

Alliance for Nanotechnology in Cancer

Program assessment

Bibliometric and portfolio analysis

Interviews

Request for Information outcomes

Executive Summary

The National Cancer Institute (NCI) Alliance for Nanotechnology in Cancer (Alliance) program has promoted cross-disciplinary and collaborative research to develop nanotechnologies for improving cancer interventions. In its third year, Phase 2 of the Alliance program was evaluated both qualitatively and quantitatively to determine the productivity, efficiency, collaboration, interdisciplinarity, research focus and specialization and innovation. Overall the evaluation has found that the year three milestones as described in the Program Book as well as many goals as described by the program's RFAs have been met.

The evaluation was performed as a combined effort between the NCI Office of Science Planning and Assessment (OSPA) and the Office of Cancer Nanotechnology Research (OCNR) in support of the request for program reissuance. The evaluation focused on Phase II of the program (2010 to present) and was comprised of bibliometric analysis, portfolio analysis, a Request for Information, and phone interviews with experts in the field.

Some of the key findings in this report include:

- 1) The data indicate that although there is a growing proportion of NCI applications to the Parent R01 Program Announcement that are integrating nanotechnology into their research plans, they persistently score lower and are less likely to be funded than non-nanotechnology applications. This would indicate a persistent gap in NCI funding in the RPG pool supporting nanotechnology.
- 2) There are data that indicate the need for cancer nanotechnology training centers is largely fulfilled by the presence of the Alliance Training Centers. However, considering the impact and successes demonstrated by the Training Center program in the bibliometric section, it is clear that these models serve as a powerful nexus of interdisciplinary scientist training.
- 3) The scientific output of the Centers was very strong, especially when considered a metric that integrates the cost per publication and citation at a grant level. Also, when these publications were categorized into research or clinical subcategories, it is evident that the research generated by the Alliance is meeting a majority of the goals for the field that were outlined in the 2010 caNanoPlan, as well as achieving the goal of translating these discoveries into the clinical arena.
- 4) Key personnel of the Centers have become more multidisciplinary. The Alliance is comprised of researchers who were typically either dominant in nanotechnology research or in biomedical cancer research. As a result of being a part of the Alliance the publication record of personnel with either background has become more multidisciplinary. This also means the cancer research field has gained researchers from engineering and basic nanotechnology fields as well as expanded the scope of research performed by scientists traditionally funded by the NCI.
- 5) Interviews with nine leading members in the field of cancer nanotechnology, including six who have not been funded through the program, indicate that scientific community views

Alliance Program as very beneficial to the advancement of cancer nanotechnology research. The interviews also offered great insight into some of the barriers to the translation of nanotechnology into clinical applications.

- 6) A Request for Information was issued to allow for a wider portion of the scientific community to submit their thoughts on the Alliance and the cancer nanotechnology field as well. They provided opinions on the progress of the field, barriers slowing its progress, and desirable future formats for the program. They also provided their thoughts on both training and commercial development in the field.

Overall Phase II of the Alliance for Nanotechnology in Cancer has been very successful in meeting or exceeding its goals in the areas outlined in the caNanoPlan as well as in the translation of technologies to the clinic. However, the central aspects of this success were accomplished through the support of large, multidisciplinary groups as well as networks among researchers in the field. When compared to the other nanotechnology supported in the NCI, it is clear that this type of specialized funding is beneficial to the research community and progress in the field. A third round of the program would enable further discoveries and maturation of the knowledgebase in nanomaterials and nano-devices and will strengthen transitioning of nanotechnologies to the clinical environment.

Introduction

The NCI Alliance for Nanotechnology in Cancer was established in 2004. The research pillars of the Alliance are the Centers of Cancer Nanotechnology Excellence (Centers, U54). Eight Centers were funded in the first phase of the Alliance from fiscal year 2005-2009, and a second round of five year awards was made in fiscal year 2010 (Full list in Appendix A). Five Centers were funded in both rounds. The combined total cost for the nine Phase II Centers was approximately \$24M in FY2013. This is the largest part of the Alliance's approximately \$32 million budget. In addition to nine Centers, the OCNR awarded 25 other grants and cooperative agreements (12 U01-Platforms, 6 R25-Training Centers, and 7 K99/R00s; full list in Appendix A) in the second Phase of Alliance funding.

