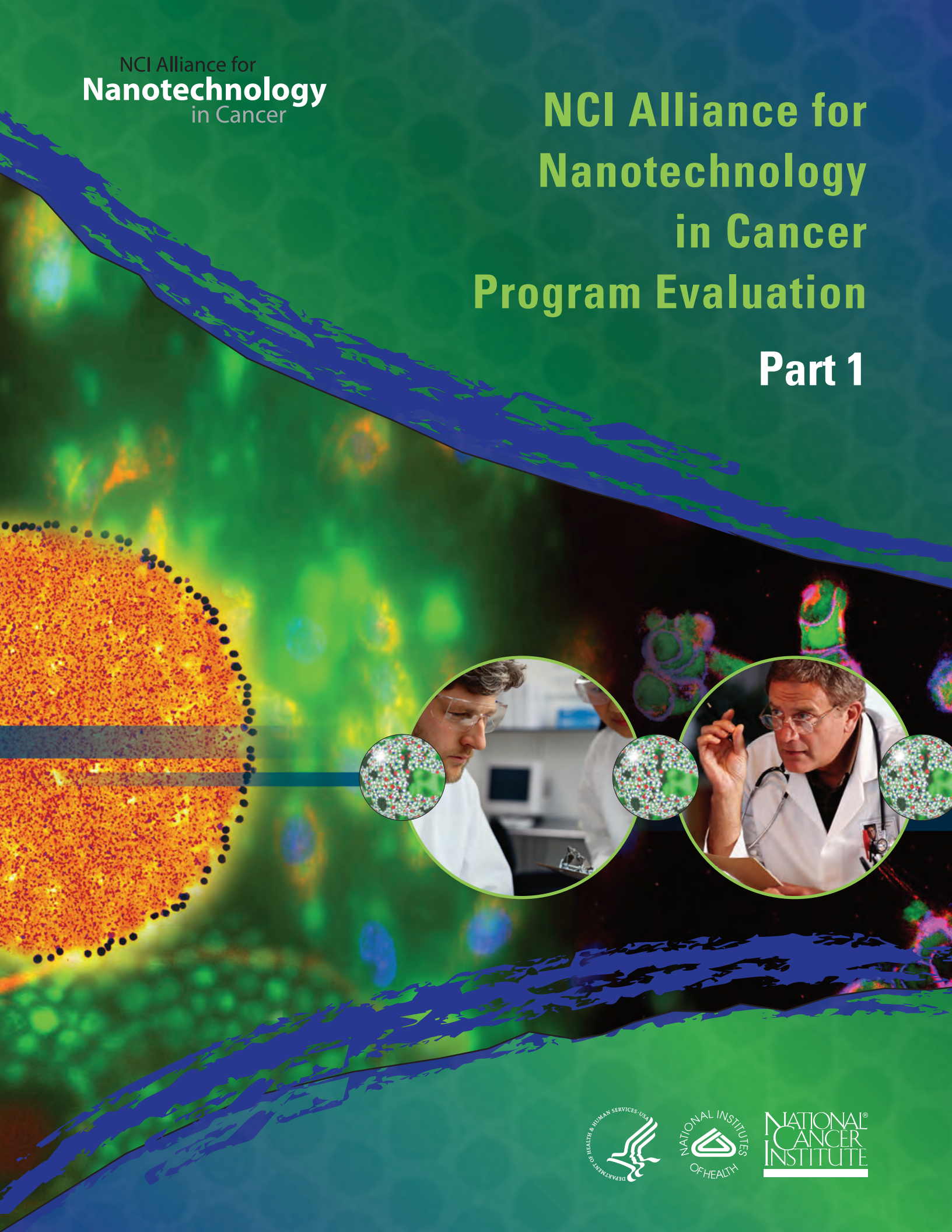
NCI Alliance for
Nanotechnology
in Cancer

NCI Alliance for Nanotechnology in Cancer Program Evaluation

Part 1



National Cancer Institute

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1. Background

The Alliance for Nanotechnology in Cancer (ANC), established in 2004, serves as a national resource that links physical scientists, engineers, and technologists working at the nanoscale with cancer biologists and oncologists specializing in the diagnosis, prevention, and treatment of cancer. The ANC program and its infrastructure have been designed to rapidly advance new discoveries and to transform them into cancer-relevant applications with a potential clinical utility. The aggressive, scientific, and translational goals of the program were outlined in the Cancer Nanotechnology Plan which was published in 2004 and accompanied the RFAs (CA-05-024, -025, -026).

In the current funding period, the ANC operates as an integrated constellation of 8 Centers for Cancer Nanotechnology Excellence (CCNEs) and 12 smaller collaborative Cancer Nanotechnology Platform Partnerships (CNPPs), together with the Multidisciplinary Research Training and Team Development awards (11 awardees) and the National Characterization Laboratory (NCL). The CCNEs are thematically and geographically diverse centers which are the core of the ANC network and infrastructure. The first 3 years of the program have shown the effectiveness of the multi-disciplinary teaming in accelerating science and technology development. A steady flow of innovation from nanotechnologists and biologists is opening up new opportunities for prevention, diagnosis, and treatment of the disease. These innovations are, in turn, evaluated by oncologists, who provide on-going guidance for the further technology development. Several principal investigators within the program originate from disciplines that are non-traditional for NIH sponsored research. These researchers benefit from the partnerships with biologists and clinicians in terms of understanding the needs of contemporary oncology and subsequently can direct their research towards the most relevant oncological problems. The resulting collaborative projects formed under such partnerships are described in the Appendix. Initially, these efforts occurred mainly through the interactive research *within* each center. The centers have evolved into research organisms having distinct area(s) of technical excellence and core resources (*e.g.,* fabrication and materials development, diagnostic assays, toxicology, *in vivo* technology validation, informatics etc.). Moreover, with time, numerous opportunities for *synergistic* collaborations across the ANC have emerged, resulting in several joint projects among different centers. These *inter-center* activities involve not only joint scientific developmental efforts, but also the exchange and cross-training of young scientists.

In summary, even though the ANC is only 3 years old, the Alliance has succeeded in being highly innovative, productive, and translation-oriented. The re-issuance of RFAs will allow for the maturing of the field of cancer nanotechnology, evolving the program towards even stronger emphasis on clinical translation, and developing further ties with other NCI programs and divisions. The main organizational solutions of the proposed re-issuance will largely replicate the successful and efficient structure of the original ANC. However, we propose few changes and improvements, reflecting 'lessons learned' from first 3 years of the program: 1) in order to promote the clinical translation further, we will focus the operation of each center on developing an *entire solution* with a prospective clinical utility (single application focus). To reflect the maturation of several technologies developed in the centers, we expect several Phase 0 and Phase I clinical trials to emerge. Their planning will be performed through collaboration with DCTD, while their funding will occur through existing NIH clinical trial funding mechanisms and other sources; 2) to further draw upon diversified capabilities of the centers, we would formulate joint *Grand Challenge* projects to be announced every 18 months; 10% of set-aside budget will be maintained to fund them through the duration of the program; 3) the platform partnership projects (currently funded as R01s) will be issued as cooperative agreement U01s to promote further NCI-investigator interactions and active management of the program.

ANC Characteristics

Distinctive aspects of the ANC program that has contributed to its success include an appropriate combination of geographically-distributed large and smaller research groups (CCNEs and CNPPs, respectively). These ANC components provide diverse and complementary capabilities to work collectively in support of the six key "opportunity areas" outlined in the initial RFAs. *Active program management* structure (U54 cooperative agreement) ensures frequent and close communication

between investigators and the NCI program staff members. Importantly, the cooperative agreement mechanism allows the NCI to guide (if necessary) the research direction of project(s), and to promote and facilitate the collaborative efforts among the awardees. The NCI program staff members have actively contributed in both of these areas.

The Alliance is *governed* by the Coordinating and Governance Committee (CGC). CGC membership includes at least one member from each CCNE, NCI Program Director, and public advocacy group representative. The CGC meets three times per year to assess scientific progress, identify new research opportunities, establish priorities, and consider policy recommendations. In addition, each CCNE has its own *Steering Committee* (in some cases scientists from one CCNE serve on the steering committee of the other); few of the CCNEs have formed *Industrial Advisory Committees* that provide help in developing commercialization strategies. *Principal Investigator* (PI) meeting, held annually in autumn, is a main venue enabling ANC investigators to meet in person and exchange their ideas and experiences. These annual meetings consist of oral and poster presentations, and working group meetings. ANC PI meetings are designed to promote interactions of junior investigators and graduate students with senior PIs. NCI also invites parties who can aid investigators in commercializing technologies and translating them to the clinic.

ANC Achievements

- The ANC has generated very strong scientific output during the past 3 years (Appendix), which includes over 600 peer-reviewed publications in highly regarded scientific journals (an average impact factor ~ 7) and more than 200 patent disclosures/applications. Moreover, the funding support from ANC has allowed the program participants to secure significant additional research and developmental funds from the federal government, philanthropic sources, industry, and foreign governments to further build upon research seeded by the Alliance program.

- In addition to scientific advances, the association of the program with nearly 50 industrial entities (ranging from PI-initiated start-up companies to collaborations with large multi-national firms) has established a vital commercial outlet for produced technologies. Currently, these companies along with the investigators from the ANC, are engaged in 5 nano-therapy and imaging clinical trials. Several additional companies have a nanotechnology application in advanced, pre-IND stage of technology development. Many of them have successfully applied and received Phase I funding through the NCI SBIR Development Center.

- Through the operation of *Nanotechnology Characterization Laboratory* (NCL), over 130 different nanoparticle formulations have been evaluated. The program has also contributed to centralized information base for the results of these characterization efforts – caNanoLab database has been developed in collaboration with NCICB and is accessible to the users from the research community. In addition, NCL has fruitfully collaborated with FDA on establishing approaches to regulatory clearance of these technologies (Appendix – NCL Progress Report).

- ANC investigators formed the community which is at the fore-front of the new field of cancer nanotechnology and are driving its progress. The multi-disciplinary teams, consisting of researchers from diversified, yet synergistic, disciplines, are developing the ability to speak a common research language and work together towards a common goal. The development of these teams resulted in 43 multi-PI joint publications with several more being prepared for submission. Moreover, the integration and active participation of oncologists into the technology development, although occurring slowly, are becoming a reality.

Collaborations with other NCI programs and divisions: Several investigators of the Alliance are also supported by other large NCI programs (e.g., SPOREs, EDRN, ICBP, and MMHCC) as well as through other synergistic NIH nanotechnology initiatives (e.g., PEN (Program of Excellence in Nanotechnology) from NHLBI and Nanomedicine Roadmap), and individual R21 and R01 projects from NHGRI, NIGMS, and others. This broad programmatic participation allows for propagation of the knowledge

developed under the Alliance program into other program areas. Similarly, NCI OTIR program staff has established communication with several groups and divisions within NCI to promote the interactions with ANC investigators. For example, recent discussions with DCTD leadership (Drs. Doroshow and Tomaszewski) led to establishing a strategy for combining drug formulations which failed in the past toxicology evaluations at NCI with new nanotechnology-based localized delivery vehicles for prospective elimination of harmful toxicity profiles. DTP staff (Dr. Creekmore) has continuously been providing advice on the drug development issues and participated in site visits. Similarly, Clinical Center researcher (Dr. Dahut) joined program staff on several site visits. CTEP (Dr. Wright) and OTIR has established joint seminar series to raise awareness of the nanotherapeutic developments occurring in early to medium stage companies and to initiate clinical evaluation collaborations with these companies. Several ANC investigators have also visited with DTP and CTEP for advice on strategies in therapeutic development. CIP (Drs. Clarke and Farahani) and OTIR staff has established discussions on joint program opportunities and collaborations of NTROI network and the ANC. Close interaction with NCICB (Dr. Buetow and Mr. Basu) resulted in the development of database for storage and dissemination of nanomaterials characterization results. Finally, training efforts are planned jointly with OCTR (Ms. Lohrey and Dr. Gorelic) and CRCHD (Drs. Springfield and Bailey) and will be further strengthened by joint training initiative for underserved students and PIs which is under planning with CRCHD.

Collaborations with other agencies: Active relationship with FDA has been established through the collaborative effort of Nanotechnology Characterization Laboratory and Inter-Agency Oncology Task Force (IOTF). NIST is supporting physical characterization of nanomaterials at NCL. The Alliance has on-going relationship with NSF on training programs – 4 IGERT centers with oncology training focus are co-funded by NCI. There is also active discussion on participation of the Alliance investigators in NSF National Nanotechnology Infrastructure Network (NNIN). DOE Nanotechnology Centers have communicated with NCI on sharing nanomaterials characterization protocols.

2. Purpose of RFA

The major goal of reissuing these RFAs is the continuation of the Alliance for Nanotechnology in Cancer as a coordinated program to further explore nanotechnology tools, devices, and formulations in applications relevant to cancer prevention, diagnosis, and treatment. Building upon technology development achieved in the current initiative, the reissued program will continue to have a strong translational nature. The main organizational solutions will largely replicate the successful and efficient structure of the original ANC. Nonetheless, new RFAs will be issued as an *open competition* initiative to ensure the proper influx of new ideas, technologies, and investigators.

The proposed Alliance structure will involve Centers of Excellence, platform projects, and training mechanisms. Each center will consist of 3-5 interactive and synergistic research projects focused on developing a complete *solution* in one of the following areas:

1. Early diagnosis using *in vitro* assays and devices or *in vivo* imaging techniques;

2. Multifunctional therapeutic solutions;

3. Devices and techniques for cancer prevention and control;

4. Tools for preventing, detecting, and eradicating metastasis.

Each of the centers will need to demonstrate the translational potential of the entire technological solution in at least two different organ systems. The investigators will be encouraged to develop at least one application for cancer of those organs, where the disease is characterized by low survival rates: brain, lung, ovary, and pancreas.

Similar to the original ANC, each center will be expected to:

- Integrate with NCI-designated Cancer Center and/or Specialized Program of Research Excellence (SPORE);
- Affiliate with academic or research centers devoted to engineering or physical sciences;
- Establish relationship with for profit organization(s) for commercial technology outlet;
- Ensure data sharing capabilities compatible with Cancer Biomedical Informatics Grid (caBIG) at NCICB;
- Establish appropriate education, training, and outreach programs.

The detailed scientific recommendations and priorities for cancer nanotechnology over the next 5-10 years have been established at three *Strategic Scientific Nanotechnology Workshops* held by NCI in February-March 2008. These recommendations will be used in the preparation of new RFAs. The workshops report (to be published in Cancer Research), agenda, and list of attendees are given in Appendix.

The original ANC Program involved the support of different teams with an early emphasis on technology development. The proposed continuation will solicit centers focused on developing an *entire solution* with a prospective clinical utility (single application focus) and further emphasis on supporting translational research and creating and sharing resources for validation of the technology platforms developed and implemented by the different centers. Through the proposed single application focus of each center, centers would become synergistic rather than competitive and further active collaborations should emerge. Similarly, focus on researching different organs should promote highly interactive environment for validation work. To reflect the maturation of several technologies developed in the centers, we expect several Phase 0 and Phase I clinical trials to emerge. Their planning will be performed through collaboration with DCTD, while their funding will occur through existing NIH clinical trial funding mechanisms and other sources. The diversified backgrounds of investigators would be put further to work by formulating joint *Grand Challenge* projects drawing on the personnel of several centers. These projects will be announced every 18 months; 10% of set-aside budget will be maintained to fund them through the duration of the program.

The satellite, smaller programs in the form of U01s (instead of R01s from 1st issuance) will be maintained to promote further innovation in single project, multi-investigator environment. The training program based on K99/00 and R25 awards will be established in place of F32/F33s. Nanotechnology Characterization Laboratory (NCL) will continue its function of performing nanomaterials characterization towards translational efforts.

Program Structure and Management

The Coordination and Governance Committee (CGC) will be established to bring together the components of the Alliance program. The committee will consist of: 1) principal investigators of all centers (U54 awardees), 2) two representative PIs of nanotechnology platforms (U01 awardees), 3) two NCI-OTIR program staff members, and 4) one representative of NCL. Responsibilities of this committee will include review of progress of the research activities against NCI program goals, development of collaborative protocols, identifying technology impediments to clinical translation, and developing strategies for sharing technologies and validation results. CGC will meet three times a year (at least once in person). CGC Executive Committee (CGC EC) will be formed to provide for the continuity of the leadership between these meetings; four PIs and two NCI staff members will be selected to participate in this committee which will meet at least monthly by telephone conference.

There will be two additional Advisory Committees put in place: 1) Industrial Advisory Board and 2) NIH Working Committee. The former, consisting of representatives from for-profit organizations (5-6

members) involved in the commercialization of nanotechnology-based oncology solutions will provide guidance and advice on translational strategies. The latter will include representatives from NCI organizational units (e.g., DTP, CIP, Cancer Prevention Division, NCICB, and CCR), as well as other NIH institutes and initiatives (e.g., NIBIB, NHLBI, Nanomedicine Roadmap), and Federal agencies (e.g., FDA, and NIST). Representatives of both committees will be invited to participate in the ANC Investigators meetings; in addition they will meet by telephone conference 2 times a year.

3. Current Portfolio Analysis

A search for new (Type 1, 2) RPG applications (R01, P01, R03, R15, R21, R33, R41, R42, R43, R44) using "nanotechnology" as a keyword in abstracts, summary statements, and title in QVR yielded *159* total applications that had NCI as primary contact for fiscal year 2007 (FY07). This number nearly doubled, in fiscal year 2008, to *313* total applications. Approximately 50% of these applications were scored each year and nearly 40 applications were funded in FY08. This proportion translates to approximately $10.58 million of new funding in fiscal year 2008, compared to the $6.07 million dollars invested in FY07. Thus, overall interest in research related to nanotechnology grew rapidly, whereas the success rate of funded applications remained about the same. The latter statistics would support the need for continuation of RFAs to further solidify this area of research and technology in the NCI portfolio. These trends also held for NIH-wide applications. Further, detailed portfolio analysis, which includes also training and funding trends over last five years (instead of only two years in the Table below), is given in Appendix.

Activity	Categories	FY07 - NIH/NCI	FY08 - NIH/NCI
RPG (Type 1,2)	Total Applications	586/159	1067/313
	Unscored Applications	272/81	533/142
	Scored Applications	314/78	534/171
	Funded Applications	97/22	112/38
	Total Cost for FY	$30.59M/$6.07M	$33.28M/$10.58M

Table 1. Portfolio analysis for nanotechnology grants at NIH and NCI. The U54 cooperative agreements (ANC is only NCI-sponsored nanotechnology U54 program) are not included here.

4. Justification for Use of RFA Mechanism

The development and clinical use of new high technologies, including nanotechnology requires continuous fostering of these applications within the NIH and NCI portfolios. Large contingent of the applications in these areas come from engineers and physical scientists who traditionally are not well established within NIH funding landscape. The portfolio analysis above indicated significant increase of the number of applications; however, the funding success rate remained about the same. In addition, the overall budget dedicated to nanotechnology at NCI remains relatively low (approximately $70M/year, including budget of this initiative), while the potential pay-off from this research is considered high.

The budget set-aside associated with the re-issuance of RFAs will:

1. Allow for attracting more cancer nanotechnology applications;
2. Lead to the improvement of the quality of these applications;
3. Strengthen the training in this area (which is under funded to-date (see Appendix));
4. Enable formation of multi-disciplinary teams required by the nature of research in this area;

5. Maintain at least part of cancer nanotechnology infrastructure assembled under first CCNE RFA.

The organizational complexity of Centers of Excellence and diversity of involved science requires the use of special review panels, as for the previous CCNE RFA. Only, such specially formed panels could cover the wide range of cancer nanotechnology topics (*e.g.,* early detection, molecular imaging, multifunctional therapeutics, etc.) and range of projects maturity; but more importantly, grasp the cohesive integration of these topics into the assembly of centers and satellite platform projects.

5. Justification of Use of Cooperative Agreement

The ANC is a highly integrated program in which the NCI's role goes well beyond the normal stewardship of awards. NCI program staff members interact frequently with awardees in order to ensure speedier progress, to develop baseline protocols, and to promote a collaborative environment across the ANC network. These interactions occur at multiple levels. At the highest level, the Coordinating and Governance Committee (CGC) is a partnership between CCNE directors and NCI program director to stimulate interactions amongst all the CCNEs and to identify appropriate priority needs. Working groups (WGs), chaired by NCI program staff member, coordinate various activities with investigators that possess shared scientific knowledge and interests across the Alliance in order to facilitate progress and establish inter-Alliance teaming and collaborations. Direct one (investigator) to one (program staff) communication allows for substantive involvement to guide project direction and preempt any possible delays or complications concerning meeting projects' aims and milestones. Several collaborative efforts among centers and centers and platforms have been suggested by program staff and successfully carried forward by the ANC investigators.

NCI program staff members also play an active role in facilitating interactions between investigators and NCI divisions and laboratories (e.g., CIP, DTP, CTEP, IMAT, NCL, OBBR, SBIR Development Center) and other federal agencies such as the FDA and NIST. The vast resources of NCI have been utilized by the investigators in their quest for additional information on drug and imaging agent development strategies, regulatory issues, clinical trials, and additional funding mechanisms. The complex nature of the Alliance program involving large center operations and gathering researchers from disparate fields, benefits from the continuous involvement of the program staff as indicated in the Evaluation Document (Appendix). As such, continuation of this initiative under the Cooperative Agreement is the best forward strategy.

6. Budget

As described in Sections 1 and 2, the current Alliance structure has been established in order to promote the development of multi-disciplinary innovation teams with a focus on clinical utility of this innovation. The structure involves Centers of Excellence, platform projects, and training mechanisms. The requested funding will allow for 1) sustaining sufficient number of NCI's national resourced cancer nanotechnology centers to maintain the ANC network, 2) providing sufficient technology diversity among nanotechnology platforms, and 3) providing training for young investigators to establish their solid career foundation in this new and expanding field. The budget requested for the re-issuance is proposed as follows: A) 5-8 (U54) centers, B) 8-12 (U01) partnership teams, C) 4-5 training grants (K99/00), and D) 2 (R25) training centers.

	Centers of Excellence	Nanotechnology Platforms	Training Programs
	5-8 U54 centers @ $3-4M	8-12 U01 projects @ $0.6M	4-5 K99/00 awards @$0.5M 2 R25 awards @ $1.2M
Total/yr	$15-32M	$5-7M	$4.5-5M

Table 2. Proposed budget for second round of the Nanotechnology Alliance.

	Centers of Excellence	Nanotechnology Platforms	Training Programs
	8 U54 centers	12 R01 projects	11 F32 and F33 awards
Yr 1	$26.2M	$7.05M	$98K
Yr 2	$28.7M	$7.01M	$228K
Yr 3	$29.1M	$7.16M	$248K

Table 3. Year-by-year spending of the ANC program.

The history of funding for first three years of the Alliance initiative is given above. In addition, 5 minority supplements were funded by CRCHD for the amount of $250K.

7. Evaluation Criteria for RFA

A. Evaluation of the ANC Program by the NCI OTIR

To evaluate the ANC program on an ongoing basis, a matrix of *quantitative* performance measures was established based on the criteria outlined in the original RFAs. These measures include the following data:

1. The number of peer-reviewed publications along with journal impact factors (total of 606 publications with average impact factor of 7, including 54 high impact factor (>15) publications, and 43 multi-PI, joint publications),
2. The number of disclosed, filed, and awarded patent innovations (total of 203),
3. The number of clinical trials (5 were initiated),
4. List of established IRB and IACUC protocols for work with human patients and human clinical samples and animal testing (17 and 42, respectively),
5. List of IND, NDE, and IDE filings (1 IND awarded, 1 IDE awarded, additional 4 pre-IND discussions were held with FDA),
6. Evidence of commercial efforts leading to the translation of developed technologies (total of 50 companies are associated with the program; 24 were formed as spin-offs in last 3 years),
7. Several successful NIH grant submissions obtained by the investigators and leveraging results from the ANC program.

There is also *qualitative* value of the program in establishing true multi-disciplinary teams consisting of researchers from diversified, yet synergistic disciplines. These teams developed the ability to speak a common research language and work together towards a common goal resulting in several joint publications (Appendix). There is strong evidence of collaborative efforts of researchers who never worked together before, yet contributed to a successful outcome due to the complimentary knowledge.

The initial goals of Cancer Nanotechnology Plan have been met or exceeded. New version of Cancer Nanotechnology Plan, suitable for second Phase of the initiative will be prepared prior to issuing new RFAs. The findings of Strategic Nanotechnology Workshops (Spring 2008) will be used as guidance to the preparation of the new plan and RFAs.

The ANC program should be credited for increasing number of grant applications in cancer nanotechnology (see Section 3) with several non-traditional NIH applicants submitting proposals and getting them awarded. Despite all these successes, there is a strong need for the continuation of RFAs dedicated to U54 and U01 mechanisms for reasons stated in sections 4 and 5.

B. Independent Evaluation of the ANC Program

An independent panel (2 NIH staff members and 1 NCI staff member) was formed to evaluate the Alliance program and its progress and to provide comments and/or recommendations for the proposed renewal. The panel was provided with Scientific Status Program Report (issued in Spring 2008), reports from NCI Strategic Cancer Nanotechnology Workshops, and survey of program stakeholders conducted by Science and Technology Policy Institute (STPI). STPI interviews concerned rationale and program design, effectiveness of NCI program management, strategies towards promoting multidisciplinary collaborations, techniques used for clinical translation, and other topics. The interviews involved several groups: investigators, trainees, nanotechnology and oncology experts not participating in the program, NCL staff, program staff from NCI, NIH, and staff of other federal agencies.

The panel's assessment of the program and its recommendations for the continuation are given in the Appendix and will be used in the development of new RFAs. Briefly, the panel noted:

- A successful beginning of actively managed program resulting in the development of multi-disciplinary teams, numerous scientific achievements, and early stage of clinical technology demonstrations;
- Need for additional strategies fostering further team development and inter-center collaboration development;
- Need for additional mechanisms facilitating close interaction of CCNEs and CNPPs;
- Need for the continuation of efforts supporting clinical translation including active role of NCL, closer communication with FDA, and the need for interactions of program investigators with existing NCI infrastructure;
- Need for the continuation of the ANC program beyond the five-year mark to build upon the developed infrastructure.

Award Description

The Alliance Program Characteristics

1.1 Introduction

The NCI Alliance for Nanotechnology in Cancer comprises four programs: Centers of Cancer Nanotechnology Excellence (CCNEs), Cancer Nanotechnology Platform Partnerships (CNPPs), Multidisciplinary Research Training and Team Development awards, and Nanotechnology Characterization Laboratory (NCL). There are over 80 projects in the program and they include basic research, applied translational projects, and cores. Close to 400 researchers are funded through the program; they represent seasoned and senior investigators who are leading large centers and multiproject efforts as well as junior faculty involved in the individual projects. At the heart of the program are CCNEs which are awarded as cooperative agreements (U54s). The Program Office maintains close interaction with the investigators and is involved in close monitoring of the scientific and technology progress. The NCI program management occurs in conjunction with the operation of the Coordinating and Governance Committee (CGC), an oversight body that gathers individuals from the centers and also has representation from NCI and the advocacy community.