From a historical perspective, the essence of the two Phases of Center funding is the same: multidisciplinary integration of multiple projects and cores toward using nanotechnology to improve cancer interventions. The second Phase RFA was not for competing continuation/renewals; all applicants were weighted on the merit of their new application with programmatic input regarding portfolio gaps.

The overall goal of the Alliance Program is to develop new biomedical nanotechnology and accelerate its integration into cancer-relevant applications. The Centers are responsible for the majority of this effort and are charged with translating their research into clinical practice. In addition, the Centers are meant to be models for interdisciplinary, transformative biomedical research groups where the scientific and social interactions engendered by the center-based structure leads to greater innovation than comparable individual awards. The Center program goals, adapted from the RFA CA-09-012, that are relevant to this evaluation are:

- To form efficient, collaborative networks of cancer nanotechnology research and development within each center and with other Alliance awards.
- To develop research capabilities and programs enabling multidisciplinary team research advancing cancer prevention, detection, diagnosis, and/or treatment.
- To achieve a high level of innovative scientific output.

Data Gathering Methodologies

Publications and Citations:

In order to compile a comprehensive publication database, PubMed was searched using the grant codes for each award of the Alliance and then each yearly and interim progress report was reviewed for publications which were not found in PubMed. All publications were assigned an award number and if more than one Alliance grantee reported the same publication due to collaborations then the publication was assigned all award numbers associated with it. The database is kept in EndNote and then exported to MS Excel for manipulation and analysis as well as for importing the dataset into other programs for further analysis. Using Scopus, the PMIDs of Alliance publications were used to retrieve citation and scientific topical focus

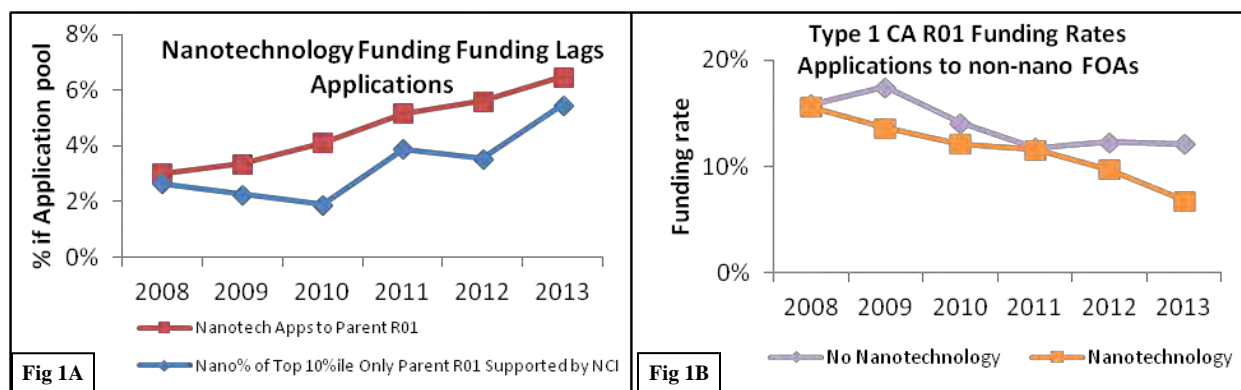
information. When a publication could not be found in Scopus, citation information was retrieved manually using Google Scholar.

Control groups were determined as follows: “Top 10 percentile type 1 R01” applications and “all type 1 Parent R01 FOA” applications to NCI for FYs 2008-2013 were retrieved using QVR via standard methods. These applications were assigned a nanotechnology label by searching for the wildcard term “nano*” in the application’s title, abstract, FOA, and RCDC terms. The resulting pool was manually screened to remove false positives (terms like “nanog” or “nanomolar”). Grant numbers were used to search PubMed and citation information was retrieved using Scopus. Total citations were estimated by multiplying Scopus-retrieved citations by the fraction of PubMed/Scopus found publications to compensate for papers not indexed in Scopus. “Most-funded NCI investigators” were determined using NIH Project Reporter to identify scientists with the highest number of NCI awards; publication and citation data were retrieved as above. Grant numbers for other center awards (ICMIC, ICBP, NDC, Alliance associated Cancer Centers, NHLBI PEN) were used to retrieve publication and citation data as above. Impact Efficiency was determined for Alliance awards and controls using formula described in the text.