1.2 Program Infrastructure

1.2.1 Centers of Cancer Nanotechnology Excellence

The primary goal of the Centers of Cancer Nanotechnology Excellence (CCNEs) is to integrate nanotechnology development into basic and applied cancer research. Each Center is affiliated with an NCI Comprehensive Cancer Center and engages engineering and physical science departments of the university. By leveraging existing NCI resources, these Centers are bridging gaps in the development pipeline from materials discovery to preclinical testing. The CCNE awardees (in alphabetical order) are:

- **Carolina Center of Cancer Nanotechnology Excellence, University of North Carolina, Chapel Hill, North Carolina.** This Center is focused on the fabrication of "smart," or targeted, nanoparticles and other nanodevices for cancer therapy and imaging. Principal Investigators: Rudolph Juliano, Ph.D., and Joseph DeSimone, Ph.D. (University of North Carolina).

- **Center for Cancer Nanotechnology Excellence Focused on Therapy Response, Stanford University, Palo Alto, California.** This Center uses nanotechnology-enabled diagnostic tools to advance cancer detection and therapy techniques. Principal Investigator: Sanjiv Sam Gambhir, M.D., Ph.D. (Stanford University). [Awarded February 2006]

- **Center of Nanotechnology for Treatment, Understanding, and Monitoring of Cancer, University of California, San Diego, California.** This Center focuses on smart, multifunctional, all-in-one platform device solutions capable of targeting tumors and delivering payloads of therapeutics. Principal Investigator: Sadik Esener, Ph.D. (University of California, San Diego).

- **Emory-Georgia Tech Nanotechnology Center for Personalized and Predictive Oncology, Atlanta, Georgia.** This Center aims to innovate and accelerate the development of nanoparticles for cancer molecular imaging, molecular profiling, and personalized therapy. Principal Investigator: Shuming Nie, Ph.D. (Emory University and Georgia Institute of Technology).

- **MIT-Harvard Center of Cancer Nanotechnology Excellence, Cambridge, Massachusetts.** This Center is focused on diversified nanoplatforms for targeted therapy, diagnostics, noninvasive imaging, and molecular sensing. Principal Investigators: Robert Langer, Ph.D. (Massachusetts Institute of Technology), and Ralph Weissleder, M.D., Ph.D. (Harvard University, Massachusetts General Hospital).

- **Nanomaterials for Cancer Diagnostics and Therapeutics, Northwestern University, Evanston, Illinois.** This Center is designing and testing nanomaterials and nanodevices for highly sensitive in vitro detection platforms. Principal Investigator: Chad Mirkin, Ph.D. (Northwestern University).

- **Nanosystems Biology Cancer Center, California Institute of Technology, Pasadena, California.** This Center focuses on the development and validation of tools for early detection and stratification of cancer through rapid and quantitative measurement of panels of serum and tissue-based biomarkers. Principal Investigator: James Heath, Ph.D. (California Institute of Technology).

- **The Siteman Center of Cancer Nanotechnology Excellence at Washington University in St. Louis, St. Louis, Missouri.** This Center has a comprehensive set of projects for the development of nanoparticles for in vivo imaging and drug delivery, with special emphasis on translational medicine. Principal Investigator: Samuel Wickline, M.D. (Washington University in St. Louis).

1.2.2 Cancer Nanotechnology Platform Partnerships

Cancer Nanotechnology Platform Partnerships (CNPPs) were awarded to 12 individual investigators and reflect a cross-section of technologies, disciplines, cancer types, geographies, and risk/reward profiles, and will link universities to NCI-designated Cancer Centers. The awards, in alphabetical order by principal investigator, include:

- **Nanotherapeutic Strategy for Multidrug Resistant Tumors, Northeastern University, Boston, Massachusetts.** Principal Investigator: Mansoor Amiji, Ph.D.

- **DNA-linked Dendrimer Nanoparticle Systems for Cancer Diagnosis and Treatment, University of Michigan, Ann Arbor, Michigan.** Principal Investigator: James Baker, Jr., M.D.

- **Metallofullerene Nanoplatform for Imaging and Treating Infiltrative Tumor, Virginia Commonwealth University, Richmond, Virginia.** Principal Investigator: Panos Fatouros, Ph.D.

- **Detecting Cancer Early With Targeted Nano-probes for Vascular Signatures, University of California, San Francisco, California.** Principal Investigator: Douglas Hanahan, Ph.D.

- **Photodestruction of Ovarian Cancer: ErbB3 Targeted Aptamer-Nanoparticle Conjugate, Massachusetts General Hospital, Boston, Massachusetts.** Principal Investigator: Tayyaba Hasan, Ph.D.

- **Hybrid Nanoparticles in Imaging and Therapy of Prostate Cancer, University of Missouri, Columbia, Missouri.** Principal Investigator: Kattesh Katti, Ph.D.

- **Near-Infrared Fluorescence Nanoparticles for Targeted Optical Imaging, The University of Texas M.D. Anderson Cancer Center, Houston, Texas.** Principal Investigator: Chun Li, Ph.D.

- **Integrated System for Cancer Biomarker Detection, Massachusetts Institute of Technology, Cambridge, Massachusetts.** Principal Investigator: Scott Manalis, Ph.D.

- **Novel Cancer Nanotechnology Platforms for Photodynamic Therapy and Imaging, Roswell Park Cancer Institute, Buffalo, New York.** Principal Investigator: Allan Oseroff, M.D., Ph.D.

- **Multifunctional Nanoparticles in Diagnosis and Therapy of Pancreatic Cancer, State University of New York, Buffalo, New York.** Principal Investigator: Paras Prasad, Ph.D.

- **Nanotechnology Platform for Targeting Solid Tumors, The Sidney Kimmel Cancer Center, San Diego, California.** Principal Investigator: Jan Schnitzer, M.D.

- **Nanotechnology Platform for Pediatric Brain Cancer Imaging and Therapy, University of Washington, Seattle, Washington.** Principal Investigator: Miqin Zhang, Ph.D.

1.2.3 Multidisciplinary Research Training and Team Development

Multidisciplinary Research Training and Team Development fellowship awards were granted to postdoctoral trainees to allow for multidisciplinary training. The awards, in alphabetical order by trainee, are:

- **Nanoparticle-Bioconjugates as Cancer-Treating Agents, Texas A&M University, College Station, Texas.** Trainee: Sofi Bin-Salamon, Ph.D.

- **Nanoscale Mechanisms of Hsp90 and Its Co-chaperones, Yale University, New Haven, Connecticut.** Trainee: Ivo P. Doudevski, Ph.D.

- **Targeted Delivery Via Protein-Carbohydrate Interactions, Liquidia, Inc., Research Triangle Park, North Carolina.** Trainee: Ashley L. Galloway, Ph.D.

- **Liposomal Delivery of High LET Emitters to Cell Nuclei, Johns Hopkins University, Baltimore, Maryland.** Trainee: Yah-El Har-El, Ph.D.

- **Geldanamycin-Mediated Uptake of Nanoparticle Probes, Purdue University, West Lafayette, Indiana.** Trainee: Giselle M. Knudsen, Ph.D.

- **Nanolabels of Active Proteases for Cancer Detection, University of California, San Francisco, California.** Trainee: Mark D. Lim, Ph.D.

- **Single Walled Carbon Nanotube Based Tumor Vaccines, Memorial Sloan-Kettering Institute for Cancer Research, New York, New York.** Trainee: Rena J. May, Ph.D.

- **Short-Interfering RNA-Gold Nanoparticle Bioconjugates: A New Cancer Therapy, Northwestern University, Evanston, Illinois.** Trainee: Adam B. Braunschweig, Ph.D.

- **Design of Affinity Capture Agents for Akt1 Using in situ Click Chemistry, California Institute of Technology, Pasadena, CA.** Trainee: Steven W. Millward, Ph.D.

- **Targeted Photoactivated Nanopartcicles for the Treatment of Ovarian Cancer, Massachusetts General Hospital, Boston, MA.** Trainee: Daniel Neuman, Ph.D.

- **Nanoprobes and Integrated Nanodevices for Cancer Detection and Treatment, University of Colorado Health Services, Superior, CO.** Trainee: Wounjhang Park, Ph.D.

The NCI is also collaborating with the National Science Foundation (NSF) to fund four **integrative training and team development awards** for U.S. science and engineering doctoral students to focus on interdisciplinary nanoscience and technology training programs. The funded programs are:

- **Integrative Nanoscience and Microsystems, University of New Mexico,** Albuquerque, New Mexico, a collaboration between the University of New Mexico's Center for High Technology

Materials within the School of Engineering, College of Arts and Sciences, and Cancer Research and Treatment Center. Principal Investigator: Diana Huffaker, Ph.D.

- **NanoPharmaceutical Engineering and Science, Rutgers University,** New Brunswick, New Jersey, a collaboration between Rutgers, New Jersey Institute of Technology, and University of Puerto Rico. Principal Investigator: Fernando Muzzio, Ph.D.

- **Nanomedical Science and Technology, Northeastern University,** Boston, Massachusetts, a collaboration between the Dana-Farber Cancer Institute and Massachusetts General Hospital. Principal Investigator: Srinivas Sridhar, Ph.D.

- **Building Leadership for the Nanotechnology Workforce of Tomorrow,** University of Washington, Seattle, Washington. This joint institute for nanotechnology involves University of Washington, Pacific Northwest National Laboratory, and Fred Hutchinson Cancer Research Center. Principal Investigator: Marjorie Olmstead, Ph.D.

1.2.4 Nanotechnology Characterization Laboratory

The Nanotechnology Characterization Laboratory (NCL), the only intramural component of the Alliance, operates at the NCI's Frederick research facility and is performing and standardizing the preclinical characterization of nanomaterials developed by researchers from academia, government, and industry. The NCL is serving as a national resource and knowledge base for cancer researchers and will facilitate the accelerated regulatory review and translation of nanomaterials and devices into the clinical realm. The NCL works in concert with the National Institute of Standards and Technology (NIST) and the U.S. Food and Drug Administration (FDA).

Award Map

NCI Alliance for Nanotechnology in Cancer – Program Structure

NCI Alliance for Nanotechnology in Cancer

Performance Matrix
(Milestones and Achievements)

Progress Towards Milestones of Cancer Nanotechnology Plan

Cancer Nanotechnology Plan, published in 2004 set aggressive translational goals for the Alliance initiative. This plan represented an integrated program of activities to use nanotechnology as an enabler of rapid clinical and research advances and as a means of lowering the barriers to technology development and commercialization by the private sector.

As indicated in RFA, the Alliance program DID NOT intend to fund materials scale-up needed for the IND or IDE filing or subsequent clinical trials. The projects funded under the program represented a mix of developmental scientific projects and translational projects aiming specific, future clinical application. However, several investigators funded through the program have strong entrepreneurial background, managed to raise additional funds, and established many spin-off companies in last 3 years, while maintaining ties with other small and large for-profit entities. The interaction between the investigators and their universities and these companies provided for a strong opportunity towards technology translation and thus allowed for addressing several highly translational milestones of the Cancer Nanotechnology Plan.

The following pages detail programmatic milestones outlined in the Cancer Nanotechnology Plan and corresponding scientific and technology achievements met in last 3 years. The color coding is as follows: Green –milestone met, Yellow – approaching the milestone, Red – milestone not met.

New version of Cancer Nanotechnology Plan, suitable for second Phase of the initiative will be prepared prior to issuing new RFAs. The findings of Strategic Nanotechnology Workshops (held in spring 2008) will be used as guidance to the preparation of the new plan.

Topic Area	Near Term Goal	Project PI	CCNE/CNPP	Summary of Accomplishments
Molecular Imaging and Early Detection	Begin clinical trials of nanotechnology-assisted automated assay for rapid detection of genetic abnormalities (cancer biomarkers)	Paul Mischel	Caltech/UCLA CCNE	Preliminary glioblastoma analysis, conducted as an add-on to an existing clinical trial, demonstrated the ability of microfluidics integrated nanoelectronic sensors to analyze tissues in multiplex approaches, not possible in the past. Working with Comprehensive Cancer Center Director Judy Gasson, the investigators will be including microfluidics integrated nanoelectronic sensors as tissue profiling technologies into two additional clinical trials.
		Chad Mirkin	Northwestern CCNE	NanoSphere, Inc., founded by the PI, recently received IDE approval for nano-enabled biobarcode diagnostic assay. Preliminary clinical demonstration is being conducted using banked samples of men who had undergone radical prostatectomy as primary therapy and who had serial serum samples collected following surgery. Half of the men in the sample set had developed elevations in their PSA levels after surgery, and were labeled as relapsing. The other half of the men had PSA levels that were undetectable when measured with conventional PSA immunoassays. The evaluation of these serum samples using the bio-barcode approach and the correlation of the data with traditional ELISA approach will produce a new insight into monitoring of low PSA levels.
	Refine in vitro nanotechnology systems (cantilevers, nanowires, nanochannels) for rapid, sensitive analysis of cancer biomarkers	Shan Wang	Stanford CCNE	Developing a magneto-nano sensor protein chip and a magnetic sifter based on magnetic nanoparticles that allow rapid conversion of discrete biomolecule binding events into electrical signals. Biological sensing is accomplished by affinity labeling of both the sensor surface and magnetic nanoparticles. The magneto-nano sensor then detects the attachment of the biomolecules through the magnetic field induced by the magnetic nanoparticles. The magnetic sifter will rapidly segregate biomolecules on the basis of the tunable magnetic properties of the magnetic nanoparticles that bind them. PI co-founded a company, MagArray, Inc., which is providing scale-up capability of sensors.
		Scott Manalis	MIT CNPP	Nanofabricating an integrated biomarker detection system with preconcentrator based on SMR (suspended microchannel resonator) nanosensor platform. Demonstrated the SMR's capability of measuring analyte concentration with a dynamic range in excess of 10^4. New candidate biomarkers will be tested along with original proposed PSA marker.

Topic Area	Near Term Goal	Project PI	CCNE/CNPP	Summary of Accomplishments
In Vivo Imaging	File IND application to begin clinical trials of nanoscale MRI contrast agent capable of identifying fewer than 100,000 actively aggressive cancer cells	Miqin Zhang	U. Wash. CNPP	Demonstrated new polyol-mediated synthesis process to produce highly dispersed, stable, and ultra-small iron oxide nanoparticles with amine functional groups allowing for conjugation of functional ligands, such as targeting, therapeutic, or imaging agents. In vivo application of this nanoparticle with a model targeting ligand, chlorotoxin (CTX), revealed ability to cross blood-brain barrier and was confirmed in brain tumors of a genetically engineered mouse model using MRI and optical imaging. Currently in the process of scale-up for toxicology studies after pre-IND meeting with FDA.
	Conduct clinical trials for three targeted nanoscale imaging agents using a variety of imaging modalities, including MRI, ultrasound, and near-infrared optical imaging	Ralph Weissleder	MIT/Harvard CCNE	Based on success of earlier MION and Combidex nano-imaging agents that are currently in clinical trials, the PI has developed different libraries of magnetic nanoparticles (MNPs) by systematically exploring (a) polymeric coatings (which determine pharmacokinetics), (b) central metal cores (which determine detectability by MRI), and (c) surface modifications with small molecules and peptides (to facilitate targeting). Altogether PI has screened well over 1,000 distinct nanomaterials. From these optimization procedures arose four specific preparations useful for targeting that have been scaled up for in vivo testing. The synthesis of these MNPs is now highly reproducible. All particle types feature more iron per particle, higher R2s per iron, and higher R2s per MNP than earlier nanoparticle systems. The new MNPs have 5 to 7 times higher R2s on a per mole of iron basis and 30 to 60 times higher R2s on a per mole of MNP basis as compared to previous formulations.
		Gregory Lanza	Washington University CCNE	Integrin-targeted perfluorocarbon nanoparticles, combining molecular imaging with local drug delivery, allow for verification and quantification of therapeutic delivery and additionally provide prognostic information about the expected response to the treatment. The clinical trial in Australia will be initiated by Kereos spin-off company, while further pre-IND discussions with FDA are taking place.
		Michael Phelps	Caltech/UCLA CCNE	Clinical trial including 8 volunteers evaluates biodistribution of [^{18}F]D-FAC and [^{18}F]L-FAC PET probes. Recruitment of patients with autoimmune disorders as well as patients with lymphomas, pancreatic and ovarian cancers is underway. The clinical research studies using the FAC family of molecular probes are carried out by Caius Radu, Owen Witte, Michael Phelps, and Johannes Czernin at UCLA.
		Shuming Nie	Emory/GT CCNE	Demonstrated imaging of mice inoculated with C4-2B prostate cancer cells using delivery of targeted quantum dots (QDs) conjugates intravenously. The investigators were able to detect as few as 500,000 cells in mouse tibia. Additional studies are being carried out to evaluate and demonstrate clinical utility in collaboration with Washington University CCNE and UCSF CNPP for future IND-filing.

Topic Area	Near Term Goal	Project PI	CCNE/CNPP	Summary of Accomplishments
		Sanjiv Sam Gambhir	Stanford CCNE	New instruments and strategies for photoacoustic molecular imaging using RGD-targeted carbon nanotubes have been developed. These allow for the first time the use of photoacoustics to monitor the imaging of cancer. Chronic toxicology studies of single wall carbon nanotubes have already been accomplished and published recently in mouse models showing the safety of intravenously administered nanotubes. Discussions have begun with FDA for IND submission to utilize targeted CNTs via colorectal delivery for clinical translation of nanotubes.
Reporters of Efficacy	Begin clinical trials for nanoscale ex vivo device that can rapidly assess apoptosis			None of the projects submitted to initial RFAs (both CCNE and CNPP) addressed this topic.
	Develop capabilities for monitoring disruption of vascular networks associated with primary solid tumors and metastatic lesions	Erkki Ruoslahti	UCSD CCNE	Developed self-accumulating nanoparticles, in collaboration with Michael Sailor (UCSD CCNE) and Sangeeta Bhatia (MIT/Harvard CCNE) by conjugating a novel peptide sequence (CREKA, a penta-peptide selected by phage display that can target the clotted plasma protein) onto the surface of 50-nm superparamagnetic iron oxide nanoparticles. Accumulation of these nanoparticles in tumor stroma induce additional local clotting and thereby attract more CREKA-coated iron oxide nanoparticles, resembling to some extent the role platelets play in wound healing. The investigators envision that such accumulation could be used to 1) physically disrupt vasculature at the primary tumor site to prevent additional metastatic growth as well as 2) visually enhance MR contrast via increased concentration of iron oxide nanoparticles to better diagnose disease.
		Roger Tsien	UCSD CCNE	By incorporating known substrates for tumor proteases, the PI has synthesized circularized DNA-peptide conjugates that can be conjugated onto multivalent nanoparticles small enough to diffuse into solid tumors. In the absence of proteases, aggregation will be prevented as double helix DNA formation is topologically forbidden until at least one circle is cut. After demonstrating lack of aggregation in the absence of proteases, conditional aggregation of nanoparticles is being tested in animals bearing tumor models.. PI will also test supralinear, aggregation-induced signal enhancement for optical, magnetic, and ultrasound imaging and energy absorption.

Topic Area	Near Term Goal	Project PI	CCNE/CNPP	Summary of Accomplishments
	Develop nanoscale devices to identify and quantify biological and chemical changes (other than apoptosis) resulting from therapeutic treatment	Garry Nolan	Stanford CCNE	Developed composite organic-inorganic nanoparticles (COINs) Raman nanoparticles for immuno-detection of extra- and intra-cellular proteins in single cells. To measure Raman spectra in single cells, the PI also designed and constructed a Raman microscopy device (Integrated Raman BioAnalyzer, or IRBA) to detail the spectral signatures of the parameters measured. Showed that the system was capable of cell specific detection of the CD54 antigen on U937 expressing cells compared to nonexpressing H82 small-cell lung cancer cells. Additional demonstrations of the COIN Raman technology revealed ability to detect and distinguish subpopulations in primary human cells, namely, CD8 expressing T cells, among a heterogeneous population of primary human peripheral blood mononuclear cells (PBMC).
		Michael Cima	MIT/Harvard CCNE	Prototype devices have demonstrated in vivo detection of hCG produced by extopic tumors. Devices were filled with either nonfunctionalized magnetic relaxation switch (MRSw) nanoparticles or MRSw nanoparticles functionalized to detect hCG-β. The recognition occurs through setting the threshold of the detection below magnetic signal associated with the aggregate of nanoparticles, but above the signal originating from single particle.
		Gang Bao	Emory/GT CCNE	Developing molecular beacons and other activatable nanoprobes to detect tumor-marker genes in vivo with high specificity and sensitivity, allowing for better understanding of tumor biology and leading to better cancer diagnosis and therapy. Molecular beacons are dual-labeled antisense oligonucleotide nanoprobes that are designed to fluoresce only when hybridized with target mRNA.
	Demonstrate proof of concept for ex-vivo nanoscale devices that can be used with a variety of therapeutics to determine biodistribution in vivo	Michael Phelps	Caltech/UCLA CCNE	Designed, fabricated and tested three generations of microfluidic devices (along with H-R. Tseng) for automated production of [^{18}F]-labeled PET imaging probes. In collaboration with Joseph DeSimone at the UNC CCNE and Liquidia Technologies, Inc., preliminary studies have been conducted with PRINT nanoparticles labeled with the radioisotope ^{64}Cu and sequentially imaged in small animals via microPET to obtain nanoparticle in vivo biodistribution properties for future therapeutic development.
	Begin clinical trials with one optical imaging agent capable of showing surgical margins using nanoscale agents	Andrew Kummel	UCSD CCNE	Develop a nanofabrication-enabled technique to selectively capture cancer cells from breast tissue. In touch preparation, the surface of the excised tumor is pressed against a slide to sample cells from the entire surface of the tumor. To evaluate the system's ability to detect cancer in surgical margin, touch preps were performed on cross-sections of excised breast tumor from 37 patients to ensure a large number of well-characterized samples free from the effects of cauterization. The slides were stained with both Hoechst and cytokeratin and analyzed both manually on a selected portion of the slide and fully with an automated microscope.

Topic Area	Near Term Goal	Project PI	CCNE/CNPP	Summary of Accomplishments
Multifunctional Therapeutics	File IND to begin clinical trials of one targeted sensitizer	Robert Langer	MIT/Harvard CCNE	Performed preclinical studies of aptamer-targeted nanodelivery of chemotherapeutic for prostate cancer applications. The technology has been licensed to BIND Biosciences Inc, a new biotechnology company with a focus on commercializing targeted therapeutic nanoparticles. The lead indication which BIND is actively pursuing is hormone refractory prostate cancer among other non-oncology indication.
		David Cheresh	UCSD CCNE	Developed nanoparticle-based delivery of doxorubicin using RGD to Vß3 integrin targeting. Suppression of angiogenesis and metastasis was observed. The plans are to scale up nanoparticle platform to incorporate novel drugs and file IND in joint collaboration with pharma company.. This agreement would also include formal toxicity studies and GMP manufacturing of current cRGD-targeted nanoplatform against pancreatic metastasis reported recently in PNAS.
		Mark Davis	Caltech/UCLA CCNE	Clinical evaluation of IT-101 – a conjugate of camptothecin and a linear, cyclodextrin-based polymer is performed by Calando Pharmaceuticals, spin-off company formed by Mark Davis from Caltech CCNE. This is an open-label, dose-escalation study of IT-101 administered in patients with solid tumor malignancies.
	File IND to begin clinical trials of one multifunctional therapeutic complete with accompanying therapeutic assessment tool	Samuel Wickline	Washington University CCNE	Developing a targeted PFC nanobeacon in conjunction with a novel entropy receiver that is twice as sensitive for ultrasonic detection of targeted nanoparticles. The overarching goal is to provide for both primary diagnosis and patient management tool.
	Develop nanoscale devices capable of multivariate targeting and intervention	Miqin Zhang	U. Wash. CNPP	Demonstrated that chlorotoxin-targeted, dual-modal (Cy5.5) iron oxide nanoparticles reveal in vitro therapeutic potential against brain cancer metastasis by sequestering and inhibiting surface-bound MMPs. Currently in the process of scale-up for toxicology studies after pre-IND meeting with FDA.
		Kattesh Katti	U. Missouri CNPP	Gum-arabic coated gold nanoparticles targeted via gastrin receptor-mediated mechanism have been synthesized using novel process that allows for yield over 99% and can be used to image as well as bring radioactive drug payload to cancer cells. In collaboration with Leland Chung at the Emory/GT CCNE, the PI found that an accumulation of radioisotope gold in androgen-independent bone metastatic prostate cancer cells causes subsequent cytotoxicity to the cancer cells.
	File IND application to being clinical trials of one nanoscale therapeutic targeting RES			None of the projects submitted to initial RFAs (both CCNE and CNPP) addressed this topic.

Topic Area	Near Term Goal	Project PI	CCNE/CNPP	Summary of Accomplishments
Prevention and Control	Demonstrate proof of concept for nanoscale device capable of monitoring genetic changes associate with early cancer process and hyperplasia with the aim of preventing subsequent development of cancer	Hong Wu	Caltech/UCLA CCNE	By utilizing a single-cell resolved immunohistochemical technology, developed in collaboration with CCNE PIs James Heath and H.R. Tseng, on three well-annotated, genetically-defined mouse models (Pten conditional deletion, Myc transgenic and MAKT transgenic) of human prostate cancer, the PI plans to identify biomarkers that define disease progression, the initiating oncogenic lesion, and response to therapy.
		Leland Chung	Emory/GT CCNE	Completed an evaluation of molecular signal network mediated by p2-Microglobulin (J32-M)-androgen receptor (AR)- phosphorylatcd cyclic AMP responsive to element binding protein (p-CREB) in primary and bone metastatic human prostate cancer tissues using a multiplexed quantum dot immunohistochemical assay method (QD-IHC) in collaboration with Ruth O'Regan and Shuming Nie from the Emory/GT CCNE.
Research Enablers	Develop nanoscale harvesting devices for proteomics analysis and biomarker identification	Michael Cima	MIT/Harvard CCNE	In vivo device-based detection of IL-2 has been demonstrated in mice with devices filled with either nonfunctionalized magnetic relaxation switch (MRSw) nanoparticles or MRSw nanoparticles functionalized for biomarker detection. This device could be implanted during a biopsy procedure and used to locally monitor tumor biomarker, chemotherapeutic agent, and tumor metabolite concentrations. The ability to repeatedly sample the local environment, in addition to sampling easily accessible fluids, could improve both early detection of metastasis and personalized therapy.
	Create prototype for real-time, in situ genome sequencing of malignant and pre-malignant cells	Owen Witte	Caltech/UCLA CCNE	Developed optimized nanotechnology-based **N**ucleic **A**cid **C**ell **S**orting (**NACS**) assay for monitoring immunotherapeutic response in melanoma. Preliminary demonstration was carried out using banked samples from patients with metastatic melanoma being treated with experimental tumor immunotherapy with further development of in situ monitoring of biomarkers in process.
	Develop instrumented cell coculture systems biology research	James Heath	Caltech/UCLA CCNE	A new-generation microfluidic cell array was designed and fabricated to allow parallel cell culture in its 12 individually addressable cell culture chambers. A laptop computer will be utilized to control the embedded microfluidic valves and pumps, enabling automated operations from the initial cell loading and culture media exchange to allow introduction of imaging contrast agents and subsequent imaging quantification.
		Michael Heller	UCSD CCNE	Developed new dielectrophoretic nanodevices that will allow rare cancer cells, high-MW DNA nanoparticulates and other cancer biomarkers, as well as drug delivery nanoparticles to be rapidly isolated and detected directly from whole or minimally diluted blood or plasma. Achieved the separation of 40 kb DNA nanoparticulates and 10 micron silicon particles.

Topic Area	Near Term Goal	Project PI	CCNE/CNPP	Summary of Accomplishments
	Refine cell and cell-component labeling with nanoparticulates such as QDs for application to studies of integrated pathways and processes in cancer	Ruth O'Regan	Emory/GT CCNE	Developing practical, multiplex immunohistochemistry methods using quantum dots (Q-Dot IHC) which could be used to multiplex up to six biomarkers. Current improvements made on the multiplexing protocol will ensure a reproducible and reliable assay for quantitative assessment of tissue biomarkers in clinical studies of pre-operative breast cancer patients that are treated with chemotherapy prior to surgery. To date almost 40 patients have been accrued of which paraffin-embedded specimens are available prior to chemotherapy, midway through chemotherapy and after chemotherapy for correlative studies. The PI plans to examine the expression of breast cancer-related proteins in these specimens using conjugated Q-Dots, and correlate their expression with response to chemotherapy.
		Jianghong Rao	Stanford CCNE	Developing quantum dot sensors for highly sensitive detection of MMP enzymes. The design is based on bioluminescence resonance energy transfer (BRET) between a bioluminescent protein Renilla luciferase and QDs. Investigators have successfully applied intein-mediated protein splicing chemistry to prepare Qdots-RLuc8 conjugates. This new QD sensor can detect MMP-2 and MMP-7 activity in both buffer and in mouse serum with 5 ng/mL sensitivity.
	Develop toxicology database for nanoscale devices and nanoparticulates	David Sept	Washington University CCNE	Create a nanoparticle informatics resource that includes a comprehensive taxonomical database of available nanoparticle technologies and a general toolbox for pharmacokinetics and pharmacodynamics modeling of targeted drug delivery and diagnostics using nanoparticles. This includes the development of a nanoparticle ontology that will characterize and relate the physical, chemical, and pharmacological properties of nanoparticles used in cancer diagnostics and therapeutics, the development of a general pharmacokinetics and pharmacodynamics framework for modeling targeted and nontargeted nanoparticles, and incorporation of both the ontology and pharmacokinetics modeling into a caBIG compatible Web service.
	Create a scientific framework for regulatory approval of nanoscale diagnostics, therapies, and preventative agents	Sangeeta Bhatia	MIT/Harvard CCNE	The Toxicity Core seeks to provide Alliance investigators the ability to rapidly characterize the potential toxicity of novel nanomaterial formulations using a standard panel of in vitro and in vivo assays. Models of basal and tissue-specific toxicity will be made available to test formulations in vitro, and a subset of these will be tested in mice. Promising formulations will be subsequently evaluated by the Nanotechnology Characterization Laboratory (NCL).

Independent Panel Evaluation

Independent Evaluation of the ANC Program

An independent panel (2 NIH staff members and 1 NCI staff member) was formed to evaluate the Alliance program and its progress and to provide comments and/or recommendations for the proposed renewal. The panel was provided with Scientific Status Program Report (issued in spring 2008), reports from NCI Strategic Cancer Nanotechnology Workshops, and survey of program stakeholders conducted by Science and Technology Policy Institute (STPI). STPI interviews concerned rationale and program design, effectiveness of NCI program management, strategies towards promoting multidisciplinary collaborations, techniques used for clinical translation, and other topics. The interviews involved several groups: investigators, trainees, nanotechnology and oncology experts not participating in the program, NCL staff, program staff from NCI, NIH, and staff of other federal agencies.

The panel's assessment of the program and its recommendations for the continuation follows along with the STPI survey.

Panel

Dr. Catherine Lewis
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Division of Cell Biology and Biophysics
National Institute of General Medical Sciences, NIH

Dr. Denis Buxton
Chief
Advanced Technologies and Surgery Branch in the Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute, NIH

Dr. Daniel Gallahan
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Division of Cancer Biology
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September 3, 2008

TO: Piotr Grodzinski, Program Director, NCI Alliance for Nanotechnology in Cancer

FROM: Denis Buxton, NHLBI
Daniel Gallahan, NCI
Catherine Lewis, NIGMS

SUBJECT: NCI Alliance for Nanotechnology in Cancer – NIH Program Evaluation

The NCI Alliance for Nanotechnology in Cancer was established in 2005 through the publication of three RFAs. The first and largest of these was an RFA (RFA-CA-05-024) to set up Centers of Cancer Nanotechnology Excellence (CCNEs). The CCNEs were envisioned to be a national resource that would integrate nanotechnology development into basic and applied cancer research to facilitate the rapid application of nanotechnology into the clinic. This initiative was based on the premise that nanotechnology has potential in cancer research and treatment to develop nanomaterials and nanoscale devices for molecular imaging and early detection, *in vivo* imaging, reporters of efficacy, multifunctional therapeutics, prevention and control, and research enablers. The purpose of the RFA was to establish interdisciplinary research teams that would identify approaches, validate and translate nanotechnology for a variety of cancer applications up to and including pre-clinical testing.

The second RFA (RFA-CA-05-025), titled "Multidisciplinary Career Development in Cancer Nanotechnology", was designed to provide individual postdoctoral fellowships (F32s) and senior fellowships (F33s) for training of a cadre of researchers capable of applying nanotechnology to cancer research and clinical oncology.

The third RFA (RFA-CA-05-026), titled "Cancer Nanotechnology Platform Partnerships, (CNPPs)", was designed to support RPGs to develop nanotechnology platforms for basic, applied, and translational multidisciplinary research using nanotechnology in cancer research.

To achieve these goals the program was designed to overcome a series of obstacles;

- The need for cross-disciplinary collaborations to enable the integration of the fundamental biological knowledge base with physical sciences and engineering approaches to address cancer processes
- The widening "gap" between discovery and early development of diagnostics and therapeutics;
- The requirement for cross-cutting technology platforms;
- The critical lack of available standards or publicly available datasets of characterized (e.g., physically, chemically, and physiochemically) nanoscale devices and their interactions with living systems; and
- The application and adaptation of extant technology to mission-oriented tasks

Responses to Questions Addressed to the NIH Evaluation Panel

1. To what extent has the Alliance been meeting the goals established by the initial RFA?

a. Are the Principal Investigators moving towards the anticipated goals?

The Alliance is at a relatively early stage, less than three years into the initial funding period. It is thus important to view progress realistically. Multidisciplinary collaborations take time to gel, since in many cases there is a lack of a common language between the different disciplines. The establishment of these multidisciplinary teams is thus a significant move forward.

Despite the early stage of this analysis, significant progress has been made by the Alliance investigators, as outlined in the Spring 2008 Program Update. The first three years of the Alliance have resulted in an impressive output of publications (606) and patent applications/disclosures (203). Among the most significant publications are 54 that are listed as high-impact Alliance papers (> 15), in journals such as *Nature*, *Nature Materials*, *Nature Nanotechnology*, *Nature Biotechnology*, *Science*, *Cell*, and *Cancer Cell*. Collaborations between different centers in the Alliance show evidence that a number of groups are succeeding in reaching across institutional barriers to promote team science that includes investigators outside their own centers. Thirteen inter-Alliance collaboration projects are highlighted in the Spring 2008 Program Update, with their resulting publications (pages 26-42). Perhaps the most impressive progress of the Alliance is demonstrated by the research advances that have addressed the scientific barriers outlined at the outset of the program. These are summarized in the Spring 2008 Update (pages 50-90) in the areas of: (1) molecular imaging and early detection; (2) in vivo imaging; (3) multifunctional therapeutics; (4) reporters of efficacy; (5) prevention and control; (6) research enablers. These advances represent the leading edge of the Alliance in terms of their promise to deliver useful cancer diagnostics and therapeutics.

Current challenges of the Alliance are to establish a greater degree of collaboration between CCNEs, to promote more active participation of clinicians, and to develop diagnostic and therapeutic strategies that are less redundant across the different research groups. Although there are a number of activities in place to facilitate collaborations and to disseminate information across the Alliance, it is evident from the awardees interviews that barriers exist as disincentives for collaboration. These include competition for resources, intellectual property concerns, and technologies that are not yet sufficiently mature to benefit from collaboration. Participation of clinicians is also at an early stage, based on reports from the awardees indicating that oncologists and clinicians have been somewhat skeptical and difficult to engage in nanobiology research. Translation into the clinic is thus not yet a clear outcome of the Alliance so far. Finally, development of nanotechnologies that are based on approaches and strategies other than those of "smart" nanoparticles is a challenge for the Alliance since most of the current efforts appear to be focused on this class of research in nanotechnology

Participation of the Alliance with industrial partners, as a stepping stone to move nanotechnology into the clinic, is off to a good start. At the current time, Alliance investigators have played key roles in founding at least two dozen companies (see Spring 2008 Update, pages 99-118). Although it is still early days for many of these efforts, a number of the companies have made substantial progress towards planning Phase I clinical trials, such as Avidimer Therapeutics, Insert Therapeutics, and Calando Pharmaceuticals. It is not entirely clear to what extent the industrial partnerships have been based on technologies developed primarily through the Alliance, but the fact that the Alliance investigators are involved in commercializing and leveraging their technologies is a promising achievement of the Alliance initiative as a whole.

b. Are the goals achievable within the next reissuance period?

It is likely that progress would be significantly faster during a second funding period. While in an open competition it is probable that not all current centers would be re-funded, those that are funded again would have a big head-start in not having to put together infrastructure and collaborations. A rapid pace of technology development is expected in the next renewal period, with a resultant increase in the number of technologies reaching pre-clinical readiness.

One question that arises from the interviewee comments is the degree that the technologies developed through the Alliance will be translated into clinical applications through the current structure. While collaborations with industry are an integral part of the first cycle, there is skepticism from some PIs whether this will be enough to move the technology forward. Assistance for translational components (e.g. manufacturing and scale-up) could facilitate this process.

One area that will need more attention is the FDA approval for research in large animals; this will need to be addressed directly in the next issuance. The requirement for grams of material for analysis by the NCL is a concern for a number of the centers. The overall goal of moving nanoparticles from the basic research environment to the NCL for analysis and then on to the FDA for approval will require specific language as well as the funds to support it.

Incentives to support further collaborations among the CCNEs and CNPPs would strengthen cross-fertilization and maximize the strengths of different groups. A re-allocation of funds to specifically promote collaborations, as suggested by several of the awardees, might foster more extensive interdisciplinary working relationships and reduce competition between groups. Development of new cross-cutting technology platforms, beyond those of smart nanoparticles, may be necessary to maximize progress towards the Alliance goals.

The lack of available standards or publicly available datasets of characterized materials and nanoscale devices and their interactions with living systems remains at an early stage. Reports from the awardees and from the nanotechnology Characterization Laboratory (NCL) indicate that many of the centers are not yet interacting with the NCI for a variety of reasons. Support for this activity as well as incentives may be required to achieve this goal.

c. Are the principal investigators building a multidisciplinary community as anticipated through the formation of the centers and the governance structure?

A central theme that comes out of all the PI interviews is that the Alliance has resulted in bringing together the physical scientists with the biologists and clinicians. This should be recognized as an essential first step towards the Alliance goals. The consensus view is that collaborations within centers and platform sites are moving forward well. Most PIs refer to the establishment of interdisciplinary research groups for each of their projects. In many cases it appears that the physical scientists were initially more enthusiastic, while clinicians have been more reluctant and slower to recognize the potential of nanotechnology for cancer. However, several interviewees indicate that progress is being made in this direction.

The establishment of collaborations between components of the Alliance has been less consistent. While a number of collaborations are highlighted in the brochure and in interviewee responses, there are also interviewee responses indicating that these are more limited relative to establishment of internal collaborations. In some cases this appears to reflect a suspicion of "competitors", while a lack of funds to aid in establishment of collaborations is also cited. Consideration of the need for a pool of money for this purpose, as cited in section 1b above, might be part of the renewal process for the Alliance.

The success of the cross-disciplinary training programs, which are an important component of the Alliance, will most likely have an impact on the community as a whole by the end of 10 years of the program. While it is still too early to reflect on the best methods for training the next generation of experts in nanotechnology for cancer research, there are a number of different strategies underway that will no doubt achieve the goal of producing well trained individuals in this field.

2. What were the anticipated outcomes and are they being achieved?

The key anticipated outcomes were the development of multidisciplinary teams to promote the development of nanotechnology for cancer diagnostics and therapeutics; the application of these teams to the development and translation of these technologies to cancer; and the training of a cadre of investigators capable of applying nanotechnology to the cancer field. It is clear from the Spring 2008 Program Update (pages 50-90) and from the interview responses outlined in the report from the STPI (Science and technology Policy Institute), that significant progress is being made in all areas.

Notable among these is a cyclodextrin-based nanoparticle, IT-101, a conjugate composed of a potent anticancer drug camptothecin and Cyclosert™, a proprietary polymer delivery vehicle. This material, developed by Mark Davis and colleagues at the California Institute of Technology, has the effect of rendering sparingly soluble anticancer drugs water soluble and is cleared from the body by the kidney. Phase I trials indicate that the particles display favorable pharmaco-kinetic properties and promising efficacy against solid tumors in patients. Phase II trials are being planned.

A second notable achievement is that made by Chad Mirkin and his colleagues at Northwestern University in developing a Biobarcode assay that allows for detection of cancer protein markers with six orders of magnitude greater sensitivity than is obtainable using conventional assays. The Biobarcode assay, which can detect as few as 100 molecules of a protein marker in a drop of blood, uses magnetic microparticles and gold nanoparticles conjugated to antibodies against the PSA protein, a marker for prostate cancer. Each gold nanoparticle is attached to hundreds of "barcode" DNA strands that amplify the signal from each PSA molecule. The PSA agglomerates the magnetic and gold particles; a magnetic field is then used to collect the agglomerated particles so that the DNA barcodes can be measured. This method can be used to monitor patients after radical prostatectomy, in which case the PSA level is "zero" based on conventional diagnostic tools. The barcode assay can be used to show an increase in the PSA concentration post-surgery, signaling a recurrence of the disease which would otherwise not be detected. Thus, the barcode assay holds great promise as a highly sensitive diagnostic tool for the early detection of cancer or its recurrence.

3. Was the initiative successful at increasing the level of research in the area of cancer nanotechnology?

There is no doubt that the Alliance has been successful in increasing the level of research in cancer nanotechnology. Many researchers who had no previous experience in applying nanotechnology to cancer have been attracted into multidisciplinary teams. This includes investigators from the physical scientists who had not previously applied their skills to biological problems; investigators who have been involved in applying nanotechnology to biological systems, but have now refocused their efforts towards the cancer field; and biologists and clinicians who had no previous experience of nanotechnology, but have been made aware of the potential of the technology for cancer diagnostics and therapeutics.

Efforts to establish collaborations with clinicians and with industrial partners have no doubt been accelerated by the Alliance initiative and increased funding for cancer nanotechnology. Similarly, efforts to provide a spectrum of training opportunities in cancer nanotechnology will generate an increase in the next generation of scientists who will continue to address the challenges and barriers in cancer research using tools developed through this program.

The focus in the Alliance on the development of nanoparticles for cancer diagnosis and therapy may need to be expanded to bring in different kinds of approaches. Strategies to remodel cellular machinery, redirect signal transduction or gene expression are examples of fertile areas to explore in cancer nanotechnology.

4. Are the anticipated benefits from the development of nanotechnology for cancer diagnosis and therapy applications and pursued under this program, significant?

The potential of nanotechnology for the diagnosis and treatment of cancer is enormous, and the work being pursued through the program is highly significant. The early detection of cancer through multiplexed highly sensitive detection of biomarkers, and through sensitive and specific molecular imaging of tumors, is a key need in oncology, and nanotechnology has the potential to make major contributions to both areas. Similarly, enhanced therapeutics through targeting of drug delivery and tumor ablation will decrease the morbidity and mortality resulting from off-target side-effects of current generation cancer therapeutics.

a. Would these benefits have been accomplished had other investigator-initiated funding mechanisms been utilized?

While there were clearly some pre-existing collaborations ongoing that may have been accomplished without the program, for example using investigator-initiated mechanisms such as the Bioengineering Research Partnerships, this appears to represent a minority of the achievements of the Alliance. In most cases the advances would not have been made without the establishment of multidisciplinary groups through the Alliance, since the essential multidisciplinary teams would not have formed in most cases without the stimulus provided by the Alliance.

In addition, the training components of the Alliance have been successful in attracting students and postdocs as a result of the establishment of this initiative. The Multidisciplinary Research Training and Team Development and NSF training collaborations also would not have occurred without the Alliance. The trainees from these components will play an essential role in the future application of nanotechnology to cancer.

It is clear that the centers have provided the vehicle for a number of activities that would not have otherwise occurred. The critical mass of technology support and team-oriented science has created an excellent training environment and opportunity for collaboration. Nonetheless, it is not entirely clear how the distribution of activities between the centers and platforms has contributed to the progress to date or what the best overall structure should be, based on the performance so far. At some point it may be worthwhile considering what the centers are contributing that the platforms would not, or how the combination of centers and platforms could be made more flexible in the future to be sure the Alliance remains responsive to evolving needs as it moves through the next period of support. The centers may, in fact, be a less effective organization to facilitate multi-disciplinary research once sufficient infrastructure, training, industrial spin-offs, and clinical partnerships are in place.

5. Are the results to date worth the initiative's cost?

The Alliance is an expensive program, and so it is important to consider how efficiently it is meeting its goals. However, it would be short-sighted to try to gauge the cost-benefit ratio without looking at the long range potential of the program. Many of the outcomes from the Alliance will take a number of years to come to fruition. The investigators from both ends of the scientific spectrum who have been attracted into interdisciplinary teams to apply nanotechnology to cancer are likely to become increasingly productive as they become more familiar with the problems to be solved. A wide range of technologies are currently being developed by the Alliance members; many will take several years to reach pre-clinical and clinical application, and while their potential is enormous, their clinical utility commercial success cannot yet be predicted. However, even if only a small percentage of these

technologies are successful, the potential for moving the field of cancer diagnostics and therapeutics forward is very high.

6. As the program utilized a cooperative agreement mechanism, has the NCI staff associated with the initiative been helping to ensure success of the program?

By NIH standards, the Alliance has been unusually interactive between program staff and the extramural investigators. Novel features include the inclusion of milestones and monthly reporting from the sites to NCI. There is a general consensus from Alliance participants that the involvement of NCI staff has been very positive. The site visits from program staff are viewed as particularly useful. The engagement of program staff has been helpful in facilitating collaborations between investigators. It appears that program staff have been successful in walking a delicate line between micro-management and engagement, and have been sensitive to the needs of individual centers in terms of management. Program staff may need to exercise caution in finding the right balance between directed research (DARPA-like) and investigator-initiated research to ensure that creativity and exploration of new ideas are maximized. There is some concern that the similarity across research groups in technologies and goals may be driven by the directed research approach. Finally, there is a sense that the monthly reporting requirements for the CCNEs may be overly burdensome. Response to the milestones has been mixed; some awardees find them helpful in focusing while others find them unnecessarily intrusive and not helpful.

The Alliance annual meetings are viewed as extremely effective and well organized by many of the Alliance investigators. These meetings provide good opportunities for the initiation of collaborations across groups and for students and postdocs to interact with individuals from other programs. The technical working groups are viewed as "works in progress" so far, primarily because participation in these groups is limited to a few individuals from each research group. There is hope that the effectiveness of these groups will increase in facilitating interactions as they gather momentum

7. Can the infrastructure generated by the Alliance program become a long-lasting vehicle for developing the discovery technologies with prospective cancer clinical utility?

The current infrastructure consists of four components; the CCNEs, the Platform Partnerships, the Multidisciplinary Research Training and Team Development, and the NCL. While elements of this infrastructure may prove useful for long-term support of discovery technologies for cancer, the optimal configuration of support at this time is currently difficult to predict. As a new generation of researchers with interdisciplinary skills is trained through the Alliance, it may be that the need for centers is diminished since self-assembly of investigator-initiated groups to tackle specific problems may become more facile. Expanded use of the Platform Partnership mechanism could represent a more flexible way to support technology development at that point. As technologies become more mature, an increased focus on translational assistance may become essential. The NCL could continue to play a significant role in that process, and will no doubt also continue to develop standards, a critical need for the field.

The existing structure appears to be an effective use of the funds and may be the most useful organization in the current time frame. Nonetheless, the barrier of moving the technology through the NCL into the clinic is a formidable one. A major gap in the current scheme is to get to the next level of facilitating translation to the clinic. A push towards new platforms to support this process should be considered. An organizational structure that promotes internal adjustments and flexibility would be ideal. Management of this initiative should consider how to realign the organizational structure on an ongoing basis and as new needs emerge.

8. Considering the outcomes of the Alliance program in its first 3 years of existence, would you continue the program beyond the 5 year mark?

The Alliance program should be continued beyond the five-year mark. The expectation is that progress in a second period of funding would be accelerated due to pre-existing infrastructure and collaborations. The failure to fund a second cycle of the Alliance would short-change the investment that has been made during the first cycle. This project should be viewed in terms of its ten-year goals. Collaborations among the different groups need time to develop; the process and timeline from the basic research lab to the NCL to the FDA to the clinic will take time to work out; true investment by clinicians will require establishing credibility for the utility of nanotechnology directed towards cancer diagnosis and therapeutics. Although expectations about the return on the investment need to be realistic, one of the Alliance awardees has stated that if just one clinical trial results from each of the eight CCNEs, the Alliance program will have been a huge success by the standards of industrial R & D investment.

STPI Report

IDA
STPI

July 2008

MEMORANDUM

TO: Expert Review Panel, NCI Alliance for Nanotechnology in Cancer
FROM: Brian Zuckerman, PhD, Science and Technology Policy Institute (STPI)
SUBJECT: Summary of Findings from Interviews with Alliance Stakeholders

The purpose of this memo is to summarize findings from stakeholder interviews conducted in support of an expert panel review of the NCI Alliance for Nanotechnology in Cancer ("Alliance") programs. The interviews were intended to supplement summary information about program outputs already available through investigator progress reports and other documentation. Their primary purpose was to characterize perceptions and opinions from both program participants and external stakeholders regarding program goals, implementation, management, and effectiveness.

Following a brief explanation of interview methodology, this memo summarizes interview findings by theme. Themes include:

- Rationale and Current Program Design, pg. 3
- Approach to Program Management, pg. 3
- Use of Milestones as a Management Tool, pg. 4
- Annual Alliance Meetings, pg. 4
- Communications and Integration Working Group, pg. 4
- Technical Working Groups, pg. 5
- Dissemination Strategies, pg. 5
- Scientific Progress, pg. 6
- Training, pg. 7
- Strategies to Promote Multidisciplinary Collaboration within Alliance Centers and Projects, pg. 8
- Collaborations between Alliance Members, pg. 8
- Interactions with the NCL, pg. 9
- Interactions with the Division of Cancer Treatment and Diagnosis, pg. 10
- Collaborations with Industry, pg. 10
- Perspectives from DARPA, pg. 11
- Perspectives from FDA, pg. 11
- Suggestions for the Future, pg. 11

Summaries of selected individual interviews are provided as Appendix A; these summaries have been reviewed and approved for inclusion by the interview participants.

Data Collection Methods

Stakeholder interviews were conducted via telephone by at least two STPI staff members following discussion guides based on an evaluation framework for the Alliance Programs (discussion guides are included as Appendix B). Potential interviewees were identified from target groups in consultation

with Alliance program staff. Candidates were then contacted via email and invited to participate in voluntary telephone interviews. A total 38 individuals[1] were invited to participate, and 29 chose to do so, for an overall response rate of 76%. As shown in Table 1, however, response rate differed substantially by group; direct award recipients (PIs, fellows, and administrators) and NCI representatives were more likely to participate while external stakeholders and clinicians were less likely to do so.

Table 1. Interview Participants and Response Rates

Participant Type	Number Invited	Number Participated	Participation Rate
Award Recipients [Awardees]			
Principal Investigators, CCNE	8	8	100%
Administrators, CCNE	3	3	100%
Training Coordinators, CCNE	1	1	100%
Principal Investigators, Platform Partnerships	5	5	100%
Alliance Ruth L. Kirschstein NRSA Fellows	2	2	100%
Clinicians or other collaborators on CCNE or Platform projects	5	2	40%
NCI Employees [NCI]			
Alliance program staff[2]	1	1	100%
Nanotechnology Characterization Laboratory	1	1	100%
Center for Cancer Research	2	1	50%
Developmental Therapeutics Program	1	1	100%
Cancer Training Branch or Office of Centers Training and Resources	2	1	50%
Cancer Imaging Program	1	0	0%
External Stakeholders [External]			
National Nanotechnology Infrastructure Network awardees	1	0	0%
Joint NCI-NSF Integrative Graduate Education and Research Traineeship (IGERT) coordinators	1	1	100%
Representatives from other science funding or regulatory agencies (DOE, DARPA, NSF, FDA)	4	2	50%

Interview findings are summarized by theme below. The tags [Awardees], [NCI], and [External] at the end of each summary point indicate which group or groups of interviewees provided the information in question. In a few cases, additional factual information was added to the summary at the request of OTIR staff members; these additions are enclosed in double brackets and marked as additions.

[1] In the case of the Alliance program staff, all members were invited to participate, but they have been counted as a single respondent because the interview was conducted as a group.
[2] See Note 1.