I – Quantitative Portfolio and Bibliometric Analyses

Nanotechnology Research Project Funding

Nanotechnology, as a research theme, has steadily grown in its proportion of NCI applicants to the Parent R01. Searching abstracts and Research, Condition and Disease Categorization (RCDC) terms for all type 1 R01 applications to the Parent R01 FOA from 2008-2013, while excluding those for nanotechnology-specific FOAs, nanotechnology themed applications more than doubled (from 3.0% to 6.5%; Red line, Figure 1A).



Interestingly, while nanotechnology-themed applications are on the rise in the NCI R01 pool, scoring for these applications still lags behind that of the overall NCI R01 application pool. In Figure 1A, the blue line represents the percentage of Parent R01 FOA applications that scored in the top 10% that were nanotechnology-themed. While this proportion has also increased from 2.7% to 5.5% from 2008-2013, indicating growing acceptance of highly innovative nanotechnologies into biomedical research, it has grown slower than the increase in the proportion of nanotechnology-themed Parent R01 applications. Furthermore, examining the

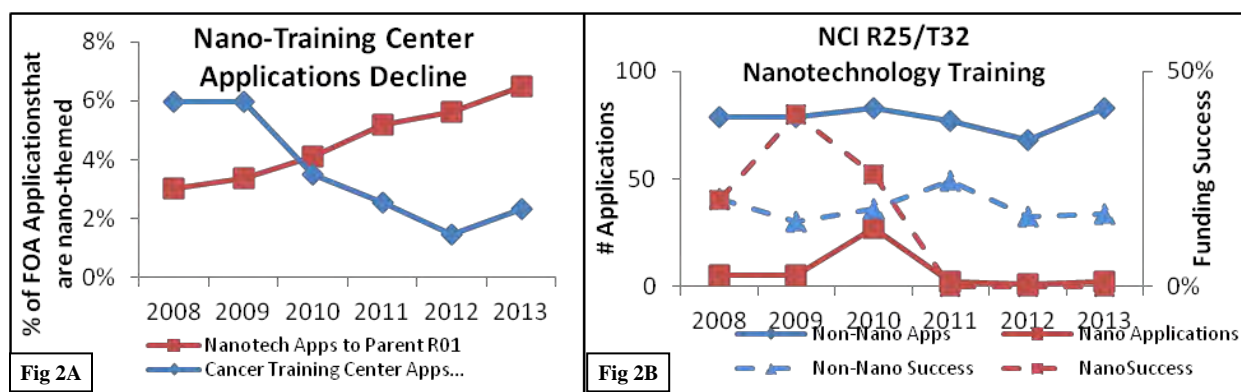
funding rates of nanotechnology-themed applications to the Parent R01 reveals a persistently lower likelihood of funding as compared to the non-nanotechnology applicant pool (Figure 1B).

Overall, these data indicate a growing pool of applicants that are integrating nanotechnology into their research plans, yet a persistent lower scoring and funding rate for these applications. This would indicate a persistent gap in NCI funding in the RPG pool supporting nanotechnology.

Nanotechnology Training Center Funding

For the future of nanotechnology integration into the biomedical research continuum, it is essential to train young researchers to meld the techniques associated with these distinct fields. An examination of all NCI applications to T32 or R25 training center FOAs demonstrates, prior to the RFAs for the second Phase of the Alliance in 2009, around 6% of these applications were nanotechnology in theme (Figure 2A). However, even as nano-themed R01 applications exhibit strong growth, after the Alliance was funded the proportion of new nanotechnology training center applications has steadily declined down to 2% of the 2013 applications. Furthermore, the funding success of these proposed training centers, after a peak in 2010 as six Alliance Training Centers were awarded, has dropped to zero since 2011 while non-nano NCI training centers have steadily been funded at around 20% (Fig 2B). Currently, there are only two active NCI nanotechnology training center grants outside of those funded through the Alliance.