Summary of Findings

Rationale and Current Program Design

- **Rationale for Alliance.** The rationale for the Alliance programs was to address what was perceived as a critical need to facilitate collaboration among cancer biologists, nanotechnologists, and clinicians on nano-enabled technologies to improve diagnosis, treatment and prevention of cancer. [NCI]
- **Context for Alliance.** At the time the Alliance programs were launched, there were no other large-scale nanotechnology programs at NCI or anywhere else at NIH. The Roadmap Nanomedicine Initiative and the PEN Program at NHLBI started in the same year. [NCI]
- **Alliance Structure.** After consulting with the extramural community, OTIR decided on a multi-pronged strategy for extramural funding:
  - The CCNE centers were created to address the need for large-scale multidisciplinary teams. The cooperative agreement mechanism was used to ensure that it remained milestone-driven and so that NCI could be actively involved in managing the program. [NCI]
  - The Platform R01s were intended to provide a mechanism of support for development of specific technologies outside of the centers. [NCI]
  - For training, an individual fellowship program was chosen in preference to an institutional training program because NCI believed it would allow them more flexibility in selecting the best talent and controlling the number of fellows supported annually based on available funding. [NCI]

Approach to Program Management

- **Division of Labor.** Alliance program staff members hold a standing weekly meeting and also interact informally about the programs on a daily basis. Responsibility for individual awards is split topically among Alliance staff members, so there is not a separate management structure for the CCNEs relative to the Platforms or other Alliance components. [NCI]
- **Management Approach.** Program staff described their general approach to program management as steering a middle course between NIH's typical investigator-driven grants management style and DARPA's goal-driven, top-down management approach. Program staff stated that they are sensitive to the need to avoid micro-managing and attempt to match their level of involvement with the needs of each awardee. CCNE and Platform PIs agreed that the Alliance program staff members are unusually well-informed, helpful, and accessible but do not attempt to micro-manage. [NCI; Awardees]
- **Site Visits.** Several PIs remarked that the frequent site visits have been particularly useful, both in terms of receiving constructive feedback and building relationships. Intramural staff members frequently participate in Alliance workshops and site visits. [Awardees; NCI]
- **Reporting Requirements.** One CCNE PI and all of the administrators interviewed mentioned that they found the program's reporting requirements to be excessive. They suggested that the need for monthly reporting in particular should be re-evaluated now that the Centers are well-established. The Communications and Integration Working Group (see below) has made specific recommendations for revising the reporting requirements. [Awardees]
- **Facilitating Collaborations.** Many of the PIs described situations in which the program staff had facilitated useful contacts with potential collaborators, NCI staff members, individuals in the private sector, and others. [Awardees]
- ***Identifying Funding Opportunities.*** PIs also appreciated the program staff's willingness to work with them individually to identify opportunities to leverage additional resources through other NCI programs and mechanisms such as SBIR, R01/R21, Early Detection Research Network (EDRN), Mouse Models of Human Cancer Consortium (MMHCC), and imaging programs. [Awardees]
- **Coordination with NCI Intramural and Extramural Programs.** Program staff members reported having conducted internal discussions about opportunities for synergy with the

Cancer Therapy Evaluation Program (CTEP), the imaging programs, the intramural Center for Cancer Research Nanobiology program, caBIG, and the Developmental Therapeutics Program (DTP) and its Rapid Access to Intervention Development (RAID) program. [NCI]

Use of Milestones as a Management Tool

- **Rationale for Milestones.** The Alliance programs are somewhat unusual at NIH in that they use milestones as a management tool. Program staff stated that the underlying rationale for the milestones was to keep the PIs focused on specific goals and clearly communicate expectations. Most PIs agreed that these are potential benefits of the milestone approach, although more skeptical PIs questioned whether the milestones were necessary to achieve these goals. [NCI; Awardees]
- **PI comfort level.** The degree of comfort on the part of the PIs with the milestone approach appeared correlated with their backgrounds; those who came from an engineering or industry background and those who had previous experience with funders such as DARPA appeared most enthusiastic, while others described it as a difficult cultural adjustment. [Awardees]
- **Importance of Flexibility.** Several PIs praised the program staff for their willingness to work with the investigators to alter the milestones as needed. Some viewed this as a departure from typical NCI culture. For those who expressed reservations about milestones, flexibility to make such revisions was frequently described as a key issue. Without it, they cautioned, resources could be wasted in pursuit of sub-optimal approaches and better opportunities could be missed. [Awardees]
- **Milestone focus.** Several PIs also suggested that milestones should focus exclusively on achieving concrete steps towards translation or understanding biological drivers for cancer rather than adherence to specific technological approaches. They cautioned that the latter approach is more likely to result in development of technologies that solve no problems and/or closing off the possibility of pursuing more promising solutions as they emerge. [Awardees]

Annual Alliance Meetings

- **Effectiveness.** Several PIs described the Alliance annual meetings as extremely effective. Alliance meetings were frequently described as a good venue for identifying and meeting with potential collaborators. [Awardees]
- **Quality.** One PI commented that he prefers to send students to Alliance meetings rather than the biggest meetings in the field because the quality of science and participants is so high and because they are small enough to permit individual interactions. Another compared these meetings favorably with DARPA-run PI meetings. [Awardees]

Communications and Integration Working Group

- **Purpose.** The Communications and Integration Working Group (CIWG) is intended to facilitate sharing of information, resources, and best practices across the Alliance. A representative other than the PI (typically an administrator) participates on behalf of each CCNE. Group activities are coordinated by Dr. Jerry Lee. [Awardees; NCI]
- **Current Activities.** The group maintains an intranet site on cancer.gov that only Alliance members can access. A calendar and newsletter have recently been launched. [Awardees; NCI] [[Note from Alliance program staff: the CIWG is currently holding monthly meetings.]]
- **Future Plans.** At a recent retreat, the CIWG discussed several new ideas to facilitate communications and integration:
  - Outreach opportunities such as Alliance-wide participation in NSF-sponsored "Nano Days" events;
  - Implementing an exchange program for Alliance postdocs (see discussion under 'Collaborations Between Alliance Members');

- Creating a "best practices" manual that would collate information on successful management practices from across the CCNEs. Participants are enthusiastic that such a manual could help to facilitate sharing of ideas and tools that have been effective at some of the Centers as well as capturing tacit knowledge to help orient future staff members. [Awardees]

Technical Working Groups

- **General Perceptions.** Opinion on the success of the technical working groups appeared mixed. Most PIs described them as "works in progress" that have not yet reached their full potential. Several PIs described the tabulation of existing nanoparticle technologies as a particularly helpful working group activity. [Awardees]
- **Diagnostics Working Group.** The diagnostics working group appears to have been the most active of the technical working groups in terms of coordination. To facilitate comparison of performance among the labs working on sensing technologies, members of the working group agreed that everyone should measure HCG from a central source. PIs and program staff emphasized that the goal was not necessarily to test which technology was furthest along; it was considered more important to help identify common problems that members could address collaboratively. OTIR staff member Dr. Larry Nagahara was described by the PIs as pivotal in spearheading this effort by arranging logistics such as access to reagents and a forum for sharing results. [Awardees]

Note from Alliance program staff: Although they were not discussed specifically in interviews, there are two additional Alliance Working Groups: a ***Nanotheranostics Working Group*** and an ***Informatics Working Group***. The Nanotheranostics Working Group acts as a forum for exchanging ideas, information, and expertise for facilitating the development of multifunctional nanotechnology-based tools supporting both diagnostics and therapy. The group includes two representatives from each of the CCNEs as well as select representatives from the Platform Partnerships. In general, these representatives include those Alliance investigators whose projects are aimed at developing novel nanotherapeutics as well as investigators with expertise in tumor targeting. Principal investigators from relatively advanced (demonstrated proof of concept in at least one animal model) therapeutics projects have met with NCI experts in the Developmental Therapeutics Program (DTP), Center for Cancer Research (CCR), and Cancer Therapy Evaluation Program (CTEP) with the goal of formulating a preclinical development plan for their respective technologies. The Informatics group is run by Dr. Linda Molnar and is being developed jointly with caBIG and caNanolab. Databases are currently being installed at Washington University, Emory, and Stanford with plans to disseminate further.

Dissemination Strategies

- **Alliance-Level Dissemination Activities.** Program level dissemination activities performed by OTIR program staff include:
  - Maintaining an Alliance website that includes lay-language summaries of discoveries;
  - Maintaining a nano.cancer.gov mailbox to answer questions from the public; and
  - Staffing a booth at major oncology conferences. [NCI]
- **CCNE Dissemination Activities.** CCNE PIs described pursuing a range of strategies for disseminating information to targeted groups. These included:
  - Partnerships with K-12 schools, science museums, and other public forums such as the virtual community "Second Life";
  - Providing testimony to Congress and participation in state level planning processes;
  - Development of curricula and seminar series for medical students;
  - Publication of review articles, papers in lay science journals (e.g. Scientific American), and popular press articles suitable for use in educational efforts;
  - Presentations at clinician and technology conferences;
  - Presentations to patient groups and other community gatherings. [Awardees]

- **Use of caBIG.** Most PIs described dissemination efforts through caBIG as limited so far, although one CCNE (Washington University) mentioned aggressively making use of the resource. Some explained that their work does not currently have a strong informatics component that would be a natural fit for dissemination via the caBIG system. Others mentioned unresolved intellectual property issues as a barrier preventing them from using caBIG. [Awardees]
- **Other Online Dissemination.** Resources such as data, algorithms, protocols, seminar webcasts, and curriculum materials have been disseminated by Alliance members online but outside of the caBIG framework. [Awardees]

Scientific Progress

- **Platforms.** Most of the Platform PIs described progress in cell culture and/or animal models, but none of the Platform projects appeared close to beginning human trials. [Awardees]
- **Diagnosis and Sensing.** Several of the CCNE projects aimed at diagnosis or sensing are already using banked human samples for retrospective studies. [Awardees]
- **Therapeutics.** Several of the CCNE projects related to therapeutics are conducting efficacy and safety studies. Few projects (Mark Davis, Caltech and Calando Pharmaceuticals; Michael Phelps, UCLA; Tom Kipps, UCSD; Sam Wickline, Greg Lanza and Kereos Inc., Washington University) have entered Phase I clinical trials [Awardees, NCI]
- **Examples of Scientific Advances.** Selected examples of advances discussed in interviews are described in the table below, but please note that the table should be used for illustrative purposes only. For a more complete summary of scientific progress, please see the Alliance Progress Report. [Awardees]

Category	Advance	Institution	Award Type
Therapeutics	Discovered new polymer carrier for certain anti-cancer drugs. Developed procedures to synthesize, did toxicology and now efficacy studies in animals. Expect to be in Phase I trials in 1-2 years.	Emory-GATech	CCNE
	In mice, suppressed metastatic disease by 92% with angiogenesis targeted liposomes.	UCSD	CCNE
	In studies with SKOV-3 human ovarian adenocarcinoma cells and MCF-7 human breast adenocarcinoma cells, demonstrated 100-fold increase in sensitivity to chemotherapy.	Northeastern	Platform
In Vitro Detection, and Diagnosis	Developed technology to do multiparameter blood-based profiling for human cancer patients. Measured on order of 12 proteins per patient for 25 patients. Succeeded in stratifying patients as well as surgery. Just got IRB approval to expand protein measurements from 12 to 25 per patient.	Caltech	CCNE
	Developed a clinical assay for detecting recurrence in prostate cancer patients immediately after surgery. Work based on retrospective study of banked human samples.	Northwestern	CCNE
	Have advanced quantum dot molecular technology to the point where clinical development is possible. Ready to start retrospective studies using preserved human tissue specimens.	Emory-GATech	CCNE

Category	Advance	Institution	Award Type
In vivo Imaging and Diagnosis	Produced first *in vivo* images of Raman nanoparticles in living subjects.	Stanford	CCNE
	Developed a very stable nanoparticle for in vivo applications that can cross the blood-brain barrier and specifically bind to brain tumor cells.	UW	Platform
	Using prototype devices for X-ray imaging using nanotubes in animal studies. Will soon be used to image phantoms.	UNC	CCNE
	Demonstrated the ability to go to a database of proteomics and genomic signatures, identify a target, translate to probe, create the probe, and validate in both mice and humans within a year. Have begun to generalize the pathway and developed 4-5 probes.	Caltech	CCNE
Fabrication, Toxicology, and Safety	Developed a unique approach to production of nanoparticles—molding process from semiconductor industry called Particle Replication In Non-wetting Templates, (PRINT). Produced multi-milligram quantity of particles that are being tested in animal tumor trials.	UNC	CCNE
	Irradiated gold particles in order to quantify the number of gold nanoparticles that enter cancer cells. This technique has helped better understand the endocytosis of hybrid gold nanoparticles in prostate and breast cancer cells.	Missouri	Platform
	Will soon publish a paper looking at toxicity of carbon nanotubes. Results show a lack of toxicity.	Stanford	CCNE
	Have developed two methodologies for the synthesis of monodispersed, highly sensitive nanoparticles for the delivery of bioactivated MR agents.	Northwestern	CCNE

Training

- **Multidisciplinary Training at CCNEs.** CCNE PIs credited the centers with attracting students from an unusually diverse range of backgrounds, including medical students as well as students with biology, physical science, and engineering backgrounds. Common strategies for promoting multidisciplinary training at the CCNEs included creating seminar series, assigning two mentors per student, requiring students and postdocs to train in multiple labs, and assigning students with different backgrounds to work together in interdisciplinary teams. One PI described his approach to training as "problem-based", encouraging students and postdocs to spend time in labs appropriate to the problem they are working on rather than the discipline they are training in. However, several PIs expressed concerns that students with truly multidisciplinary training and research interests may be at a disadvantage in the job market, because joint faculty appointments remain rare at the junior level. As one interviewee stated, the students may be changing faster than the system. [Awardees]
- **Challenges for Multidisciplinary Training.** Several CCNE PIs described working to establish new multidisciplinary curricula and even degree-granting programs at their institutions. Developing such programs was described as challenging because the courses have to be structured in a way that accounts for the sometimes drastic differences in background between biologists, clinicians, engineers, and physical scientists. One interviewee described a need for courses such as 'biology for engineers' that would facilitate cross-training and communication without requiring years of re-training on the part of the trainees. [Awardees]

- **Training on Platform Awards.** The Platform PIs also described supporting smaller numbers of students and postdocs on their awards. One Platform PI suggested linking fellowships with the most productive R01 programs. [Awardees]
- **NRSA Fellowships.** Of the two Fellowship recipients interviewed, one had ties to a CCNE and one did not. The one who was not affiliated with a CCNE described the experience as somewhat isolated. Lacking a strong network of contacts at the institutions most active in nanobiotechnology research, she was also facing more uncertainty with respect to her next career move. [Awardees]

Strategies to Promote Multidisciplinary Collaboration within Alliance Centers and Projects

- **Bridging to Medical Schools.** Most of the CCNE PIs reported that the CCNE acted as a bridge between the physical science and engineering communities and their medical schools. They reported that few if any collaborations of this nature involving nanotechnology existed at these institutions prior to the CCNE. [Awardees]
- **Multidisciplinary Teams.** Most PIs described deliberately creating project teams where biological scientists were paired with physical scientists as a strategy for promoting multidisciplinary collaboration. [Awardees]
- **Monthly Meetings.** One strategy commonly employed to promote scientific collaboration within the CCNE is to hold monthly meetings, sometimes via webcast or video conference if multiple locations are involved. Attendance at these meetings is mandatory for some CCNEs and voluntary for others. PIs also mentioned creating CCNE-only intranet sites, seminar series, and retreats for similar reasons. [Awardees]
- **Challenges: Engaging Clinicians.** Many of the PIs reported that the oncologists and clinicians tended to be the most skeptical and most difficult to engage in nanobiotechnology research. In some cases the Cancer Center at the CCNE institution served as a resource for identifying interested clinicians. One PI suggested that it would be useful for NCI to provide specific incentives for collaboration by clinicians such as the supplements available through the Roadmap Nanomedicine program. [Awardees]
- **Challenges: Communication Barriers.** CCNE PIs estimated that it took from one to two years for everyone to learn to speak the same language and for the CCNEs to begin functioning as cohesive and integrated communities. [Awardees]

Collaborations between Alliance Members

- **Establishing Collaborations.** Many PIs mentioned preliminary discussions at Alliance meetings as the starting point for specific collaborations with other Alliance members. OTIR program staff members were also credited with having facilitated collaboration between particular Alliance members. [Awardees]
- **Platform Projects and Collaboration.** Four of the five Platform PIs interviewed described at least one collaboration with a CCNE, and several had multiple collaborations with CCNEs or other Platform projects. The fifth Platform PI described actively seeking a collaborator to provide a nanoparticle he could use to test his targeting pathway, but at the time of the interview he had not yet found one. [Awardees]
- **CCNEs and Collaboration.** Most (but not all) of the CCNE PIs described ongoing research collaborations with at least one other CCNE or Platform project. Examples of collaborative activities included supplying another CCNE with materials, providing help evaluating materials produced by another CCNE, or coordination of research activities to reduce duplication of effort. [Awardees]
- **Other Interactions.** CCNE members also stated that they frequently participate as seminar speakers or advisory board members at other CCNEs. [Awardees]
- **Competition as a Barrier.** The barrier to collaboration stated often by PIs and administrators is that the Alliance investigators perceive themselves as in competition with one another for scarce funding resources. [Awardees] [[Note from Alliance staff: However, there are multiple

examples of successful Alliance collaboration which suggest that this barrier can be overcome in cases where strong scientific synergy exists among the researchers building the collaboration.]]

- **Competition as a Motivator.** One PI commented that competition can be a healthy motivator, especially when trying to meet grand challenges such as integration of nanotechnology into cancer research. [Awardees]
- **Proposed Exchange Program.** Several interviewees observed that competition is less of a barrier to collaboration among postdocs and graduate students, who are not yet sufficiently established to compete for funding on their own. Exchange of postdocs and graduate students across the Alliance has therefore been suggested by the CIWG as an alternative strategy for promoting collaboration. Such exchanges are currently rare, but interviewees speculated that the problem is not lack of interest but administrative complications. Specifically, there is no obvious mechanism for funding such activities. The CCNE at Northwestern may soon issue an RFA to support pilot projects that include exchange of postdocs using funding raised from a private donor, but this is probably not a feasible long-term solution for supporting an exchange program across the Alliance. [Awardees]
- **Other Barriers.** Other barriers to collaboration within the Alliance identified by PIs include intellectual property concerns, insufficient resources, and technologies that are not yet sufficiently mature to benefit from collaboration. [Awardees]
- **Importance of Collaboration.** Several interviewees argued that collaborations should only be encouraged in cases where strengths and resources are truly complementary and collaboration advances the goals of both research programs. Others pointed out that collaborations that do advance the goals of the research should be valued equally, regardless of whether or not the collaborator is a member of the Alliance. [Awardees]

Interactions with the NCL

- **Integration with Alliance.** OTIR program staff view the NCL as an integral part of the Alliance. They meet with NCL staff every week and perform technical reviews bi-annually. [NCI]
- **NCL Role.** In addition to providing characterization support to Alliance PIs, the original goal for the NCL was to develop a standard assay cascade to which all nanomaterials could be subjected. [[Note from Alliance program staff: This consolidated characterization effort will enable uniformity in materials evaluation and the development of standards.]] The NCL staff later determined that materials and needs were too varied for a single cascade, so emphasis shifted to developing individual protocols. 25-28 protocols have been developed so far, and three of them have become ASTM-recognized consensus standards. Acting as a liaison to FDA and NIST is also part of the charter of the NCL. [NCI]
- **Characterization Work for Alliance Projects.** NCL staff estimated that about one third of their current characterization activities are for Alliance-related projects. Most of the rest involve collaborations with other NCI-supported programs such as the former Unconventional Innovations Program (UIP) and with other investigators from academia and industry. NCL staff reported that collaborations are usually initiated by the NCL rather than by the NCI PIs. Following an in-person meeting to discuss technical issues and other concerns, investigators are invited to submit concepts. Alliance PIs have access to a shortened application process. Those PIs who reported having collaborated successfully with the NCL described staff as helpful and knowledgeable. In particular, PIs mentioned that NCL staff were able to provide useful advice about common pitfalls in characterization. [NCI; Awardees]
- **NCL Perspective on Barriers to Collaboration with Alliance.** NCL staff described two groups of Alliance projects with which they have not collaborated so far: 1) Alliance projects that are immature in terms of development and therefore not yet at a point where collaboration with NCL would be useful; 2) Alliance projects that are sufficiently mature but have chosen to fund their characterization work through other means. NCL staff speculated that barriers for the latter group may include intellectual property concerns. [NCI]
- **PI Perspective on Barriers to Collaboration with NCL.** In interviews, several PIs cited the large quantities of material required by NCL as the primary reason for their failure to

collaborate. From the perspective of these PIs, however, the issue was one of cost rather than maturity; they viewed it as too expensive to provide NCL with the quantities of material they required. [[Note from Alliance program staff: Large quantities of material are required for evaluation under standard assay cascades. NCL does work with several investigators in earlier stage collaborations with significantly smaller quantities.]] Others reported that they are still focusing on solving device-related problems and not yet ready for characterization work. None of the PIs who have funded characterization work independently elaborated on their reasons for doing so. [Awardees]

- **Informal Interactions between NCL and Alliance PIs.** Several PIs, including some that have not sent material for characterization, reported that they have received useful advice from NCL about how to negotiate the FDA approval process. For example, one PI reported that the NCL had advised him to develop a particular technology as three separate concepts rather than a single drug/imaging modality. [Awardees]

Interactions with the Division of Cancer Treatment and Diagnosis (DCTD)

- **Relationship to Alliance.** There is currently no formal relationship between the Alliance and the Developmental Therapeutics Program (DTP), but staff members on both sides mentioned that they had discussed how Alliance projects could be transitioned to the RAID program in the future. [NCI] [[Note from Alliance program staff: Recent discussions with Drs. Jim Doroshow and Joe Tomaszewski (Director and Deputy Director of DCTD, respectively) led to establishing a strategy for combining drug formulations which failed in past toxicology evaluations at NCI with new nanotechnology-based localized delivery vehicles in order to eliminate harmful toxicity profiles.]]
- **Nanotechnology-related Applications to RAID.** There have been a few nanotechnology-related applications to the RAID program so far, but none of them have been Alliance-affiliated. DTP's perception is that those with sufficiently mature concepts who could have applied have chosen to raise their own money instead. [NCI]
- **Advice to Alliance Investigators.** Several CCNE investigators have come to DTP for preliminary advice on strategies and common errors in development. [Awardees] [[Note from Alliance program staff: CTEP has also been approached by investigators for similar advice.]]

Note from Alliance program staff: OTIR and CIP have started to collaborate on developing joint programmatic opportunities in nanotechnology-based imaging. OTIR and CTEP have established a seminar series to bring to NCI speakers from early to medium stage companies involved in nanotherapeutics development. Several sessions were held and now CTEP staff are actively engaged in interactions with these investigators for guiding further development and planning.

Collaborations with Industry

- **Industry Collaborators.** Alliance PIs described many examples of successful research collaboration with industry, including both large and small firms. However, several PIs commented that it is easier to collaborate with smaller firms because they tend to be more agile and more willing to do pilot studies without making excessive intellectual property demands. [Awardees]
- **Licensing and Spinoffs.** Several PIs have licensed technologies for development by outside firms, while others have chosen to form their own spinoff companies. At least two of the five Platform PIs interviewed and most of the CCNE PIs were able to describe at least one Alliance-related spinoff. [Awardees]
- **Attracting Venture Capital.** Most PIs appeared to be confident about their ability to attract venture capital, although a few (mostly from universities without a history of attracting venture capital) expressed concerns. [Awardees]

Perspectives from DARPA

- **DARPA Approach to Research Management.** The interviewee from DARPA explained that his organization typically operates by identifying specific "hard problems" and then attacking them strategically. The DARPA management style is more goal-driven and more hands-on than is usual at NIH. [External]
- **Use of Milestones.** DARPA's use of milestones was described as critical; success or failure to meet milestones forms the basis for go/no-go decisions for each project every 12 months. The general idea is to encourage teams to "fail early and often" so that only the best and most promising approaches continue to be pursued. [External]
- **Competitions and Re-teaming.** It is also common for DARPA to hold competitions between teams pursuing different approaches at a neutral test center in order to identify the best one. It is also common for DARPA to "re-team" people (i.e., mandate collaboration as a condition for continued funding) if DARPA sees potential for synergy. [External]

Perspectives from FDA

- **Importance of Government-Funded Bio-Nano Research.** The interviewee from FDA reported that they see the Alliance as important because it brings more discoveries into the public domain, which helps FDA to learn about the state of the science and incorporate findings into the regulatory process. [External]
- **FDA-NCL Relationship.** The relationship between FDA and the NCL was described as particularly useful and productive. FDA provided input into several of the characterization protocols developed by NCL and currently refers sponsors to those protocols as guidelines. [External]

Suggestions for the Future

- **Regulatory Uncertainty.** Many of the Alliance PIs and other stakeholders identified the uncertainty surrounding the toxicology and safety of nanoparticles as a major barrier for nanomedicine. They suggested that NCI should work more closely with FDA to identify and address potential regulatory hurdles. [Awardees; NCI]
- **Funding Gap for Clinical Trials.** Several PIs observed that CCNE funds are not sufficient to sustain prospective clinical trials, but there is currently no mechanism to expedite the process of obtaining additional funds for this purpose from NCI and/or through other channels. At least one CCNE PI described a project that is currently ready to begin prospective clinical trials, but funding has not yet been secured. If the Alliance wants to push technologies into the clinic as quickly as possible, this funding gap should be addressed. [Awardees]
- **Overarching Research Strategy.** Several PIs suggested that the time is right for the Alliance programs to start thinking about an overarching strategy for identifying and collectively addressing any perceived "gaps" in knowledge that could become bottlenecks in the process of bringing nanotechnology into the clinic. Some went as far as to state that, once these problems are identified, NCI's resources in the next round of Alliance funding should be devoted to systematically attacking them, perhaps using a model similar to the problem-driven management strategies employed by DARPA. Others suggested a more democratic but equally aggressive approach, perhaps modeled on the kind of comparative and collaborative work begun in the diagnostics working group. [Awardees]
- **Trans-NIH Coordination.** Several interviewees noted that NCI has been a leader at NIH in advanced technology development, especially nanotechnology. Observing that this work has had spillover benefits in many other areas of biomedical science, they suggested that NCI should explore bilateral collaboration with other ICs and/or trans-NIH initiatives to share the cost of developing nanotechnology Platforms. [Awardees; NCI]
- **Reserving Funds for Pursuit of New Opportunities.** Several CCNE PIs suggested that a small percentage of CCNE funds should remain uncommitted so they can be allocated to pursue

promising new opportunities as they arise. The current lack of uncommitted funds means that nothing new can be added without taking money away from an existing project. Some CCNEs already incorporate "pilot" projects into their research strategies, but these funds are typically used for the purpose of drawing new investigators into nanobiotechnology research. [Awardees]

- **Funding for Alliance-Wide Collaboration.** CCNE administrators suggested that there should be a separate pool of money for activities to promote Alliance-wide collaboration. Under current arrangements, the CIWG has to secure funding from individual Centers in order to support activities such as newsletters, calendars, etc. that benefit all Alliance members. Similarly, a central pool could be used to more easily facilitate collaborative activities such as exchange of postdocs across the Alliance. [Awardees]

Current Portfolio Analysis (Expanded): (As of 7/7/08)

Briefly describe current NCI/NIH grant and cooperative agreement/application portfolio (and other related projects) for the research area, specifically addressing: (a) funded (active) grants, contracts, and cooperative agreements; (b) pending (scored) but unfunded grants: (c) applications not scored; and (d) any related research funded by other NIH Institutes and/or centers (ICs). Include the current and one previous fiscal year in the analysis.

Nanotechnology RPG Overall (As required by Concept Policy)

Activity	Categories	FY07 NIH (NCI)	FY08 NIH (NCI)
RPG (Type 1,2)	Total Applications	586 (159)	1067 (313)
	Unscored Applications	272 (81)	533 (142)
	Scored Applications	314 (78)	534 (171)
	Funded Applications	97 (22)	112 (38)
	Total Cost for FY	$30.59M ($6.07M)	$33.28M ($10.58M)

A search for new (Type 1, 2) RPG applications (R01, P01, R03, R15, R21, R33, R41, R42, R43, R44) using "nanotechnology" as a keyword in abstracts, summary statements, and title in QVR for yielded 159 total applications that had NCI as primary contact for fiscal year 2007. This nearly doubled, in fiscal year 2008, to 313 total applications. Approximately 50% were scored each year and nearly 40 applications were funded in fiscal year 2008. This translates to approximately $10.58 million dollars of new funding in fiscal year 2008, comparable to the $6.07 million dollars invested in fiscal year 2007. Thus, overall interest in research related to nanotechnology grew rapidly, whereas the success rate of funded applications remained about the same.

Additional Analysis

Nanotechnology R01 Research (Trans-NIH Nanobiology and Nanomedicine PA/PAR)

Activity		FY04	FY05	FY06	FY07	FY08
R01	NIH (Scored)	39	27	35	43	70
	NIH (Funded)	10	9	11	14	14
	NCI (Scored)	3	8	11	14	34
	NCI (Above Payline)	1	2	3	2	13
	NCI (Funded)	1	2	4	1	8*
	NCI (Total Cost)	$274K	$1.27M	$2.42M	$2.70M	$5.54M

Since the launch of the NCI Alliance for Nanotechnology in Cancer program, the overall number of cancer nanotechnology R01 applications received from the trans-NIH PA/PAR and were scored has increased more than 10 times (3 → 34). Currently, more than 62% of applications over the payline are being funded, which corresponds to a total cost investment of approximately $5.54 million for FY08.

Nanotechnology Training

Activity		FY04	FY05	FY06	FY07	FY08
F32/F33	NIH (Received)	8	15	45	31	33
	NIH (Funded)	3	7	9	6	4
	NCI (Received)	4	8	21	15	19
	NCI (Funded)	1	4	5	1	3
	NCI (Total Cost)	$58K	$231K	$357K	$304K	$297K

Activity		FY04	FY05	FY06	FY07	FY08
K99	NIH (Received)	0	0	0	15	9
	NIH (Funded)	0	0	0	2	1
	NCI (Received)	0	0	0	4	3
	NCI (Funded)	0	0	0	0	0
	NCI (Total Cost)	0	0	0	0	0

Activity		FY04	FY05	FY06	FY07	FY08
T32	NIH (Received)	6	4	8	17	10
	NIH (Funded)	1	1	1	2	0
	NCI (Received)	0	0	1	1	4
	NCI (Funded)	0	0	1	0	0
	NCI (Total Cost)	0	0	$202K	$202K	$202K

Activity		FY04	FY05	FY06	FY07	FY08
R25	NIH (Received)	0	0	2	4	4
	NIH (Funded)	0	0	0	0	0
	NCI (Received)	0	0	0	2	3
	NCI (Funded)	0	0	0	0	0
	NCI (Total Cost)	0	0	0	0	0

A similar analysis was conducted for relevant training mechanisms with the keyword "nanotechnology." An RFA for F32/F33 trainees was part of the Alliance program (CA05-025) and was reissued twice (CA06-010, CA08-003). Based on comparison of landscape before and after the initial RFA, there is a clear trend of increased interest in *cancer* nanotechnology training as F32/F33 applications increased nearly **5 times** (4→19), with more than 50% received in response to the general F32/F33 PA. A similar increasing trend for NCI is seen in both individual training awards (K99) and institutional training awards (T32, R25), with a combined total of 1 application in FY06, 7 applications in FY07, and 10 applications in FY08. However, the number of these applications is still very low as compared to the overall training needs. Additionally, of the 18 combined applications, only one award (T32), in FY06, has been made so far with total cost per year of $202K.

Report

Meeting Report: Strategic Workshops on Cancer Nanotechnology

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Abstract

The National Cancer Institute (NCI) Alliance for Nanotechnology in Cancer is a comprehensive, systematized effort encompassing the academic and private sectors in multidisciplinary research and dedicated to the use of nanotechnology in cancer prevention, diagnosis, and therapy. The program is designed to move basic science discoveries into the development pipeline and eventually into clinical use. As the program approaches the midway point of its five-year funding, NCI is once again assessing the field of cancer nanotechnology to determine the current needs and gaps in this area of research. Toward that end, the NCI's Office of Technology and Industry Relations (OTIR) held three strategic workshops on cancer nanotechnology covering the areas of in vitro diagnostics and prevention, in vivo diagnosis and imaging, therapy and post-treatment. To each of these meetings, NCI's program staff invited a wide range of experts from academia, industry, the non-profit sector, and the Federal government, including those from the National Institutes of Health and the U.S. Food and Drug Administration. This meeting report is the summary and compilation of recommendations developed at these strategic workshops.

Introduction

Cancer is one of the main public health problems facing the United States. The statistics for cancer are daunting; the number of Americans who will die of cancer in 2008 is projected to be over 550,000 (nearly one in four of all deaths will be cancer related).(1) The number of people who will be diagnosed with the disease will exceed 1.4 million. With an increasing aging population, the number of people who develop cancer is only going to increase in the years ahead. On the positive side, there are over 12 million cancer survivors today in the United States and their numbers are steadily increasing, mainly due to progress in early screening and treatment. Globally, greater than 70% of all cancer deaths occur in low and middle income countries; hence, the issues surrounding cancer are clearly not a domestic matter.

More than three years ago, the National Cancer Institute (NCI) began the process of developing and funding the NCI Alliance for Nanotechnology (http://nano.cancer.gov) in an attempt to bring the power of nanotechnology to bear on developing new solutions to the major challenges of the disease.(2-6) It has been recognized that nanotechnology carries great potential; if this knowledge is applied to cancer, it could someday revolutionize the way cancer is viewed, diagnosed, and treated as a disease.(7) Moreover, nanotechnology spans all aspects of the Institute's strategic objectives ranging from tools to provide better insight into the fundamentals of cancer biology, through early diagnostics and imaging, to improving cancer treatment and care. In order to organize the discussion topically, three one-day strategic workshops were convened in spring with the following thrusts:

Workshop I:	In vitro Diagnostics and Prevention
Workshop II:	Therapy and Post-Treatment
Workshop III:	In vivo Diagnosis and Imaging

These workshops were designed to assess the status of cancer nanotechnology and determine what are the opportunities, the needs of the field, and existing knowledge gaps. At each workshop, the attendees listened to few short overview presentations from thought leaders on the technical challenges confronting the use of nanotechnology in cancer and the most promising nanotechnologies that may overcome these challenges. The talks gave the clinician (e.g., oncologist) and technologist (e.g., chemist) perspective and provided impetus for brainstorming and additional discussion. To further guide discussion, NCI staff provided attendees with a list of NCI's thoughts on possible "holy grail" applications for cancer nanotechnology. These included:

- Personalized diagnostic "nano" kit to screen for 100 cancer-associated agents within the time of a doctor's visit.
- Set of nanotechnology tools for "real-time" elucidation of cancer properties for the tumor nano/microenvironment at both the intracellular and extracellular levels.
- Tools to monitor and control biodistribution as a function of particle size, shape, and targeting scheme.
- Multifunctional particle systems capable of diagnosis and subsequent tailored therapy with controlled release.
- Robust efficacy feedback monitoring tools for novel cancer therapeutic drugs in clinical trial settings to reduce the time from months to days or hours.
- Nanoparticle platform for effective and controlled delivery of therapeutics to the brain.

- Design tools to look beyond tumor size (e.g., microenvironment, follow metastasis).

- Tool to identify tumors that are far smaller (100x, 1000x) than those detectable with today's technology.

After the opening presentations, the invited scientists were divided into three smaller working groups and worked on a list of a common questions and topics. Those included:

- Question 1: Within the theme of each workshop, what are the most important goals in cancer research (not just nano-driven) that might be achieved within the next 5 years? Within the next 10 years?

- Question 2: How and where do you see (or have seen) nanotechnology contributing to the areas identified in Question 1?

- Question 3: What are the major barriers (e.g., technical, financial, infrastructure, organizational/managerial) that would be of hindrance in reaching these goals?

A compilation of responses and recommendations compiled at the workshops are presented here.

Overarching Themes in the Recommendations

Each workshop produced a series of important and specific recommendations that are discussed below. In addition, there were several recommendations that appeared as common themes throughout the three workshops.

The Technologist and the Clinician

In spite of organizing the workshops to have overview lectures from a technologist and clinician perspective, overwhelmingly the audience pointed out the continued need for technologists, biomedical researchers, and clinicians to work together in order to make the most out of the opportunities that nanotechnology can generate. Many applauded NCI's efforts in creating multidisciplinary team science environment, and expressed hope that such efforts would continue to be expanded going forward. It was believed that he Alliance program provided a huge boost to the field of cancer nanotechnology and that the Institute should continue providing avenues for both intra- Center for Cancer Nanotechnology Excellence (CCNE)(8) and inter-CCNE partnerships to form. In addition, NCI should consider new mechanisms for creating strategic partnerships with other agencies and other fields to maximize the impact that nanoscience will have on cancer research and clinical oncology. A consensus exists that nanotechnology may be able to drive new advances that will improve cancer diagnosis, imaging, and therapy, in large part because the nature of cancer could be understood better resulting from these disparate research communities working together.

Multifunctional/Multimodal Nanotechnology Agents

Prevailing throughout the three workshops was the notion that the real (paradigm shifting) power of cancer nanotechnology will occur when an agent/platform combines two or more of the modalities (associated with workshops thrust areas) namely, diagnosis, imaging, and/or therapy. Clearly, a strong advantage for a nanoparticle system is the potential for a 'plug & play' like approach to integrate multifunctionality and multimodality. However, maintaining a more pragmatic vision, the participants recommended that 'uni-' functionality/modality be established first and subsequently translated to the clinic. The increase in the complexity of the multi-modal solution should then occur gradually. Other recommendations include:

- Integrate imaging and therapy so that the oncology community can monitor the effects of therapy in real time, both for conventional agents and for nanotechnology-enabled agents.

- Multifunctional probes – intracellular identification of markers combined with a subsequent imaging or therapeutic event

- Develop multimodal therapy using a nanoplatform that can deliver a novel form of therapy, such as heat, in combination with a standard therapy.

- Probes that can localize intracellular concentrations of an analyte and then be addressed and triggered to release a therapeutic payload.

- The high payload-carrying capacity of nanoparticles can improve sensitivity and resolution by dramatically increasing the local concentration of an imaging agent at a tumor.

In Vitro Diagnostics and Prevention Workshop

One of the keys to the growing number of cancer survivors is emergence of early diagnostics of the disease. The participants at this workshop believed that further advances to develop and adopt new nanotechnology methodologies that enable cancer to be discovered earlier in its development and ultimately to prevent it from occurring in the first place was paramount. A positive feedback loop mechanism (diagnosis, treatment, and monitoring of treatment results) will be important for pushing this field forward. Early detection methods will be enabled by improved early-stage biomarkers and followed by more effective therapies designed to target early stage disease. As a result, developing new early detection methodologies becomes even more important in the quest to reduce the incidence and mortality from cancer. The long term vision for developing new *in-vitro* diagnostics is to be able to take a body fluid, a blood sample for example, and determine the presence of low-abundance biomarkers, characteristic to cancer that would ideally identify the type of tumor present, specify the appropriate therapy, and predict the outcome of that therapy.

Specific recommendations for future development include:

Early Detection

- The development of modular diagnostics based on bodily fluids, such as blood, serum, cerebrospinal, urine, stools, or saliva. In certain cases, breathe as a collection source. Elucidating the variables that are needed to optimize the modules for a particular bodily fluid.

- Multifunctional capabilities, one platform capable of detecting nucleic acid and protein.

- Develop new in vivo diagnostics that would pinpoint tumors and their metastatic lesions (e.g., Detecting rare cancer cells as on cancer-associated molecules).

- Nanotechnology should lead to new assays with lower cost and higher sensitivity markers.

- Nanotechnology-based detection and analytical technologies could be incorporated into a multiplexed nano-probe that could be inserted (or targeted) into a tumor, act as sensors of the local environment, and that are then removed when the probe is excised.

Therapy and Post-Treatment Workshop

Targeted cancer therapies represent a glimpse into the future of oncology with ERBB and VEGF based therapies being the first successful examples of using targeted approaches. Similarly, it has been demonstrated that 'nano-carriers' delivery can improve the efficacy of anticancer drugs and reduce the associated toxicities. The participants at this workshop shared a common vision that that nanoparticles will be able to improve the therapeutic index for a wide variety of anticancer drugs, and that this improvement alone will be of great potential benefit. Moreover, multifunctional aspects and the monitoring therapeutic response using 'smart' nanoparticles will also represent a paradigm-changing event in oncology.

Specific recommendations for future development include:

Therapeutic Development, Delivery, and Monitoring

- Develop a monitoring test (ultimately to be designed for home use) for monitoring disease response to therapy and disease progression; the immune system to determine if the immune system is attacking the tumor or supporting it, information that would contribute to clinical decision-making.

- Create endpoint measurements in addition to apoptosis to assess therapeutic efficacy.

- Develop nanomaterials and targeting strategies aimed specifically at the tumor microenvironment.

- Develop tumor cell surface targeting ligands to deliver nanoparticles to the tumor site in humans.

- Improve the pharmacokinetics of current nanocarriers in order to decrease the toxicity of their drug payloads.

- Understand how nanomaterials affect cell signaling and drug response.

- Development of new chemistries that would trigger drug release from a nanoparticle only at the site of a tumor

- Develop new biomaterials that would change the biodistribution patterns of nanomaterials and their drug cargos.

- Create methods for 'programming' nanoparticles for use in personalized anticancer therapy.

- Activation of targeted nanoparticle could enable timed release of imaging agents and drugs, while bidirectional communication with the nanoparticle would provide therapeutic feedback.

This workshop group also recommended that the NCI continue its efforts to work with FDA and clinicians to address the unique features of nanoparticles and the opportunities to change the approval paradigm as far as modularity and personalized therapies are concerned. The group also recommended that the NCI and its Nanotechnology Characterization Laboratory (NCL; http://ncl.cancer.gov) continue their efforts to develop bioanalytical methods suitable for characterization of nanoparticles and to fund efforts for mathematical modeling that might help drug developers rationalize their choice of a specific nanoparticle for a particular application. To accomplish these goals, the audience identified several critical needs. These included the need for relevant animal

models of human cancer; the development of a streamlined approach to evaluate toxicology, pharmacokinetics, and the efficacy of potential nanotherapeutics, essentially expanding the scope of the NCL's mission, and along the lines of the current NCL effort; and the creation of an infrastructure for translational nanotechnology research that would feed promising therapeutics into the nation's clinical trials apparatus.

In Vivo Diagnosis and Imaging Workshop

Perhaps, the most impacting use of nanotechnology which is relatively close to the clinic is in vivo imaging. Improving diagnosis by detecting tumors at ever small stages, via in vivo imaging, opens new opportunities for improving treatment, as well as for understanding of metastasic processes. Currently, imaging provides limited information about the tumor type, with subsequent surgery and then pathology being used to actually identify the tumor and determine therapy. A vision that this workshop participants shared is to develop in vivo imaging techniques which can provide more specific information about tumor type and tumor environment and thus virtually eliminate the need for surgical biopsy prior to determining the therapy. Moreover, the group believed that nanotechnology-enabled imaging methodology would be capable of monitoring the response to therapy in real time. This, in turn, would reduce the time lapse to determine if therapy is effective, would greatly improve the quality of life for patients by getting patients off ineffective drugs that could cause adverse side effects, and would decrease the likelihood that drug resistance might develop before an effective therapy is established for particular patients.

Specific recommendations for future development include:

Imaging Tools

- Develop minimal or non-invasive methods to access to currently inaccessible organs such as brain, pancreas, lungs, and ovaries and to help better understand in vivo tumor biology.

- Develop enhanced imaging technologies and contrast agents to help diagnose, stratify, and monitor patient treatment.

- Improve spatial and temporal resolution, as well as sensitivity, in order to detect the very low tumor burdens, improve surgical guidance, and monitor the response of those small tumors to therapy.

- Achieve a broader distribution of existing imaging agents beyond the major research medical centers.

- Develop image-guided biopsies with simultaneous, multiplexed in situ analysis to eliminate the need for diagnoses based on histopathology.

- The development of more sensitive and less expensive imaging hardware, such as the development of carbon nanotube-based CT instruments.

- Develop entirely new nano-imaging strategies to change limits of detection.

- Improve detection systems for optical imaging in humans by optimizing imaging platforms to take advantage of the unique payload carrying characteristics of nanoparticles.

Additional Common Themes

In addition to establishing recommendations specific to each workshop thrust, there were several additional comments that appeared as common themes throughout the three workshops as listed below. As the level of detection is lowered and sensitivity increases, the issues associated with 'good' biospecimens and sample preparation practices were clearly viewed as a concern to translating nanotechnology platforms in a timely manner. Improving the specificity of biomarker assays (and reducing non-specific binding) was another common issue.

Other common categories, which were identified, include:

Biospecimen and Sample Preparation

- Analytical issues: Developing techniques to increase signal to background (chemists and biologists approach these problems differently. Chemists and biologists, for instance, try to increase signal, while physicists look to reduce noise and the medical community works to make sense of poor signals).

- Sample preparation issues: Improving faster and facile sample concentration techniques.

- Improved biospecimen sampling and validation, which is absolutely critical for retrospective studies and biomarker validation.

- Specimen collection issues: Preparing the patient for sample donation (e.g., nanocarriers be administered prior to sample collection to ensure trace biomarkers are recovered; in vivo collection using injected particles).

- New nano-capabilities for making metabolic correlations between anoxia response and changes in glycolysis, for example, and the development of cancer or the occurrence of metastasis.

Biomarkers

- New (and improved) recognition agents, better antibodies or antibody equivalents.

- Validation of new cancer specific biomarkers.

- Develop faster validation, higher selectivity and higher affinity systems for molecular recognition using nanotechnology

- Low-cost panel assays for multiple protein markers, such as those being developed already for ovarian cancer.

Biomedical Informatics and Modeling/Simulations

- Develop medicine metrics using database information that includes patient profiles with imaging and outcomes. There is no mechanism now for "one-stop shopping" that accumulates all the different types of imaging combined with outcome data. In addition, there is a need for automated analytical tools that can extract information from the images in a way that can be incorporated into these databases and searched.

- Develop simulations for nanodevices to predict and validate in vivo pharmacokinetic and pharmacodynamic measurement as well as to design better nanomaterials.

- Develop better models of cancer that are more predictive of response in human cancers.

Funding and Training Mechanism

The groups believed strongly that the NCI needs to continue and expand on the multiple funding mechanisms that it has developed for creating focused, multidisciplinary teams. In particular, funding should include expanded opportunities for individual investigators to work with the CCNEs and the Platform Partnerships (R01s), and for students and postdoctoral fellows to engage in more multidisciplinary training opportunities (e.g., F32/F33) in order to get the next generation of researchers firmly entrenched.

Additionally, participants expressed a desire for a Defense Advanced Research Projects Agency (DARPA)-style funding initiative for more translational projects and exploratory-based for more fundamental research. The workshop participants were in agreement regarding the value of focused research aimed at bringing cancer nanotechnology-enabled platforms into the clinic, but there were some discussions about how NCI can transition this type of applied research to the private sector providing additional funding (which is not in place, currently), while at the same time maintaining future funding for either cutting edge research or fundamental research that will feed into the translational research phase.

Summary

The strategic workshops echoed a clear consensus that cancer nanotechnology had made very significant advancements over the past three years, both in fundamental discovery and the development of practical, clinic-worthy solutions. The participants clearly believed that the NCI supported infrastructures, such as the CCNEs and NCL, have aided the cancer nanotechnology community in awareness, nurture of promising science, dissemination of 'best practices', and standardization of characterization methods. The audience viewed many more discoveries to ensue as long as funding is available to maintain and expand number of researchers working in the field.

Cancer nanotechnology field has the potential to better monitor therapeutic efficacy, provide novel methods for detecting and profiling early stage cancers, and for enabling surgeons to delineate tumor margins and sentinel lymph nodes. This field is well positioned to provide improved methods for imaging and staging cancers and for more effectively delivering therapeutics in a targeted manner to tumors. Ultimately, if the nanotechnology researchers can establish methods to detect tumors at a very early stage, that is, before tumors begin to vascularize and metastasize, cancer will become a disease that will become amenable to complete cure via surgical resection. The impact on the disease survival rates and disease management expenditures could be exceedingly high.

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8. The eight Centers of Cancer Nanotechnology Excellence (CCNEs) listed below for the NCI Alliance for Nanotechnology in Cancer are (in alphabetical order): (1) Carolina Center of Cancer Nanotechnology Excellence (University of North Carolina, Chapel Hill); (2) Center for Cancer Nanotechnology Excellence Focused on Therapy Response (Stanford University); (3) Center of Nanotechnology for Treatment, Understanding, and Monitoring of Cancer (University of California, San Diego); (4) Emory-Georgia Tech Nanotechnology Center for Personalized and Predictive Oncology (Emory University and Georgia Institute of Technology); (5) MIT-Harvard Center of Cancer Nanotechnology Excellence (MIT and Harvard University, Massachusetts General Hospital); (6) Nanomaterials for Cancer Diagnostics and Therapeutics (Northwestern University); (7) Nanosystems Biology Cancer Center (California Institute of Technology); and (8) The Siteman Center of Cancer Nanotechnology Excellence (Washington University).

Agenda

NCI Alliance for Nanotechnology in Cancer

National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

Strategic Workshop on Cancer Nanotechnology:
In-vitro Diagnosis and Prevention

February 20, 2008

Bethesda North Marriott Hotel & Conference Center
Bethesda, Maryland

WORKSHOP AGENDA

7:00 a.m. - 8:00 a.m.	**Continental Breakfast and Registration**	*Forest Glen*
8:00 a.m. - 8:20 a.m.	**Opening Remarks/Objectives** **Dr. Anna Barker, Deputy Director, NCI** **Dr. Piotr Grodzinski, NCI**	

Morning Presentations – Overview Session 1

8:20 a.m. - 8:50 a.m.	**Prof. Steven Rosen, Northwestern University** **Oncology Needs and Gaps – Wish List**	
8:50 a.m. - 9:20 a.m.	**Prof. David Walt, Tufts University** **Technical Challenges and Most Promising Technologies**	

Working Groups – Brainstorming Session 1

9:20 a.m. - 10:30 a.m.	**Divide into three discussion groups** Initial discussion - please review questions in the attachment. Develop straw-man proposal.	
	Working Group 1 *Discussion Leader –* ***Prof. George Whitesides*** *Harvard University*	*Forest Glen*
	Working Group 2 *Discussion Leader –* ***Prof. Chad Mirkin*** *Northwestern University*	*Linden Oak*
	Working Group 3 *Discussion Leader –* ***Prof. James Heath*** *Caltech*	*Timberlawn*
10:30 a.m. - 10:45 a.m.	**Coffee Break**	

Morning Presentations – Overview Session 2

10:45 a.m. - 11:15 a.m.	**Dr. Greg Shipp, Nanosphere, Inc.** **Oncology Needs and Gaps – Wish List**	*Forest Glen*
11:15 a.m. - 11:45 a.m.	**Prof. Paul Yager, University of Washington** **Technical Challenges and Most Promising Technologies**	
11:45 a.m. - 12:30 p.m.	**Reports From Brainstorming Session 1** Present initial findings and have discussion to refine issues raised.	

Working Lunch – Brainstorming Session 2

12:30 p.m. - 2:15 p.m.	**Working Group Breakout Discussions** Each group refines/recalibrates on the set of questions/ problems and develops a plan (proposal) for final presentation.	
	Working Group 1 *Discussion Leader –* ***Prof. George Whitesides*** *Harvard University*	*Forest Glen*
	Working Group 2 *Discussion Leader –* ***Prof. Chad Mirkin*** *Northwestern University*	*Linden Oak*
	Working Group 3 *Discussion Leader –* ***Prof. James Heath*** *Caltech*	*Timberlawn*
2:15 p.m. - 2:30 p.m.	**Coffee Break**	

Afternoon Presentations

2:30 p.m. - 3:30 p.m.	**Working Group Presentations** Each group presents a practical plan on where cancer nanotechnology in-vitro diagnostics and prevention will stand in the next 3, 5, and 10 years; the roadblocks and needed solutions; and what is needed in terms of Federal agency support.	*Forest Glen*
3:30 p.m. - 4:00 p.m.	**Capture Consensus Comments, Summarize, and Adjourn**	

National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

Strategic Workshop on Cancer Nanotechnology:
Therapy and Post-Treatment

March 6, 2008

Bethesda North Marriott Hotel & Conference Center
Bethesda, Maryland

WORKSHOP AGENDA

7:00 a.m. - 8:00 a.m.	**Continental Breakfast and Registration**	*Glen Echo*
8:00 a.m. - 8:20 a.m.	**Opening Remarks/Objectives** **Dr. Anna Barker, Deputy Director, NCI** **Dr. Piotr Grodzinski, NCI**	
Morning Presentations – Overview Session		*Glen Echo*
8:20 a.m. - 8:50 a.m.	**Dr. David Parkinson, Nodality** **Oncology Needs and Gaps – Wish List**	
8:50 a.m. - 9:20 a.m.	**Prof. Naomi Halas, Rice University** **Technical Challenges and Most Promising Technologies**	
9:20 a.m. - 9:50 a.m.	**Prof. James Baker, University of Michigan** **Oncology Needs and Gaps – Wish List**	
9:50 a.m. - 10:20 a.m.	**Prof. Joseph DeSimone, University of North Carolina** **Technical Challenges and Most Promising Technologies**	
10:20 a.m. - 10:30 a.m.	**Breakout Group Logistics** **Dr. Larry Nagahara, NCI**	
10:30 a.m. - 10:45 a.m.	**Coffee Break**	

Working Groups – Brainstorming Session

10:45 a.m. - 12 noon	**Working Group Breakout Discussions** Initial discussion - please review questions in the attachment. Develop straw-man proposal.	
	Working Group 1 *Discussion Leader –* ***Prof. Charles Craik*** *University of California, San Francisco*	*Timberlawn*
	Working Group 2 *Discussion Leader –* ***Prof. Sadik Esener*** *University of California, San Diego*	*Oakley*
	Working Group 3 *Discussion Leader –* ***Prof. Kit Lam*** *University of California, Davis*	*Great Falls*

Working Lunch – Reports From Brainstorming Session 1 *Glen Echo*

12 noon - 1:15 p.m.	**Working Group Presentations** Present initial findings and have discussions to refine the issues raised.	

Working Groups – Brainstorming Session 2

1:15 p.m. - 2:15 p.m.	**Working Group Breakout Discussions** (continued) Each group refines/recalibrates on the set of questions/ problems and develops a plan (proposal) for final presentation.	
2:15 p.m. - 2:30 p.m.	**Coffee Break**	

Afternoon Presentations

2:30 p.m. - 3:15 p.m.	**Working Group Presentations** Each group presents a practical plan on where cancer nanotechnology in-vitro diagnostics and prevention will stand in the next 3, 5, and 10 years; the roadblocks and needed solutions; and what is needed in terms of Federal agencies support.	*Glen Echo*
3:15 p.m. - 4:00 p.m.	**Capture Consensus Comments, Summarize, and Adjourn**	

NCI Alliance for Nanotechnology in Cancer

National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

Strategic Workshop on Cancer Nanotechnology:
In-vivo Diagnosis and Imaging

March 28, 2008

Bethesda Marriott
Bethesda, Maryland

AGENDA

7:00 a.m. - 8:00 a.m.	**Continental Breakfast and Registration**	*Rockville/ Chevy Chase Rooms*
8:00 a.m. - 8:20 a.m.	**Opening Remarks/Objectives** Dr. Anna Barker, Deputy Director, NCI Dr. Piotr Grodzinski, NCI	

Morning Presentations – Overview Session

8:20 a.m. - 8:50 a.m.	**Oncology Needs and Gaps – Wish List** Dr. James Olson, Fred Hutchinson Cancer Research Center
8:50 a.m. - 9:20 a.m.	**Technical Challenges and Most Promising Technologies** Dr. Shimon Weiss, University of California, Los Angeles
9:20 a.m. - 9:50 a.m.	**Technical Challenges and Most Promising Technologies** Dr. Renata Pasqualini, M.D. Anderson Cancer Center
9:50 a.m. - 10:00 a.m.	**Breakout Group Logistics** Dr. Larry Nagahara, NCI
10:00 a.m. - 10:20 a.m.	**Coffee Break**

Working Groups – Brainstorming Session 1

10:20 a.m. - 12 noon — **Working Group Breakout Discussions**
Initial discussion - please review questions in the attachment.
Develop straw-man proposal.

Working Group 1 — *Rockville/ Chevy Chase Rooms*
Discussion Leader: Prof. Sam Gambhir
Stanford University

Working Group 2 — *Bethesda Room*
Discussion Leader: Prof. Thomas Meade
Northwestern University

Working Group 3 — *Potomac Room*
Discussion Leader: Prof. Samuel Wickline
Washington University in St. Louis

Working Lunch – Reports From Brainstorming Session 1

12 noon - 1:15 p.m. — **Working Group Presentations** — *Rockville/ Chevy Chase Rooms*
Present initial findings and have discussion to refine issues raised.

1:15 p.m. - 1:30 p.m. — **Coffee Break**

Working Groups – Brainstorming Session 2

1:30 p.m. - 2:30 p.m. — **Working Group Breakout Discussions** (continued)
Each group refines/recalibrates on the set of questions/ problems and develops a plan (proposal) for final presentation.

Working Group 1 — *Rockville/ Chevy Chase Rooms*
Discussion Leader: Prof. Sam Gambhir
Stanford University

Working Group 2 — *Bethesda Room*
Discussion Leader: Prof. Thomas Meade
Northwestern University

Working Group 3 — *Potomac Room*
Discussion Leader: Prof. Samuel Wickline
Washington University in St. Louis

2:30 p.m. - 2:45 p.m. — **Coffee Break**

Afternoon Presentations

2:45 p.m. - 3:30 p.m.	**Working Group Presentations** Each group presents a practical plan on where cancer nanotechnology for in-vivo diagnosis and imaging will stand in the next 3, 5, and 10 years; the roadblocks and needed solutions; and what is needed in terms of Federal agency support.	*Rockville/ Chevy Chase Rooms*
3:30 p.m. - 4:00 p.m.	**Capture Consensus Comments, Summarize, and Adjourn**	

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Introduction

Technology Translation to the Clinic

Introduction

The Alliance program is dedicated to the development of new, applied technology solutions towards cancer prevention, diagnosis, and treatment which have clinical utility potential. The Alliance investigators took upon themselves to raise additional funds, establish spin-off companies, and promote the move of their laboratory-developed technologies to the commercial world. Some of the program infrastructure, namely Nanotechnology Characterization Laboratory and SBIR initiative, has been designed to accelerate and support these translational attempts.

The Nanotechnology Characterization Laboratory (NCL) was conceived at the onset of the Alliance program and has become a critical component aiding particle characterization and standardization of characterization methodologies. In concert with National Institute of Standards and Technology (NIST) and the U.S. Food and Drug Administration (FDA), the NCL takes the lead role in creating the preclinical assays needed to prepare nanoparticle-enabled advances for clinical study. The work of NCL is in close concert with the prolific activity of the investigators in forming spin-off companies and transferring technology from the university laboratories to these companies where the scale-up of nanoparticle development occurs. Several such companies have been founded in the last 3 years.

The commercial partners of Alliance investigators are also encouraged to submit Small Business Innovation Research (SBIR) proposals. The first four contracts of Phase 1 have already been awarded and are discussed further in this section.

Nanotechnology Characterization Laboratory

Nanotechnology Characterization Laboratory

The NCL performs preclinical characterization of nanomaterials intended for cancer therapeutics and diagnostics. Nanotechnology has the potential to improve cancer diagnosis, imaging, and treatment; however, the novel properties and reactivity of nanomaterials are not entirely understood. Methods and tests used in conventional preclinical pharmacological development are frequently not applicable to nanoparticles, making it difficult to unambiguously meet regulatory requirements for safety and efficacy. The NCI's Alliance for Nanotechnology in Cancer formed the NCL in collaboration with NIST and the FDA to help accelerate the transition of nanotechnology cancer drugs to patients.

The NCL was launched in September 2004 and now is fully operational, with collaborators from within the Alliance and other investigators originating from academia, industry, and government. The NCL assay cascade now contains more than 30 protocols, 20 of which are publicly available (the others are still undergoing validation). Three of these protocols have passed the final ballot stage and are becoming American Society for Testing and Materials (ASTM) International standards. To-date NCL characterized over 130 different nanoparticle formulations.

Nanoparticles submitted to the NCL include liposomes, nanoshells, nanorods, metal colloids, functionalized gold, titanium dioxide, derivatized fullerenes, dendrimers, quantum dots, nanoemulsions, nanocrystals, and polymer-based nanomaterials. The NCL has seen significant recent success with the use of these nanoparticles as platforms or carriers for otherwise insoluble or poorly soluble drugs. Nanoparticle-carried drugs often have altered pharmacokinetics (PK) and disposition profiles as compared to their native forms.

The detailed achievements of NCL are described in their 2007 Annual Progress Report which is also included in this summary.

Clinical Trials, IRB, IACUC Protocols

Clinical Trials, FDA Approvals, IRB, and IACUC Approvals

Reflecting an aggressive push for moving the innovative technologies and their proof-of-concept demonstrations in the investigators' laboratories, the Alliance program witnessed substantial amount of work with animal models, experimentation with human clinical samples, and emerging human clinical trials. In total, 5 Phase I clinical trials for nano-therapeutics and nanoparticle-based imaging agents were initiated, 1 IND and 1 IDE were obtained from FDA, 4 discussions with FDA on future IND clearance were held, 17 IRB protocols were approved, and 42 IACUC animal protocols were approved. Majority of the funds to support these efforts came from additional sources and were raised by the investigators in addition to the Alliance funds.

Calando Pharmaceuticals Clinical Trials on Nano-therapies – Caltech/UCLA CCNE: Mark Davis

Calando Pharmaceuticals, founded by Caltech/UCLA CCNE investigator Mark Davis, is currently involved in two clinical studies.

The first clinical trial is an ongoing study for IT-101. IT-101 is a conjugate of camptothecin and a linear, cyclodextrin-based polymer. This is an open-label, dose-escalation study of IT-101 administered in patients with solid tumor malignancies (http://www.clinicaltrials.gov/ct2/show/NCT00333502?term=calando&rank=1). Patients who satisfy the inclusion/exclusion criteria will receive injections of IT-101 every other week.

Camptothecin is a naturally-occurring compound possessing potent anticancer properties against a broad spectrum of tumor cell lines. Camptothecin interrupts cell division and replication by inhibiting the enzyme topoisomerase 1. Unfortunately, Camptothecin possesses significant pharmacological shortcomings including very poor solubility in water and hydrolysis from its active lactone form to an inactive, yet toxic, carboxylate form at human blood pH levels. The components of Cyclosert™ nanoparticles are ß-cyclodextrin, polyethylene-glycol and L-cysteine. Camptothecin is covalently attached to Cyclosert™ through a glycine linker to form IT-101 resulting in a 1000-fold increase in camptothecin solubility while stabilizing it in its active lactone form. Cyclosert nanoparticles are typically between 30 and 60 nm in diameter. Their hydrophilic character and close to neutral surface charge allows them to evade uptake by macrophages, which do not recognize them as foreign entities. Similarly, they can circulate for extended times in the blood stream. A long circulation half-life leads to a preferential accumulation of Cyclosert nanoparticles in tumor tissues with abnormally leaky vasculature. In mouse models, Cyclosert nanoparticles have been shown to preferentially accumulate in tumor tissue over time.

The second clinical trial is a Phase I trial of CALAA-01 which is currently recruiting participants. This is an open-label, dose-escalating study of the safety of intravenous CALAA-01 in adults with solid tumors refractory to standard-care therapies. The trial is being conducted at the UCLA Jonsson Cancer Center (UCLA) in Los Angeles, California, and at South Texas Accelerated Research Therapeutics (START) in San Antonio, Texas. The first patient was recently enrolled and dosed at START in San Antonio, Texas (http://www.clinicaltrials.gov/ct2/show/NCT00689065?term=calando&rank=2).

CALAA-01 is a small interfering RNA (siRNA) agent which targets the M2 subunit of ribonucleotide reductase formulated with Calando's RONDEL™ (RNAi/Oligonucleotide Delivery) polymer delivery system. The foundation of the RONDEL system is a linear, cyclodextrin-containing polymer that when mixed with siRNA self-assemble into nanoparticles with diameters of less than 100 nm that fully protect the siRNA from nuclease degradation in serum. Targeting ligands and stabilizers can be incorporated into the nanoparticles for organ-specific delivery of the siRNA. The siRNA delivery system has been designed for intravenous injection. Upon delivery to the target cell, the targeting ligand binds to membrane receptors on the cell surface and the RNA-containing nanoparticle is taken into the cell by endocytosis. There, chemistry built into the polymer allows to unpackage the siRNA from the delivery vehicle.

Nucleic acid-based therapies hold great promise for treating cancer. However, systemic delivery of nucleic acid-based therapeutics has proven difficult due to degradation in blood. Nanoparticle-mediated delivery strategies such as those used by Calando in the synthesis and formulation of CALAA-01 could make siRNA cancer therapies a reality.

Human Clinical Studies Using Two PET Imaging Agents - Caltech/UCLA CCNE: Caius Radu, Owen Witte, and Michael Phelps

[^{18}F]D-FAC (1-(2'-deoxy-2'-[18F] fluoroarabinofuranosyl) cytosine) and [^{18}F]L-FAC PET probes developed by the investigators have been approved for clinical studies. In parallel, application for the use of [^{18}F]L-FMAC ([^{18}F] fluoromethylallylcholine) in humans has also been submitted.

[^{18}F]FAC is a new PET probe that allows for visualization of thymus and spleen in mice and is sensitive to alterations in lymphoid mass and immune status. Studies in mice have shown that PET is useful to visualize immune responses and antitumor T cell responses. Other studies conducted in mice also showed that [^{18}F]FAC could be used to image murine models of leukemia, melanoma and glioma. [^{18}F]FAC microPET also detected early changes in lymphoid mass in systemic autoimmunity and allowed evaluation of immunosuppressive therapy. These data support the use of [^{18}F]FAC PET in a wide range of clinical applications towards cancer (*Radu et al., Nat. Med. 2008 Jul;14(7):783-8.*).

In current trial, the biodistribution of D-FAC and L-FAC probes is being determined in eight healthy volunteers. Recruitment of patients with autoimmune disorders as well as patients with lymphomas, pancreatic, and ovarian cancers is underway. The clinical research studies using the FAC family of molecular probes are carried out by Caius Radu, Owen Witte and Michael Phelps at UCLA in collaboration with Johannes Czernin there. The study is approved for maximum of 30 subjects.

[^{18}F]D-FAC, [^{18}F]L-FAC and [^{18}F]L-FMAC are produced using a microfluidic platform developed by Caltech/UCLA CCNE investigators (*Lee et al, Science 2005 Dec; 310(5575):1793-6*). Several generations of microfluidic chemical reaction circuits (CRCs) have been developed and a prototype has been licensed to Siemens.

Chemically-Engineered Adenovirus Nanoparticles (CAN) for Improved Immune Gene Therapy – UCSD CCNE: Thomas Kipps, Sadik Esener

An ongoing Phase I dose escalation study is evaluating chronic lymphocytic leukemia (CLL) patients who received direct intranodal injection of Ad-ISF35 (Immune Stimulatory Factor 35), an Ad5 (adenovirus 5) based vector that directs expression of a recombinant CD154 in transduced cells. Systemic clinical effects have been already observed following a single intranodal injection with significant reductions in leukemia cell counts and reductions in the size of all lymph nodes and spleen. Injections were well tolerated with grade 2 or less toxicity, generally lasting less than 48 hours after injection.

This clinical study is currently being modified by implementing targeting scheme, which should allow for injections containing smaller numbers of adenoviral carriers that preferentially target neoplastic cells. Direct chemical conjugation of araF-NAD+ via a PEG linker to free amino groups on the outside of the viral coat would allow for targeted delivery of the Ad5 virus via CD38+ CLL cells. The virus links to the CD38 on the surface of CLL cells or other tumors, from which the virus will be endocytosed to transfect the cell.

Kereos Clinical Trial on Nano-imaging Agent – Washington University CCNE: Samuel Wickline and Gregory Lanza

Kereos, Inc., founded by Washington University CCNE investigators Samuel Wickline and Gregory Lanza, is initiating Phase I clinical trials of its KI-0001 MRI agent in Australia. KI-0001 detects tumors by imaging angiogenesis via the $\alpha_v\beta_3$ integrin biomarker and can recognize tumors as small as 1-2 mm in size. KI-0001 may also prove useful in monitoring response to anti-angiogenic therapies. Kereos' proprietary ligand-targeted emulsion technology consists of a perfluorocarbon nanoparticle core

surrounded by a lipid monolayer. This lipid layer both stabilizes the particle and provides a virtually unlimited number of anchoring sites for targeting ligands and payload molecules. Water-insoluble payloads (lipophilic), such as chemotherapeutic agents, are incorporated into the lipid monolayer. The result is an oil-in-water emulsion of particles with an average size of approximately 250 nm. For KI-0001, $\alpha_v\beta_3$ is used as the targeting ligand and the gadolinium- tetraazacyclododecanetetraacetic acid (Gd-DOTA) complex, an imaging agent, is used as the payload.

Awarded IDE

In September 2007, the U.S. Food and Drug Administration cleared for marketing a new genetic test manufactured by Nanosphere Inc., founded by Northwestern CCNE investigator Chad Mirkin. The test will be used with the Verigene System, a clinical laboratory test system, to assess whether a patient may be especially sensitive to the drug warfarin (Coumadin). Warfarin is used to prevent potentially fatal clots in blood vessels. However, one-third of patients receiving warfarin experience a higher risk of bleeding. This increased risk of bleeding has been associated with variants of two genes, CYP2C9 and VKORC1. The Nanosphere Verigene Warfarin Metabolism Nucleic Acid Test detects some variants of both genes and is a significant advance in personalized medicine.

The test could be easily adapted to cancer diagnostics and treatment by substituting genetic sequences linked to cancer for the CYP2C9 and VKORC1 genes.

Pre-IND inquiries with FDA

- Kereos, Inc. is currently conducting pre-IND discussions with the FDA on KI-0001

- Avidimer Therapeutics, founded by University of Michigan CNPP investigator James Baker is also engaged in pre-IND discussions with the FDA. Avidimer's technology consists of a folic acid-targeted, surface-modified dendrimer which serves as a platform for targeted delivery of therapeutic or imaging agents. Currently, Avidimer is pursuing approval of a folic acid-targeted G5 polyamidoamine dendrimer coupled to anti-cancer agent methotrexate (MTX). Polyamidoamine (PAMAM) dendrimers are the most common class of dendrimers suitable for many materials science and biotechnology applications. PAMAM dendrimers are well-characterized, highly branched synthetic macromolecules that are biocompatible and nonimmunogenic. G5 PAMAM dendrimers contain, on average, 110 to 128 primary amines on their surface providing ample reactive sites for the conjugation of complex drug delivery systems and multiple chemical moieties. The high-affinity folic acid receptor is overexpressed in breast, ovary, endometrium, kidney, lung, head and neck, and brain cancers. Like many cancer chemotherapeutic agents, MTX is dose limited by side effects resulting from cytotoxicity that kills normal as well as tumor cells. Thus, by attaching both folic acid and MTX to the G5 PAMAM dendrimer the anti-cancer agent can be more effectively delivered to the tumor site.

- Miqin Zhang, a CNPP investigator at the University of Washington, has developed highly dispersed, stable iron oxide nanoparticles with amine functional groups allowing for conjugation of targeting ligands, and therapeutic and imaging agents. Zhang's group has demonstrated the ability of a nanoparticle with a model targeting ligand, chlorotoxin, to cross the blood-brain barrier in brain tumors in a genetically engineered mouse model. Subsequent, dual modality imaging with MRI and optical imaging was also demonstrated using these iron oxide particles. A pre-IND discussion with the FDA has taken place and process scale-up to produce sufficient quantities of therapeutic agent for toxicology studies is currently underway.

- Sanjiv Gambhir, Principal Investigator at the Stanford CCNE, has developed new instruments and strategies for photoacoustic molecular imaging using RGD-targeted carbon nanotubes (CNTs). Chronic toxicology studies of single wall CNTs have already been accomplished and published recently in mouse models showing the safety of intravenously administered CNTs. Discussions have begun with the FDA to guide this technology towards IND submission and utilization of targeted CNTs via colorectal delivery for colon cancer diagnosis applications.

Institutional Review Board (IRB) Approvals

To date, seventeen studies led by Alliance investigators have been approved by Institutional Review Boards (IRBs) which involve either human patients or human tissue samples. These studies are designed to test new tools, optimize strategies, identify side effects and determine efficacy and are listed in Table 1.

Table 1.

	IRB Protocol	ID Number	Institution	Investigator(s)
1	D-FAC:The biodistribution of 1-(2 deoxy-2,-^{18}fluoroarabinofuranosyl)cytosine (^{18}FAC) in healthy subjects and patients with cancer, autoimmune and inflammatory diseases	07-07-071-01	Caltech/ UCLA CCNE	Johannes Czernin
2	L-FAC: The biodistribution of 1-L-(2 deoxy-2,-^{18}fluoroarabinofuranosyl)cytosine ([^{18}F]L-FAC) in healthy subjects and patients with cancer, autoimmune and inflammatory diseases	08-02-049-01	Caltech/ UCLA CCNE	Johannes Czernin
3	Development of Microfluidics Integrated Nanoelectronic Sensor as a Diagnostic Tool for Pathologic Analysis of Cancer Tissue	05-10-062-03	Caltech/ UCLA CCNE	Paul Mischel
4	Use of conjugated nanoparticles to detect breast cancer biomarkers in archived breast cancer aspirates and corresponding surgical specimens	327-2005	Emory/ GT CCNE	Brian Leyland-Jones
5	Colon cancer tissue biomarker detection using IHC with nanocrystals	1115-2005	Emory/ GT CCNE	Brian Leyland-Jones
6	Multiplexed nanoparticle Raman tags for cancer immunohistochemical profiling	274-2005	Emory/ GT CCNE	Andrew Young
7	The Prostate Satellite Tissue Bank at Emory University	098-2004	Emory/ GT CCNE	Leland Chung
8	The Kidney Satellite Tissue Bank at Emory University	1214-2003	Emory/ GT CCNE	Andrew Young
9	Nanomaterials for cancer diagnostics and therapeutics	1567-004	Northwestern CCNE	Chad Mirkin
10	Development of barcode assays for the detection of ovarian cancer	1559-011	Northwestern CCNE	Chad Mirkin
11	Development of barcode assays for the detection of ovarian cancer and prostate cancer	1567-002	Northwestern CCNE	Chad Mirkin
12	Pre-screening breast carcinoma patients for imaging angiogenesis	08-0465	Washington University CCNE	Samuel Wickline
13	Prognostic markers in prostate cancer (PMPCA)	4453/CR0000 1953	Stanford CCNE	David Agus
14	Center for Cancer Nanotechnology Excellence focused on therapy response	5298	Stanford CCNE	Sanjiv Sam Gambhir
15	Detecting breast cancer cells with quantum dot spectroscopy from benign and malignant breast tissue	60683	UCSD CCNE	Andrew Kummel & Sarah Blair
16	CLL research consortium tissue core sample collection study	80915	UCSD CCNE	Thomas Kipps
17	Prostate fusion gene variants as a cancer biomarker	80096	UCSD CCNE	Xinjian Liu

Approved Animal Protocols

In addition to the approved protocols listed above in Table 1, Alliance investigators are also involved in numerous preclinical animal studies. Numerous Institutional Animal Care and Use Committee (IACUC) protocols developed by Alliance investigators have been approved for use (see Table 2). The breadth of new technology developments is areas of diagnostics, imaging and therapeutics is wide and these IACUC protocols will lay the foundation for future human clinical trials using nanotechnology to diagnosis, image and treat cancer in humans.

Table 2.

	IACUC Protocol	ID Number	Institution	Investigator(s)
1	Mechanisms regulating prostate growth, progression, and metastasis; Molecular imaging with quantum dots probing EMT and prostate cancer metastasis in live animals; and, Nanotechnology: Linking biomarkers with cancer behavior	022-2008	Emory/GT CCNE	Shuming Nie
2	Nanotherapeutics: Multifunctional nanoparticles for imaging, drug delivery and targeting	121-2008	Emory/GT CCNE	Dong Shin
3	Multifunctional nanoparticles for targeted imaging and therapy of human breast and pancreatic cancers	099-2005	Emory/GT CCNE	Dong Shin
4	Nanotherapeutics: multifunctional nanoparticles for drug delivery and targeting	210-2005	Emory/GT CCNE	Leland Chung
5	Evaluation of nucleic acid ligands for targeted diagnostic and therapeutic applications	0904-072-10	MIT/Harvard CCNE	Robert Langer
6	Transcription regulation by oncogenes and tumor suppressor genes	0905-064-08	MIT/Harvard CCNE	Phil Sharp
7	The pharmacokinetics of nanoparticles in animal models	0408-038-11	MIT/Harvard CCNE	Sangeeta Bhatia
8	Molecular analogy of immunological memory	0307-027-10	MIT/Harvard CCNE	Jianzhu Chen
9	Molecular imaging of solid tumors	2004N000283/3	MIT/Harvard CCNE	Ralph Weissleder
10	CLIO-based sensor implants	0107-008-10	MIT/Harvard CCNE	Michael Cima
11	Genome-wide scan for tumor suppressor genes	0601-046-10	MIT/Harvard CCNE	David Housman
12	Heating effect on tumor homing of peptide and peptide-conjugated nanoparticles	07-054	MIT/Harvard CCNE	Erkki Ruoslahti
13	Nanoscale encasement and targeted delivery of multifunctional therapeutic agents for hematologic cancer and solid tumors	2008-1297	Northwestern CCNE	Thomas O'Halloran
14	TiO2-DNA nanoparticles for prostate therapy	2007-1140	Northwestern CCNE	Gayle Woloschak
15	Multifunctional nanostructures for therapeutic targeting of breast cancer	2008-1292	Northwestern CCNE	Samuel Stupp
16	SCCNE-Project 3 acoustic nanobeacons for targeted detection and treatment of tumor angiogenesis	20080075	Washington University CCNE	Samuel Wickline

	IACUC Protocol	ID Number	Institution	Investigator(s)
17	Molecular imaging and therapy of solid tumors with a novel $\alpha_v\beta_3$-directed nanoparticle targeted to the neovasculature	20060284	Washington University CCNE	Gregory Lanza
18	Siteman Center of Cancer Nanotechnology Excellence - Small animal imaging core	200601106	Washington University CCNE	Jeffrey Arbeit
19	CCNE umbrella animal protocol	13826	Stanford CCNE	Sanjiv Sam Gambhir
20	Molecular pharmacology of cisplatin resistance	S05516	UCSD CCNE	Stephen Howell
21	Antitumor activity and pharmacokinetic studies of novel drug delivery systems in murine tumor models	S06026	UCSD CCNE	Stephen Howell
22	Pharmacology and toxicokinetic studies of a novel drug delivery system in rats	S07332	UCSD CCNE	Stephen Howell
23	Isolation and characterization of peptides homing to liver in mice	06-103	UCSD CCNE	Errki Ruoslahti
24	Targeting of nanoparticle-homing peptides conjugates to tumors	07-019	UCSD CCNE	Errki Ruoslahti
25	Breeding and maintenance of SR-A knockout mice	07-115	UCSD CCNE	Errki Ruoslahti
26	Targeting of nanoparticles to tumors and tumor treatment with drug loaded nanoparticles	08-011	UCSD CCNE	Errki Ruoslahti
27	Nanoparticles for tumor immunotherapy	S07128	UCSD CCNE	Sadik Esener
28	Pharmacological and efficacy study of nanoparticles in cancer therapy	S07388	UCSD CCNE	Sadik Esener
29	Molecular signaling pathways in vascular biology	S05018	UCSD CCNE	David Cheresh
30	Vascular responses during development, cancer, and metastasis	S06295	UCSD CCNE	David Cheresh
31	Optimal imaging parameters of contrast agents in mice	S00224	UCSD CCNE	Robert Mattrey
32	Small animal imaging core	08-040	UNC CCNE	Weili Lin
33	Mechanisms of epithelial cell tumorigenesis in the mouse	07-223	UNC CCNE	Terry Van Dyke
34	Pharmacokinetic studies of monodisperse, shape specific, biocompatible nanoparticles in mice	07-104.0	UNC CCNE	Joe DeSimone
35	Targeted delivery of therapeutic agents	08-198	UNC CCNE	Joe DeSimone
36	The role of p16INK4a in mammalian aging	05-228	UNC CCNE	Norman Sharpless
37	Photodestruction of ovarian cancer: ErbB3 targeted aptamer-nanoparticle conjugate	2005N000151/4	Massachusetts General Hospital Cancer Center	Tayyaba Hasan
38	Molecular MRI imaging of tumors	3441-05	University of Washington	Raymond Sze
39	Nanotechnology platform for pediatric brain cancer imaging	1637	Fred Hutchinson Cancer Research Center	James Olsen
40	Targeted therapy using imaging guidance	07-98-05234	M.D. Anderson Cancer Center	Chun Li
41	Targeted imaging and therapy	09-97-07434	M.D. Anderson Cancer Center	Chun Li
42	Investigation of the anti-tumor effects of conjugated metallofullerene nano-particles in rat malignant glioma model	AM10257	Virginia Commonwealth University	William Broaddus

Technology Transfer and SBIR Program

The Alliance and Technology Transfer – Participation in SBIR Program

The NCI Alliance for Nanotechnology in Cancer has played a vital role in attracting a number of high-quality research proposals to be funded through the Small Business Innovation Research (SBIR) 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 nanotechnology-related topics that have attracted submissions are:

- **Early Diagnostics Using Nanotechnology-Based Imaging and Sensing.** The goal is to develop nanotechnology-based devices with improved sensitivity and specificity for early detection and post-treatment monitoring of cancer signatures using genomic and proteomic means operating in both in vitro and in vivo environments (solicitation in 2007).

- **Multifunctional Therapeutics Based on Nanotechnology.** The goal is to develop an in vivo nanoparticle-based delivery platform with improved efficacy as compared to currently used treatments, and to incorporate an imaging agent to provide real-time feedback and monitoring of therapy (solicitations in 2007 and 2008).

- **Nanotechnology Imaging and Sensing Platforms for Improved Diagnosis of Cancer.** The goal is to develop nano-enabled platforms that can provide increased resolution both spatially and, more importantly, temporally in detecting cancer that would ultimately offer clinicians a way to maximize the chance of positive clinical prognosis. The platforms can be used for early detection/imaging of initial onset of disease, or be used as post-treatment monitoring to detect/image recurrence of disease (solicitation in 2008).

The SBIR program is divided into phases as follows:

- **Phase I - Feasibility Study.** A small business may submit a Phase I proposal in response to the topics published in an open NCI solicitation. A Phase I SBIR award is typically funded at $150,000 for a 6-month period to demonstrate the feasibility of a concept. The awarded companies also begin to pursue commitments for follow-on funding during this phase.

- **Phase II - Development.** Upon successful completion of a Phase I project, the program manager(s) may invite a company to submit a Phase II proposal for consideration. A Phase II proposal is more extensive than the Phase I proposal and should demonstrate the company's potential for rendering a product or process. Phase II proposals are typically funded at $750,000 for approximately 12-18 months.

U.S. Public Health Service (PHS) SBIR Solicitation (PHS 2007-1) received 13 Phase I applications. Four contracts were awarded for a total of approximately $600,000 from two topics, namely, Topic 240: Early Diagnostics Using Nanotechnology-Based Imaging and Sensing and Topic 241: Multifunctional Therapeutics Based on Nanotechnology. 4 companies have been awarded Phase I contracts:

- BIND Biosciences, Inc., PI: Jeff Hrkach, Ph.D.

- Liquidia Technologies, Inc., PI: Bolyn Hubby, Ph.D.

- MagArray, Inc., PI: Robert White, Ph.D.

- PDS Biotechnology Corp, PI: Frank Bedu-Addo, Ph.D.

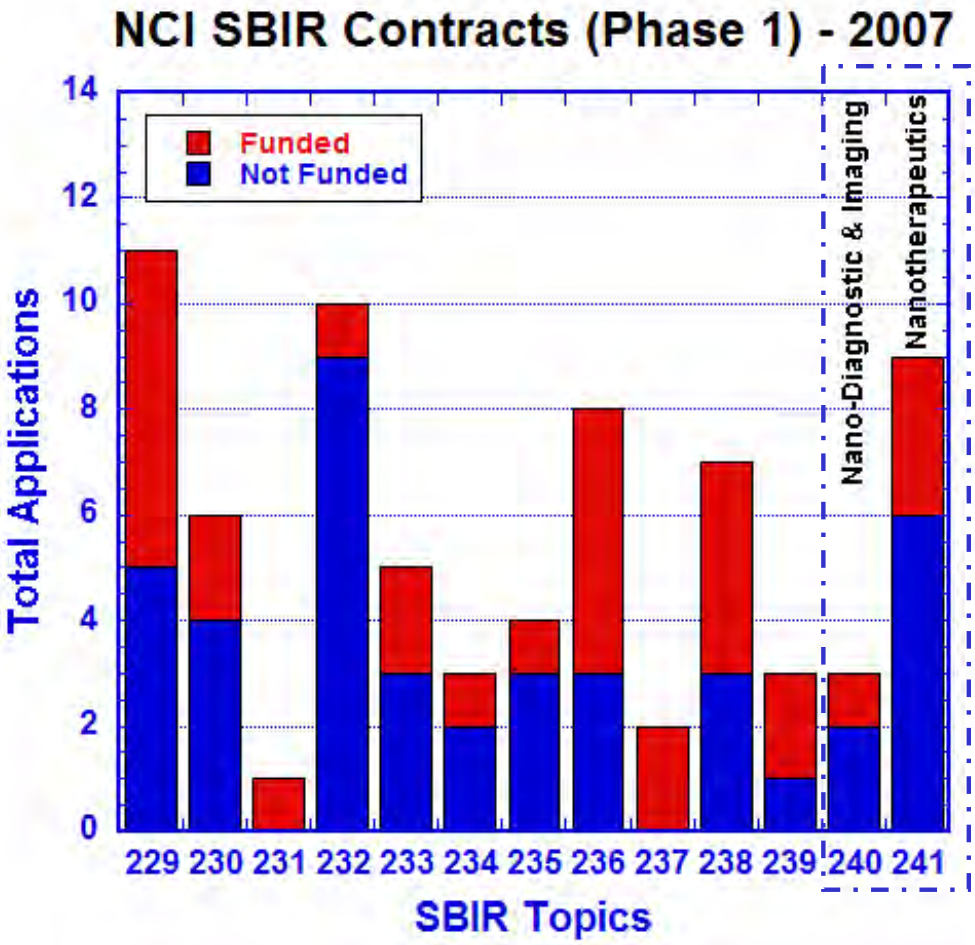
SBIR Solicitation (PHS 2008-1) has been recently announced for applications for two nanotechnology topics, namely, Topic 241: Multifunctional Therapeutics Based on Nanotechnology and Topic 252: Nanotechnology Imaging and Sensing Platforms for Improved Diagnosis of Cancer. Nanotherapeutics (241) received the *most* applications (13), while Nano-Diagnostics & Imaging *(252)* – tied 4th most

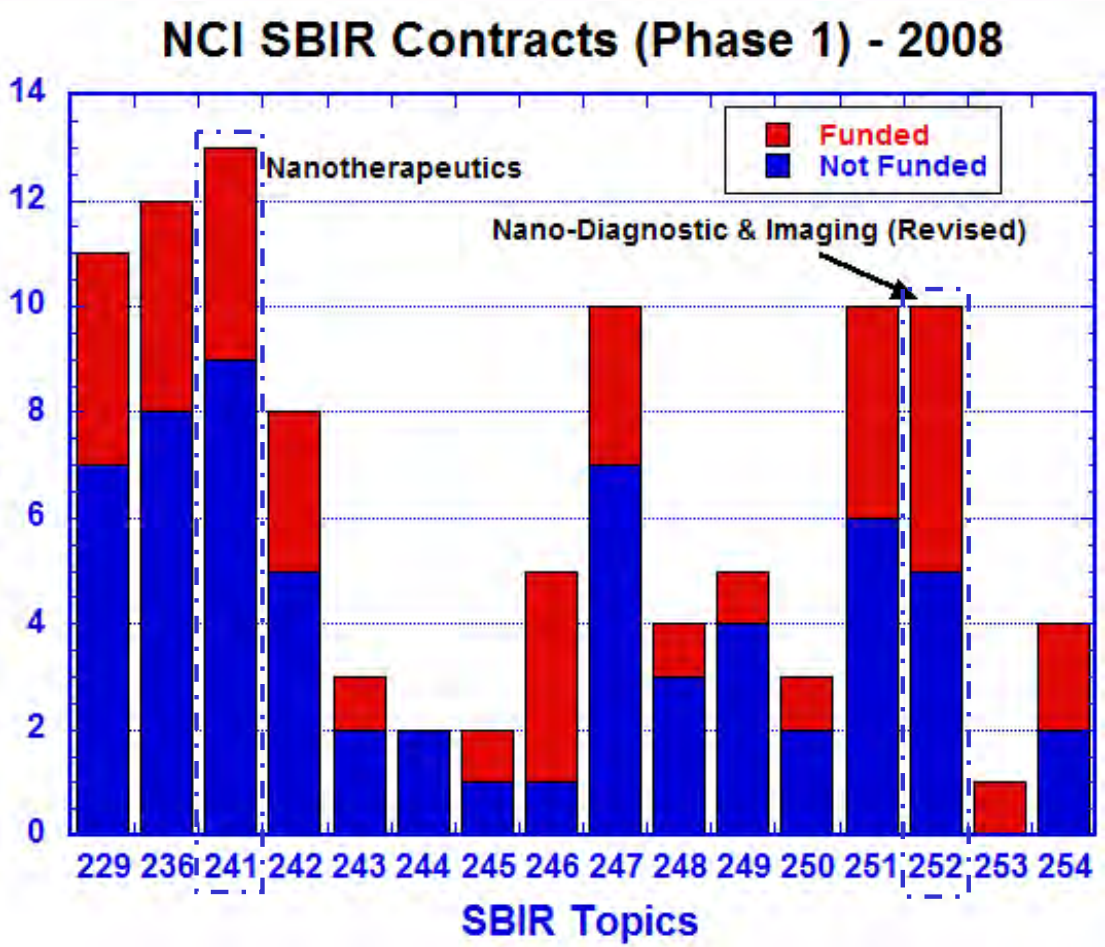
applications (10). These numbers indicate aggressively developing commercial landscape associated with cancer nanotechnology and strong interest of these companies in seeking funds from several different sources including SBIR.

We also anticipate that all companies funded last year as Phase I (see above) will be invited to submit Phase II applications.

Nanotechnology and SBIR Contracts (2007-2008)
High Number of Submitted and Funded Applications

NCI Alliance for Nanotechnology in Cancer





2007 – Nano-Topics (240 & 241) first introduced (Nanotherapeutics - 3rd most applications)

2008 – Nanotherapeutics (241) received the *most* applications,
Nano-Diagnostics & Imaging *revised (252)* – tied 4th most applications

List of Commercial Partnerships

Commercial Partnerships and Technology Start-ups

Several investigators funded through the program have strong entrepreneurial background and established many spin-off companies in last 3 years, while maintaining ties with other small and large for-profit entities. In total, 50 companies had relationships with the investigator laboratories, with 24 of them being established in last 3 years. These numbers speak to the initiative, productivity, and fund raising capabilities of the investigators involved in the program.

The following pages provide a listing of 50 companies associated with the program and brief origin of the technology, the founders, and technology/product focus. The map with geographic distribution of these companies follow.

	Company (Year Founded) Web Site	Alliance Affiliation Investigator(s)	Technology
1	Affinity Biosensors (2006)	MIT CNPP Scott Manalis	Diagnostics In vitro nanodiagnostics using a suspended microchannel resonator (SMR) to perform analysis on living individual cells
2	Alnylam Pharmaceuticals (2002) http://www.alnylam.com/	MIT/Harvard CCNE Philip Sharp	Therapeutics Novel therapeutics using liposomal-mediated delivery of siRNA and microRNA
3	American Bio-Optics (2006) http://www.americanbiooptics.com/	Northwestern CCNE Vadim Backman	Diagnostics Minimally-invasive optical diagnostics test using coherent backscattering spectroscopy to analyze how the reflected light interacts with the lining of the colon allowing for nanoscale characterization of cell architechture in order to identify patients at high risk for colon cancer
4	Avidimer Therapeutics (2003) http://www.avidimer.com/	Univ. of Michigan CNPP James Baker	Therapeutics Dual attachment anti-cancer drug and targeting moiety to the same nanoparticle via dendrimers for targeted drug delivery
5	B3 Biosciences (2007)	UNC & Stanford CCNEs Bruce Sullenger (UNC), Andy Ellington (Stanford)	Therapeutics Development of targeting strategies for siRNA therapeutics using aptamer-based moieties
6	BIND Biosciences (2006) http://www.bindbio.com/	MIT/Harvard CCNE Robert Langer, Omid Farokhzad	Therapeutics Therapeutic nanoparticles for the targeted intracellular delivery of large payloads of small molecules, nucleic acids, peptides and proteins
7	Calando Pharmaceutcals (2005) * http://www.calandopharma.com/	Caltech/UCLA CCNE Mark Davis	Therapeutics Cyclodextrin-based polymer nanoparticles for targeted delivery of siRNA
8	Calhoun Vision (1997) http://www.calhounvision.com	Caltech Robert Grubbs	Materials Light-inducible intraocular lenses based on a nanomaterial whose shape can be adjusted via light exposure
9	Carestream Health (2000)** http://www.carestreamhealth.com	Univ. of Texas CNPP Chun Li	Diagnostics Fluorescently-tagged nanoparticles for in vitro and in vivo imaging, including deep near IR penetration imaging in vivo

* Calando Pharmaceuticals and Insert Therapeutics have recently merged

** formerly the Health Group of the Eastman Kodak Company

	Company (Year Founded) Web Site	Alliance Affiliation Investigator(s)	Technology
10	Cell Ensemble (Recent) http://www.cellensemble.com/	Northwestern CCNE Bartosz Grzybowski	Diagnostics Combination of micropatterned substrates and surface chemistry to custom engineer cell shape or constrain cell motions to predetermined geometries for future anti-metastatic drug screening
11	Cell Fluidics (2008) http://www.momentum-biosciences.com/	Caltech/UCLA CCNE Hsian-Rong Tseng, Paul Mischel, James Heath	Diagnostics & Therapeutics Platform technology for personalized medicine in cancer diagnosis and therapy which integrates microfluidics with high resolution analysis of tumor cells isolated from clinical samples
12	Cellular Bioengineering (2003) http://www.cellularbioengineering.com/	UCSD CCNE Michael Sailor	Diagnostics Spectrally barcoded microparticles containing nanostructures that act as robust, non-toxic taggants for high throughput screening and encoded bead based assays
13	CytomX Therapeutics (2005) http://www.cytomx.com/	UCSD CCNE Patrick Daugherty	Diagnostics & Therapeutics Precise control of affinity, specificity and stability of peptide-based therapeutics, diagnostics, and reagents
14	Endra, Inc. (Recent)	Stanford CCNE Sanjiv Sam Gambhir	Diagnostics Photoacoustic imaging to monitor the therapeutics efficacy of oncology drugs on internal organs
15	Enlight Biosciences (2008) http://www.enlightbio.com/	Stanford CCNE Sanjiv Sam Gambhir	Technology Incubator Development of transformational enabling technologies in areas of highest potential impact within the drug discovery process. Emphasis is on technologies that strengthen the connection between preclinical research, clinical research, and point-of-care
16	GE Global Research http://www.ge.com/research/	Stanford CCNE	Diagnostics Superparamagnetic iron oxide (SPIO) nanoparticles with high-saturation magnetization and high permeability for use in magneto nano-sensors
17	Gensign (2007)	UCSD CCNE Dennis Carson, Yu-Tsueng Liu, Sadik Esener, Vineet Bafna	Diagnostics Nanodroplet reactor assay technology for in vitro diagnostics

	Company (Year Founded) Web Site	Alliance Affiliation Investigator(s)	Technology
18	Homestead Clinical http://www.homesteadclinical.com/	Caltech/UCLA CCNE James Heath	Diagnostics DNA-Encoded Antibody Library (DEAL) technology and nanosensors for high-throughput screening of thousands of proteins to predict and prevent disease and to predict how an individual patient will respond to a specific therapy
19	ImaginAb (2007) http://www.momentum-biosciences.com/	Stanford CCNE Robert Reiter, Anna Wu	Diagnostics Engineered antibody-based diagnostic imaging agents for improved diagnostic imaging
20	Insert Therapeutics (2000) * http://www.insertt.com/	Caltech/UCLA CCNE Mark Davis	Therapeutics Cyclodextrin-based polymer nanoparticles for targeted delivery of small molecule therapeutic products
21	Integrated Diagnostics (2008)	Caltech/UCLA CCNE Leroy Hood, James Heath	Diagnostics Organ-specific blood molecular protein fingerprints for diagnosis and the assessment of drugs in personal medicine model
22	Kereos (1999) http://www.kereos.com/	Washington Univ. CCNE Samuel Wickline, Gregory Lanza	Diagnostics & Therapeutics Ligand targeted emulsions containing perfluorocarbon nanoparticle cores for molecular imaging and targeted therapeutic delivery
23	Liquidia (2004) http://www.liquidia.com/	UNC CCNE Joseph DeSimone	Therapeutics Nanoparticles with precisely engineered shape, size, surface functionalization, and deformability for the delivery, controlled release, and enhanced efficacy of nanotechnology-based therapeutics
24	MagArray (2005)	Stanford CCNE Shan Wang	Diagnostics Molecular detection system based on magnetic nanotags (nanoparticles) and spin valve sensor arrays for rapid and portable DNA and protein fingerprinting
25	Materia (1998) http://www.materia-inc.com/	Caltech/UCLA CCNE Robert Grubbs	Materials Synthesis of new materials for the rapid construction of new nanotechnology-based pharmaceuticals and for use in microfluidic devices for the synthesis of radiopharmaceuticals

* Calando Pharmaceuticals and Insert Therapeutics have recently merged

	Company (Year Founded) Web Site	Alliance Affiliation Investigator(s)	Technology
26	MicroCHIPS, Inc. (2000) http://www.mchips.com/	MIT/Harvard CCNE Michael Cima, Robert Langer	Diagnostics & Therapeutics "Smart" implantable devices possessing controlled-release drug capabilities to create sophisticated therapy and monitoring systems
27	Molecular Biomarkers	Caltech/UCLA CCNE James Heath, Michael Phelps, Hsian-Rong Tseng	Technology Incubator Identify early stage technologies developed at the Alliance's Nanosystems Biology Cancer Center and technology transfer to nanotechnology start-up companies
28	Molecular Therapeutics	Roswell Park CNPP Raoul Kopelman	Diagnostics & Therapeutics Nanoparticle-based detection and therapy of brain cancer
29	Nanogen (1993) http://www.nanogen.com/	UCSD CCNE Sadik Esener	Diagnostics DNA hybridization arrays and molecular diagnostic kits and reagents for diagnostic applications
30	NanoInk http://www.nanoink.net	Northwestern CCNE Chad Mirkin	Materials Nanoscale manufacturing and application development for the life science and semiconductor industries using Dip Pen Nanolithography® and high-resolution NanoEncryption™ technology
21	Nanoparticle Biochem, Inc. (Recent) http://nanoparticlebiochem.com/	Univ. of Missouri CNPP Kattesh Katti	Diagnostics & Therapeutics Biocompatible nanoparticle production for tumor-specific diagnostic and therapeutic agents and antimicrobial agents
32	Nanosphere (2000) http://www.nanosphere-inc.com/	Northwestern CCNE Chad Mirkin	Diagnostics Nanotechnology-based molecular diagnostics capable of ultra-sensitive detection of nucleic acid and protein biomarkers using biobarcode technology
33	Nanovici *** http://www.nanovici.com/	Emory/GT CCNE Shuming Nie	Therapeutics Folate-targeted nanoparticles for therapeutic applications
34	Nodality http://www.nodalityinc.com/	Stanford CCNE Garry Nolan	Diagnostics & Therapeutics Technology platform for drug development including biomarker identification and analysis, drug discovery research and development, patient stratification, and monitoring the pharmacodynamics of therapeutics

*** Nanovici was recently acquired by Oncovista, Inc.

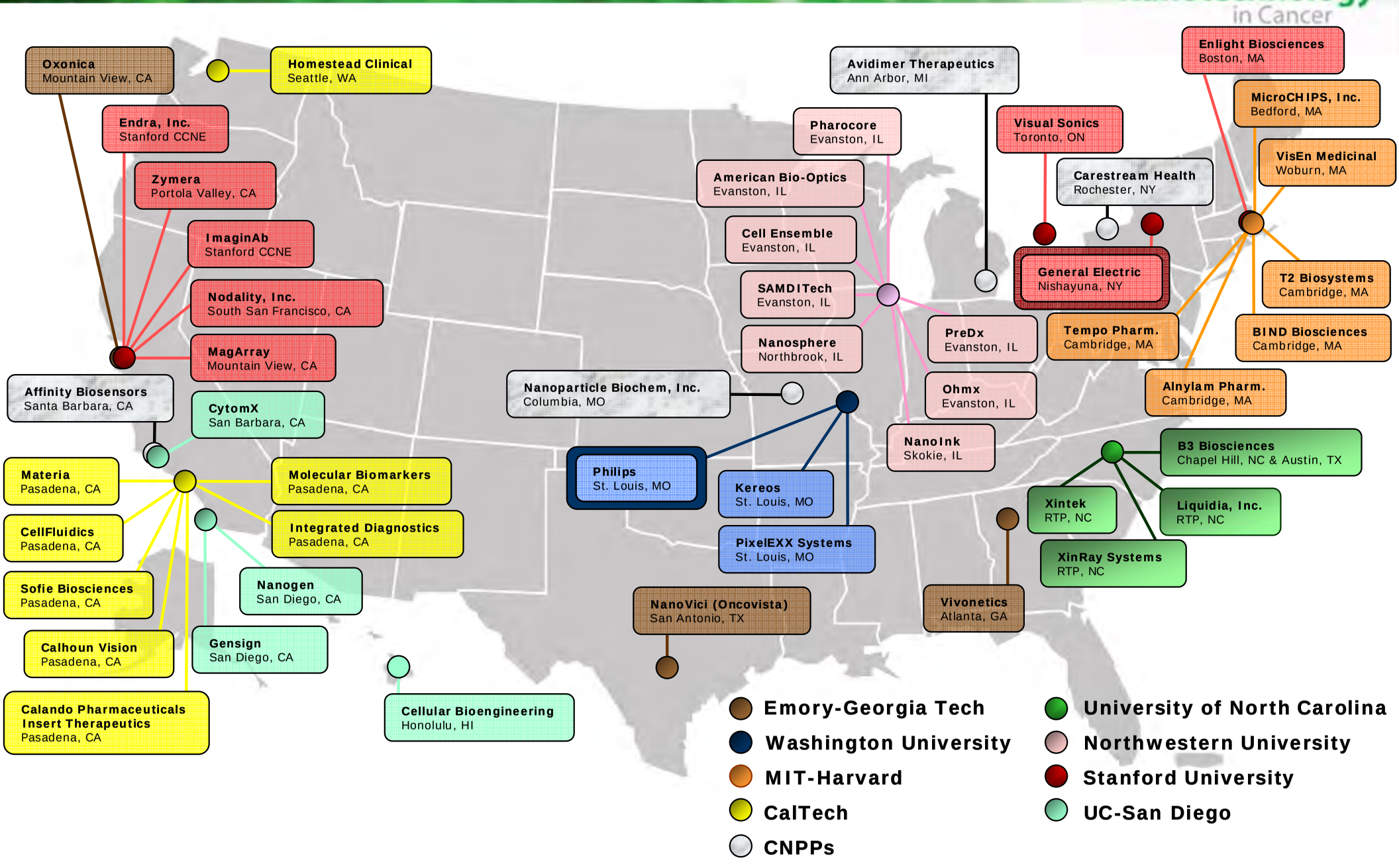
	Company (Year Founded) Web Site	Alliance Affiliation Investigator(s)	Technology
35	Ohmx (2005) http://www.ohmxbio.com/	Northwestern CCNE Thomas Meade	Diagnostics Protein detection micro-chips for a handheld point-of-care device
36	Oxonica (2002) http://www.oxonica.com/	Emory/GT CCNE Michael Natan	Diagnostics Manganese-doped titanium dioxide nanoparticle-based biomarker detection platform for ultrasensitive and simultaneous detection of multiple disease biomarkers
37	Pharocore (Recent)	Northwestern CCNE Chad Mirkin	Diagnostics & Therapeutics Nanoscale prisms for multiplex tagging of molecular entities and for use in diagnostic and therapeutic applications
38	Philips http://www.usa.philips.com/	Washington Univ. CCNE	Diagnostics High intensity focused ultrasound (HIFU) instrumentation for imaging of tumor angiogenesis and evaluation of anti-angiogenic therapies
39	PixelEXX Systems (2008) http://www.pixelexx.com/	Washington Univ. CCNE Samuel Wickline, Stuart Solin	Diagnostics Photoacoustic nanosensors to generate 3-dimensional maps of individual cancer cells for drug screening
40	PreDx (2006)	Northwestern CCNE Thomas Meade	Diagnostics & Therapeutics Bio-activatable magnetic resonance nanoparticle-based contrast agents for dual molecular imaging & targeted therapeutic applications
41	SAMDITech	Northwestern CCNE Milan Mrksich	Diagnostics High-throughput biomarker screening for in vitro nanodiagnostics using self-assembled monolayers that present biological functionality against a non-interacting background and matrix-assisted laser desorption-ionization mass spectroscopy
42	Sofie Biosciences (2008)	Caltech/UCLA CCNE Caius Radu, Owen Witte, Michael Phelps	Diagnostics Development of in vivo PET-based molecular imaging probes using microfluidics
43	T2 Biosystems (2006) http://www.t2biosystems.com/	MIT/Harvard CCNE Robert Weissleder, Robert Langer, Tyler Jacks	Diagnostics Magnetic nanoparticle assay technology for in vitro diagnostics

	Company (Year Founded) Web Site	Alliance Affiliation Investigator(s)	Technology
44	Tempo Pharmaceuticals (Recent) http://www.tempopharmaceuticals.com/	MIT/Harvard CCNE Robert Langer	Therapeutics Multi-compartmental, nanoparticle-based therapeutics for varied release rates within a single nanoparticle
45	VisEn Medicinal (2000) http://www.visenmedical.com/	MIT/Harvard CCNE Ralph Weissleder	Diagnostics Nanoparticles for fluorescence imaging applications
46	Visual Sonics (1999) http://www.visualsonics.com/	Stanford CCNE Sanjiv Sam Gambhir	Diagnostics High-resolution in vivo micro imaging systems devised specifically for non-invasive small animal research
47	Vivonetics (2002) http://www.vivonetics.com/	Emory/GT CCNE Gang Bao	Diagnostics Development of Fluorescence Resonance Energy Transfer (FRET) molecular beacons for in vitro nanodiagnostics
48	XinRay Systems (2007) http://www.xinraysystems.com/	UNC CCNE Otto Zhou	Diagnostics Joint venture between Siemens Medical Solutions and Xintek, Inc. to develop a carbon nanotube based medical CT scanner
49	Xintek, Inc. (2000) http://www.xintek.com/	UNC CCNE Otto Zhou	Diagnostics Carbon nanotube-based field emission technologies and products for diagnostic medical imaging, homeland security and information display
50	Zymera (2007) http://www.zymera.com/	Stanford CCNE Jianghong Rao, Sangeeta Bhatia, Sanjiv Sam Gambhir	Diagnostics Luminescent nanocrystal for clinical diagnostic applications

Geography of Commercial Partners

NCI Nanotechnology Alliance Commercial Partners

NCI Alliance for Nanotechnology in Cancer



Leveraged Funding

During the past 3 years, Alliance investigators have been very successful in utilizing NCI-funded nanotechnology work to leverage additional funds from various sources including Federal/State agencies, private foundations, and industrial partners. The listing which follows catalogs new and successfully renewed NIH awards won by CCNE and CNPP investigators as well as funding from other, non-NIH sources. This list is significant and ranges from small ~100K grants to large multi-million dollar donations.

Additional NIH Funding Raised by CCNEs

Grant Number	PI	Title	Start	Institute
CalTech/UCLA CCNE (PI: Heath)				
P50CA083636	**HOOD, LEROY**	Molecular Targets for Prognosis and Therapy	2008	NCI
P50CA086306	**RIBAS, ANTONI**	In Vivo Imaging of Antigen-Specific T Cells in Mice/Huma	2008	NCI
P50GM076547	**OZINSKY, ADRIAN**	Microfluidics Core	2008	NIGMS
P50CA086306	**HUANG, HENRY**	Quantitative Image Resource Core	2008	NCI
Emory-Georgia Tech CCNE (PI: Nie)				
P50CA128613	**SHIN, DONG**	SPORE in Head and Neck Cancer	2007	NCI
P20CA134223	**MELTZER, CAROLYN C. (Hui Mao/Lily Wang)**	Emory Molecular and Translational Imaging Center		
PN2EY018244	**BAO, GANG**	Nanomedicine Center for Nucleoprotein Machines	2006	NEI
R01CA133722	**YANG, LILY**	Targeted Nanoprobes For Intraoperative optical Imaging of Breast Cancer Margins	2008	NCI
R01AR052102	**BOYAN, BARBARA**	Mechanisms of Cell/Surface Interaction	2006	NIAMS
MIT/Harvard CCNE (PI: Langer)				
U54CA112967	**CHEN, JIANZHU**	RNA Interference	2007	NCI
P30CA014051	**CHEN, JIANZHU**	Flow Cytometry Core	2008	NCI
P01CA042063	**SHARP, PHILLIP**	Cancer and Gene Regulation by Short RNAs	2007	NCI
P01CA069246	**WEISSLEDER, RALPH**	Molecular Imaging of Delivery Cells (Neural Precursor and T Lymphocytes) and Targeting	2008	NCI
P01CA117969	**WEISSLEDER, RALPH**	Molecular Imaging Core	2008	NCI
R01AG029601	**HAMMOND, PAULA**	Nanoscale Electrostatic Assemblies for Multi-Agent Drug Delivery from Implant Surfaces	2007	NIA
T32CA079443	**WEISSLEDER, RALPH**	Training grant in Molecular Imaging Research	2006	NCI
Northwestern University CCNE (PI: Mirkin)				
P50NS054287	**KESSLER, JOHN (Meade/Stupp)**	Center of Excellence in Translational Human Stem Cell Research	2007	NINDS
P41RR008630	**IRVING, THOMAS (Woloschak)**	BioCAT - Biophysics Collaborative Access Team	2007	NCRR
R01GM084188	**MRKSICH, MILAN**	Peptide Arrays for Understanding Histone Biochemistry	2008	NIGMS
R01EB002100	**WOLOSCHAK, GAYLE**	Applications of TiO2-DNA nanocomposites	2005	NIBIB
R01GM073072	**SCHEIDT, KARL**	New Polarity Reversal Strategies for Organic Synthesis	2006	NIGMS

Grant Number	PI	Title	Start	Institute
Stanford University CCNE (PI: Gambhir)				
U54CA119367	**NOLAN, GARRY**	Multiparameter Nanoparticle Detection of Phosphoproteins	2008	NCI
P50CA114747	**GAMBHIR, SANJIV**	In Vivo Cellular and Molecualr Imaging Center@Stanford	2008	NCI
U01CA128427	**HANCOCK, WILLIAM (Samir Hanash)**	Glycan Markers For The Early Detection of Breast Cancer	2007	NCI
P01CA034233	**FELSHER, DEAN**	Immune Status and Tumor Regression Oncogene Inactivation	2008	NCI
R01CA135109	**DAI, HONGJIE**	Carbon Nanotubes as Multi-functional Spectroscopic Markers and Delivery Agents for Selective Cancer Cell Destruction	2008	NCI
R01CA119053	**CHEN, XIAOYUAN**	Radiolabeled RGD Peptides for Breast Cancer Imaging and Therapy	2007	NCI
N01WH74313	**LI, CHRISTOPHER (Samir Hanash)**	Identification and Validation of Circulating Biomarkers of the Early Detection of Breast Cancer in Pre-clinical Specimens	2007	NHLBI
R21CA133492	**DAI, HONGJIE**	Graphene-FeCo Nanocrystals for Highly Sensitive MRI, Cancer Imaging and Therapy	2008	NCI
R21NS059381	**JAIN, ANJALI**	Functional Genomics Tools for HER2 heterodimers and Androgen Receptor Signaling	2007	NINDS
R21CA121842	**CHEN, XIAOYUAN**	Quantum Dots for NIR Fluorescence Imaging of Tumor Angiogenesis	2007	NCI
UCSD CCNE (PI: Esener)				
P20CA134224	**MATTREY, ROBERT**	In Vivo Cellular and Molecular Imaging Centers (ICMICs)	2007	NCI
R01CA124427	**BHATIA, SANGEETA (Erkki Ruoslahti)**	Engineering Multifunctional Nanoparticles	2006	NCI
P01CA081534	**KIPPS, THOMAS**	Active Immune Therapy ot Leukemia Associated Antigens and Gene Therapy	2008	NCI
P01CA078045	**CHERESH, DAVID**	Small Molecules and Gene Delivery in Tumor Angiogenesis	2008	NCI
R21CA	**HELLER, MICHAEL**	R21 Grant		NCI
R21CA133634	**LIU, YU-TSUENG**	Prostate Fusion Gene Variants as a Cancer Biomarker	2008	NCI
R21CA129660	**CHERESH, DAVID**	Identification of Novel Pancreatic Cancer Biomarkers	2007	NCI
T32CA121938	**HOWELL, STEPHEN**	UCSD Cancer Center Training Program in Drug Development	2006	NCI
UNC CCNE (PI: Juliano)				
P01ES014635	**SHARPLESS, NORMAN**	Murine & Human In Vivo Models of Melanoma Formation	2008	NIEHS
R01CA126825	**CHO, MOO**	Systemic Delivery of CpG Oligonucleotides	2008	NCI
R01GM080981	**JULIANO, RUDOLPH**	Enhanced Delivery of Protein Biosensors: a Combinatorial Library Strategy	2007	NIGMS
R21CA118351	**CHANG, SHA**	Carbon Nanotube Field Emission Microbeam Array for Single Cell Irradiation	2006	NCI
R21CA128510	**CHANG, SHA**	Carbon nanotube field emission based x-ray pixel array micro-RT	2007	NCI

Washington University CCNE (PI: Wickline)				
Grant Number	**PI**	**Title**	**Start**	**Institute**
R01AR056468	**PHAM, CHRISTINE**	Targeted Nanotherapy in the Treatment of Inflammatory Arthritis	2008	NIAMS
R01EB008085	**WANG, LIHONG**	Recovery of Optical Absorption Coefficient in Quantitative Photoacoustic Imaging	2008	NIBIB
R01NS059302	**LANZA, GREGORY**	Fibrin-Specific Thrombolytic Nanoparticles for Acute Stroke	2007	NINDS
R01EB007276	**ACHILEFU, SAMUEL**	Near Infrared PH-Sensitive Molecular Probes for Microscopy of Cells and Tissues	2008	NIBIB
R21EY018914	**CHEN, JUNJIE**	MRI Biomarkers of Angiogenesis and Cell Injury in Retinopathy of Prematurity	2008	NEI
R21CA123537	**ACHILEFU, SAMUEL**	Multiphoton Microscopy Using Near Infrared Dyes	2006	NCI

Additional NIH Funding Raised by CNPPs

Grant Number	CNPP/PI	PI (of new awarded project)	Title	Start	Institute
1R01DK080477	Northeastern/Amiji	**AMIJI, MANSOOR**	Oral gene therapy with NiMOS for inflammatory bowel disease	2008	NIDDK
1S10RR023051	UCSF/Hanahan	**VANBROCKLIN, HENRY**	MicroPET/CT for small animal imaging	2007	NCRR
1R01CA135358	UCSF/Hanahan	**HE, JIANG**	Targeted liposomal radiotherapy of malignant mesothelioma	2008	NCI
5R21CA128460	Missouri/Katti	**KANNAN, RAGHURAMAN**	Targeted gold nanoparticle-bioconjugates for imaging breast cancer	2007	NCI
1T32EB004822	Missouri/Katti	**JURISSON, SILVIA**	Graduate training in radiopharmaceutical chemistry	2007	NIBIB
1R01GM085457	MIT/Manalis	**MANALIS, SCOTT**	High throughput monitoring of mass, density and fluorescence of single cells	2008	NIGMS
1R21EB008217			Mass-based flow cytometry	2008	NIBIB
1R01CA127369	RPCI/Oseroff	**PANDEY, RAVINDRA**	Multifunctional photosensitizers for image-guided PDT of brain tumors	2008	NCI
1R01EB007977	RPCI/Oseroff	**KOPELMAN, RAOUL (Univ. Michigan)**	Nanoparticle enabled intraoperative imaging and therapy	2007	NIBIB
4R33CA125297			Nanobiophotonics enabled tumor surgery and intraoperative PDT	2007	NCI
5R21CA111982	SUNY Buffalo/Prasad	**POMPER, MARTIN (JHU)**	PSMA-based PET ligands for prostate cancer imaging	2006	NCI
5R21CA114111			PSMA-based SPECT tracers for prostate cancer imaging	2006	NCI
5R01CA134213	U Washington/Zhang	**ZHANG, MIQIN**	Nanovectors for brain tumor diagnosis and treatment	2007	NCI
5R01EB006043			Multifuctional nanovector for diagnosis and treatment of pediatric brain cancer	2007	NIBIB
5R01GM075095			Microelectrode arrays of single cell biosensors	2006	NIGMS
1R01CA135491	U Washington/Zhang	**OLSON, JAMES**	Chlorotoxin as a targeting agent for cancer therapies	2008	NCI

Additional Other Funding Raised by the Alliance

CCNE	PI	Project Title	Sponsor
Caltech/UCLA	Lee Hood / James Heath	Innovation in the Areas of Molecular Biology, Systems Biology, and Personalized Medicine	Luxembourg Government
	James Heath	Nanowire-based Sensors, Devices and Applications	MITRE Corp.
	Clifton Shen/Mike van Dam	UC Discovery Grant - Prototypic robotic radiochemical synthesizer for routine PET tracer production & testing	State of California
	Anna Wu	Defining targets and biomarkers in prostate cancer stem cells: New Therapeutic Opportunities	Prostate Cancer Foundation (PCF)
	Anna Wu	Consortium for the development and analysis of relevant prostate cancer model systems	PCF
Emory/GT	Georgia Tech	Endowed chair in Cancer Nanotech	John & Mary Brock Foundation
	Emory	Endowed chair in Cancer Nanotech	John & Mary Brock Foundation
	Georgia Tech	Endowed chair in Cancer Nanomedicine	Gary Betty Foundation
Northwestern Univ.	Chad Mirkin	Research Instrumentation to Advance the Science and Technology Applications of Nanomaterials	State of Illinois
	Ronald Nayler	Institute for Proteomics and Nanobiotechnology at Northwestern University in Evanston, IL	NASA
	Vinayak Dravid	IDBR: Development of High Resolution Nano-Bio-Mechanical In-Vitro Imaging System	NSF
	Xu Li	Nanoparticle Contrast Agents for Enhanced Microwave Imaging and Thermal Treatment of Breast Cancer	USA MRMC
	Chad Mirkin	Lipid Dip-Pen Nanolithography of Model Bio-Membrane Systems	NSF
	Terri Wang Odom	Multi-scale Active Nanostructures; Arrays of Anisotropic Holes and Particles	NSF
	Chad Mirkin	Nanoprisms for Advanced Display	AFRL
	Lincoln Lauhon	Multifunctional Scanning Probe Instrumentation for the Investigation of Multifunctional Nanostructured Materials	ONR
	Vinayak Dravid	Materials World Network: Anisotropic Colloidal Magnetic Nanostructures with NT Bombay, India	NSF
	Thomas O'Halloran	Therapeutic Nanovessels for the Treatment and Imaging of Her2/Neu Positive Breast Cancers	USA MRMC
	Chad Mirkin	Development of a Nanoparticle-Based Ultrasensitive Panel Assay for Ovarian Cancer	ILDPH
	SonBinh Nguyen	A Reliable Strategy for Fabricating Highly Drug-Loaded Hollow Polymer Nanoparticles with Targeting Groups for Breast Cancer Therapy	ILDPH
	Northwestern CCNE	Development funds to the NU CCNE to support pilot research projects.	Nwestern U. Office of Research

CCNE	PI	Project Title	Sponsor
MIT/Harvard	MIT	Koch Institute for Integrative Cancer Research	David H. Koch
	Robert Langer / Omid Farokhzad	Targeted Nanoparticle Chemotherapy	Prostate Cancer Foundation Grant
Stanford Univ.	Stanford	The National Prostate Cancer Study	Redstone Foundation
	Sam Gambhir	Early Neoplasia Detection (END) Center at Stanford	Canary Foundation
	Shan Wang / robert White	Rapid Magnetic DNA and Protein Chip for Point of Care Molecular Diagnostics	NSF
	Shan Wang / Hendrik Ohldag	Room Temperature Spin Filter and Their Investigation with Synchrotron Radiation	DOE
	Tomczak, Ellington	Active Titanium Dioxide Nanoprobes as Biosensors for Detection and Diagnostics	NSF
	Sylvia Plevritis	Pilot: advance biocomputational aims for early detection of lung cancer	Canary Foundation
UCSD	Erkki Ruoslahti	Breast Cancer Research Program (BCRP) Innovator Award BC076050	DOD
	Erkki Ruoslahti	Armed Forces Institute for Regenerative Medicine	DOD
	Michael J. Sailor	Nitachi Chemical Research Center-UC Discovery Matching Program	Hitachi
	Howell/Trogler/Esener	DOD applications in ovarian cancer	DOD
UNC	Sha Chang	Research on the nanotechnology enabled IGRT system	Siemens Medical
	UNC CCNE	Purchase of inductively-coupled mass spectrometer	UCRF - N. Carolina
Washington Univ.	Megan Kaneda	Formulation and delivery of PFC particles bearing siRNA	AHA
	DipanJan Pan	New nanoparticle platforms for imaging of cardiovascular disease	AHA
	Tilmann Cyrus	New nanoparticle platforms for cardiovascular applications of PFC particles	AHA
	Jianjun Cheng (U. Illinois)	Development of Conjugated Polymer-Drug Nanoparticulate Delivery Vehicles	NSF
	Jianjun Cheng (U. Illinois)	Controlled Polymerization of Amino Acid N-Carboxyanhydrides	NSF
	Stuart Solin	Nanoscopic Metal-Semiconductor Hybrid Elements and Arrays	NSF
	Stuart Solin	Extraordinary Magnetoresistance Nanosensors: Fundamentals and Applications	UK EPSRC

Opportunities for Leveraged Funding

NCI Alliance for Nanotechnology in Cancer

CCNE funding has led to many new funding opportunities for the participants.
At MIT - gift from David Koch to build Institute for Integrative Cancer Research:

Koch made a $100 million gift to establish the David H. Koch Institute for Integrative Cancer Research and to build a $280 million state-of-the-art research facility. The new building will house faculty from 10 departments and Institutes and 4 hospitals.

The Koch Institute broke ground for the new building on March 7th, 2008.

Publications

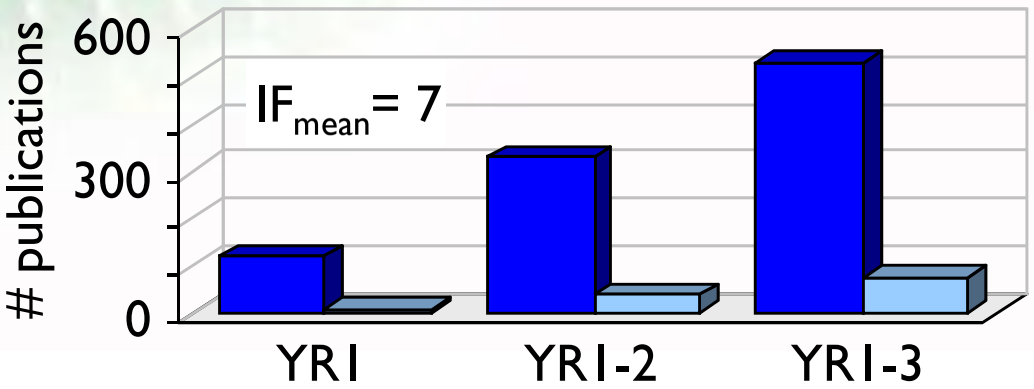
The Alliance investigators have been very prolific in publishing during the course of the program. After 3 years of the program 606 publications with average impact factor of 7 were published; 54 of these publications had impact factor above 15; an average of 5.8 publications were prepared per million dollars of funding. These statistics are gathered in the proceeding slide where breakdown among the centers (CCNEs) and platforms (CNPPs) is provided. CCNEs are more productive (per million dollar of funding) than CNPPs. This would support the notion of effectiveness of multidisciplinary team research.

Statistics - Summary

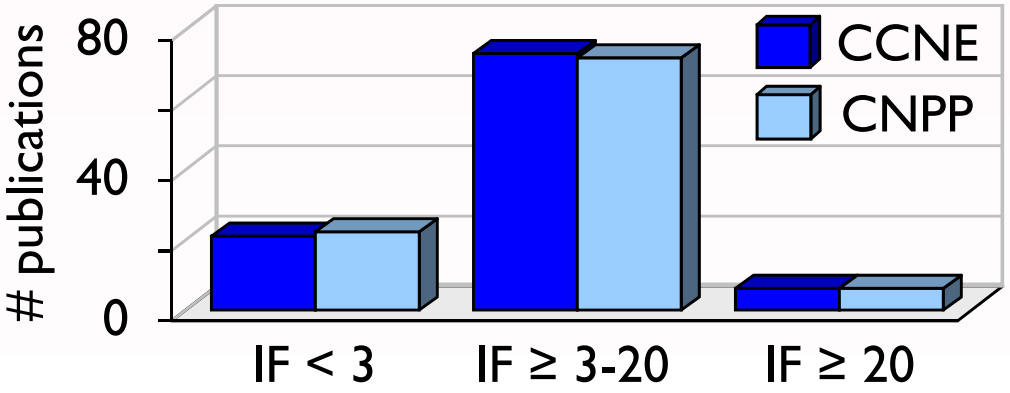
Scientific Accomplishments - Publications

NCI Alliance for Nanotechnology in Cancer

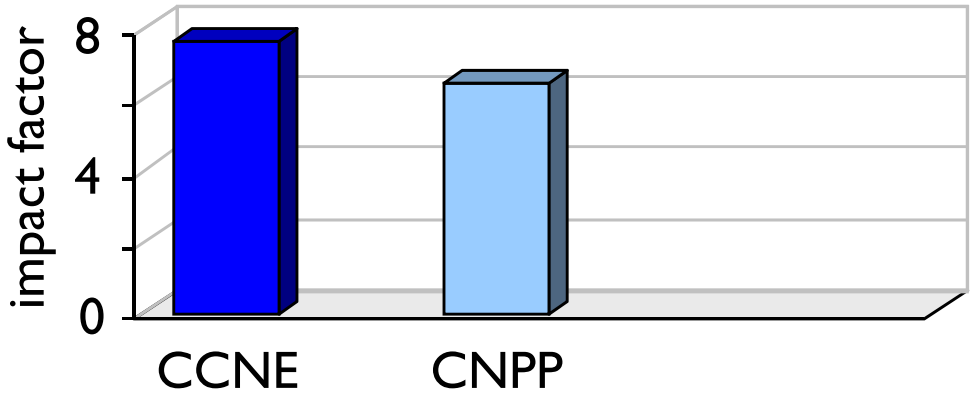
Cumulative Number of Publications



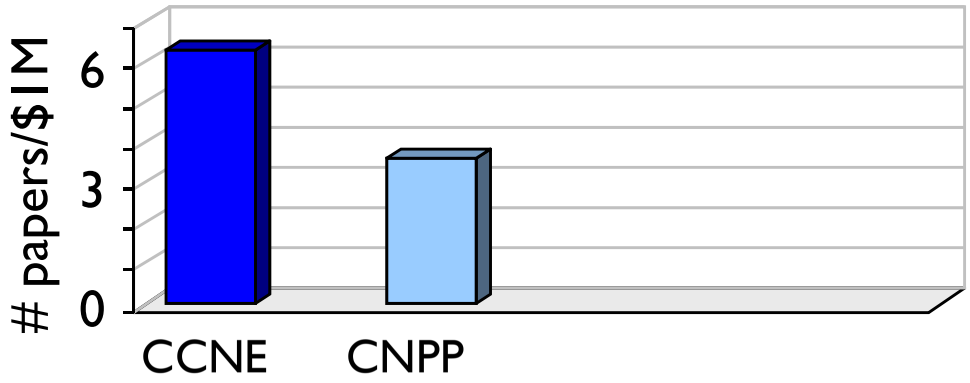
Publications' Impact Factor



Average Impact Factor



Average Number of Publications per Million Dollar of Funding



High Impact Factor Publications

Publications With Impact Factor Above 15

1. Lee, C. C., Sui, G., Elizarov, A., Shu, C. J., Shin, Y. S., Dooley, A. N., Huang, J., Daridon, A., Wyatt, P., Stout, D., Kolb, H. C., Witte, O. N., Satyamurthy, N., Heath, J. R., Phelps, M. E., Quake, S. R. and Tseng, H. R. Multistep Synthesis of a Radiolabeled Imaging Probe Using Integrated Microfluidics. **Science** *310,* 1793-6. Dec 16, **2005**. *Caltech/UCLA CCNE*

2. Lei, Q., Jiao, J., Xin, L., Chang, C. J., Wang, S., Gao, J., Gleave, M. E., Witte, O. N., Liu, X. and Wu, H. Nkx3.1 Stabilizes P53, Inhibits Akt Activation, and Blocks Prostate Cancer Initiation Caused by Pten Loss. **Cancer Cell** *9,* 367-78. May, **2006**. *Caltech/UCLA CCNE*

3. Shen, W. H., Balajee, A. S., Wang, J., Wu, H., Eng, C., Pandolfi, P. P. and Yin, Y. Essential Role for Nuclear Pten in Maintaining Chromosomal Integrity. **Cell** *128,* 157-70. Jan 12, **2007**. *Caltech/UCLA CCNE*

4. He, X. C., Yin, T., Grindley, J. C., Tian, Q., Sato, T., Tao, W. A., Dirisina, R., Porter-Westpfahl, K. S., Hembree, M., Johnson, T., Wiedemann, L. M., Barrett, T. A., Hood, L., Wu, H. and Li, L. Pten-Deficient Intestinal Stem Cells Initiate Intestinal Polyposis. **Nat Genet** *39,* 189-98. Feb, **2007**. *Caltech/UCLA CCNE*

5. Thomas, R. K., Baker, A. C., Debiasi, R. M., Winckler, W., Laframboise, T., Lin, W. M., Wang, M., Feng, W., Zander, T., MacConaill, L., Lee, J. C., Nicoletti, R., Hatton, C., Goyette, M., Girard, L., Majmudar, K., Ziaugra, L., Wong, K. K., Gabriel, S., Beroukhim, R., Peyton, M., Barretina, J., Dutt, A., Emery, C., Greulich, H., Shah, K., Sasaki, H., Gazdar, A., Minna, J., Armstrong, S. A., Mellinghoff, I. K., Hodi, F. S., Dranoff, G., Mischel, P. S., Cloughesy, T. F., Nelson, S. F., Liau, L. M., Mertz, K., Rubin, M. A., Moch, H., Loda, M., Catalona, W., Fletcher, J., Signoretti, S., Kaye, F., Anderson, K. C., Demetri, G. D., Dummer, R., Wagner, S., Herlyn, M., Sellers, W. R., Meyerson, M. and Garraway, L. A. High-Throughput Oncogene Mutation Profiling in Human Cancer. **Nat Genet** *39,* 347-51. Mar, **2007**. *Caltech/UCLA CCNE*

6. McAlpine, M. C., Ahmad, H., Wang, D. and Heath, J. R. Highly Ordered Nanowire Arrays on Plastic Substrates for Ultrasensitive Flexible Chemical Sensors. **Nat Mater** *6,* 379-84. May, **2007**. *Caltech/UCLA CCNE*

7. Berquin, I. M., Min, Y., Wu, R., Wu, J., Perry, D., Cline, J. M., Thomas, M. J., Thornburg, T., Kulik, G., Smith, A., Edwards, I. J., D'Agostino, R., Zhang, H., Wu, H., Kang, J. X. and Chen, Y. Q. Modulation of Prostate Cancer Genetic Risk by Omega-3 and Omega-6 Fatty Acids. **J Clin Invest** *117,* 1866-75. Jul, **2007**. *Caltech/UCLA CCNE*

8. Radu, C. G., Shu, C. J., Nair-Gill, E., Shelly, S. M., Barrio, J. R., Satyamurthy, N., Phelps, M. E. and Witte, O. N. Molecular Imaging of Lymphoid Organs and Immune Activation by Positron Emission Tomography with a New [18f]-Labeled 2'-Deoxycytidine Analog. **Nat Med** *14,* 783-8. Jul, **2008**. *Caltech/UCLA CCNE*

9. Wang, Z. L. and Song, J. Piezoelectric Nanogenerators Based on Zinc Oxide Nanowire Arrays. **Science** *312,* 242-6. Apr 14, **2006**. *Emory/GT CCNE*

10. Wang, X., Song, J., Liu, J. and Wang, Z. L. Direct-Current Nanogenerator Driven by Ultrasonic Waves. **Science** *316,* 102-5. Apr 6, **2007**. *Emory/GT CCNE*

11. Merrill, A. H., Jr., Wang, M. D., Park, M. and Sullards, M. C. (Glyco)Sphingolipidology: An Amazing Challenge and Opportunity for Systems Biology. **Trends Biochem Sci** *32,* 457-68. Oct, **2007**. *Emory/GT CCNE*

12. Qian, X., Peng, X. H., Ansari, D. O., Yin-Goen, Q., Chen, G. Z., Shin, D. M., Yang, L., Young, A. N., Wang, M. D. and Nie, S. In Vivo Tumor Targeting and Spectroscopic Detection with Surface-Enhanced Raman Nanoparticle Tags. **Nat Biotechnol** *26,* 83-90. Jan, **2008**. *Emory/GT CCNE*

13. Qin, Y., Wang, X. and Wang, Z. L. Microfibre-Nanowire Hybrid Structure for Energy Scavenging. **Nature** *451,* 809-13. Feb 14, **2008**. *Emory/GT CCNE*

14. Wang, X., Yang, L., Chen, Z. G. and Shin, D. M. Application of Nanotechnology in Cancer Therapy and Imaging. **CA Cancer J Clin** *58,* 97-110. Mar-Apr, **2008**. *Emory/GT CCNE*

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16. Tannous, B. A., Grimm, J., Perry, K. F., Chen, J. W., Weissleder, R. and Breakefield, X. O. Metabolic Biotinylation of Cell Surface Receptors for in Vivo Imaging. **Nat Methods** *3,* 391-6. May, **2006**. *MIT/Harvard CCNE*

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18. Swirski, F. K., Libby, P., Aikawa, E., Alcaide, P., Luscinskas, F. W., Weissleder, R. and Pittet, M. J. Ly-6chi Monocytes Dominate Hypercholesterolemia-Associated Monocytosis and Give Rise to Macrophages in Atheromata. **J Clin Invest** *117,* 195-205. Jan, **2007**. *MIT/Harvard CCNE*

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All Publications

Publications List

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