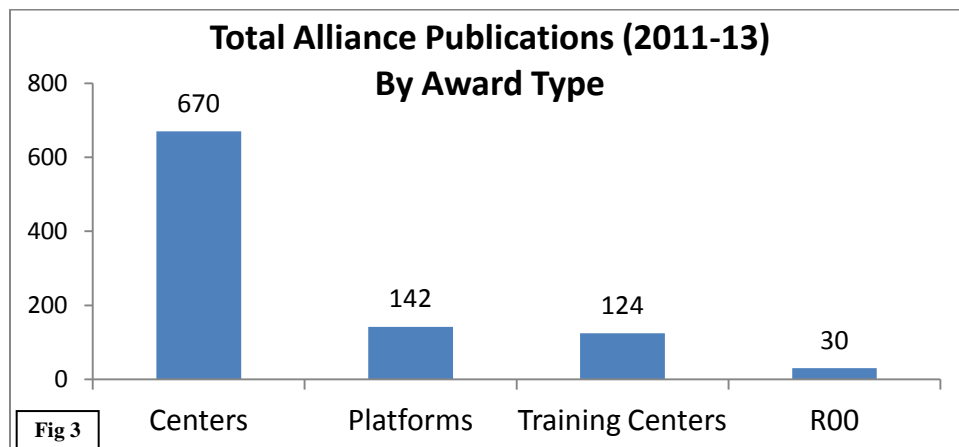
This may indicate that the need for cancer nanotechnology training centers is fulfilled by the presence of the Alliance Training Centers. However, considering the impact and successes demonstrated by the Alliance Training Center program in the bibliometric section of this review, it is clear that these center models serve as powerful nexuses of interdisciplinary scientist training. Additionally, it is important to note that of the 24 Alliance Training Center applicants, only one had applied for an NCI training center previously (data not shown) demonstrating the success of the RFA in bringing new leading investigators to the field.



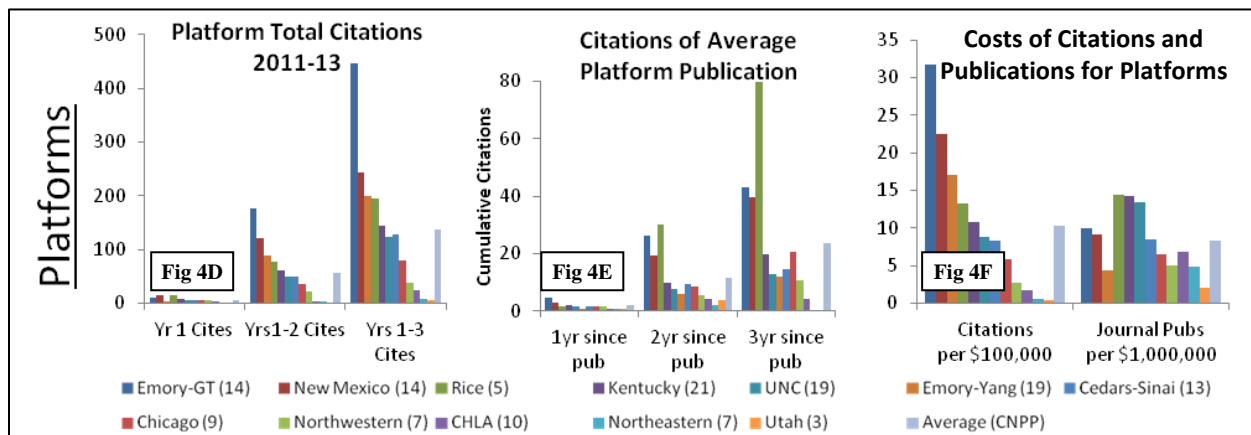
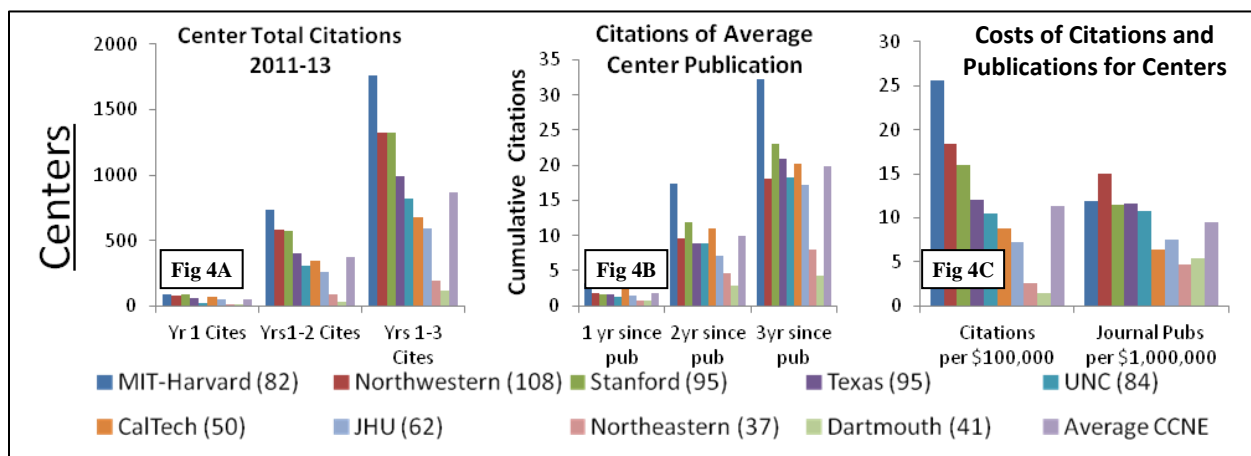
Publications and Citation Analysis:

In the first three years of Phase 2, the Alliance published nearly one thousand research papers and review articles. There was great variability in productivity between awards: nine Centers published 42-101 papers each, the twelve Platforms produced from 4 to 21 each, the six

Training Centers from 7 to 47 papers, and the seven R00 recipients wrote between 0 and 17 papers (Figure 3).



How frequently a publication is cited in the scientific literature gives an estimate of its impact on its respective field(s). Figures 4A and 4D show the cumulative total citations of all publications attributed to each award, Centers and Platforms respectively, in their first three years. These charts mimic the variability of publication quantity between awards of similar mechanisms; here the MIT/Harvard Center and Emory-Georgia Tech Platform stand out.

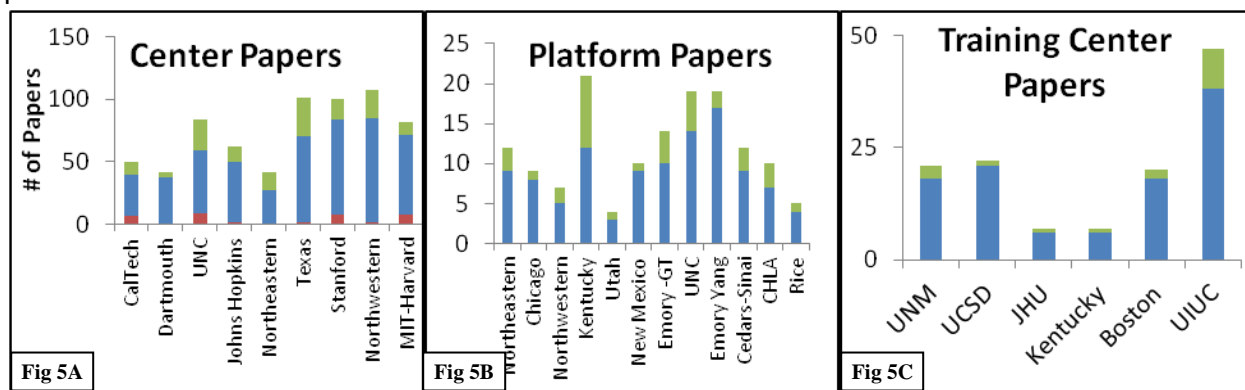


However, when one looks at the quality of individual papers, the results diversify. In Figures 4B and 4E citations were measured according to how long a paper had been published and averaged by the number of papers that had been published for a given period. This produces an average citation accumulation for an average publication from each award. Here the MIT/Harvard Center and Rice Platform stand out as producing individual papers of the highest average impact.

Figures 4C and 4F normalize citation and publication counts according to the cost of the awards over the three years of production. Denominator amounts, Citations/\$100,000 and Publications/\$1 million, were chosen as they averaged ~10 when applied across the Alliance.

Publication Topic Analysis

Every article from the Alliance was assigned to one of three main categories: Basic or Pre-Clinical, Clinical, and Review/Perspective/Opinion (Figure 5A-C). In the first three years of Phase 2 of the Alliance, 670 papers were published by the Centers. This group of publications includes 486 Basic/pre-clinical papers, 146 Review papers and 38 papers categorized as Clinical, a notable amount considering the Alliance does not fund clinical trials (Figure 5A). There were 142 papers published by the Platforms with 107 Basic/pre-clinical papers and 35 Review papers (Figure 5B). The Training Centers published 124 papers, with 107 Basic/pre-clinical and 17 Review papers (Figure 5C). Notably, only the Centers produced Clinical publications.

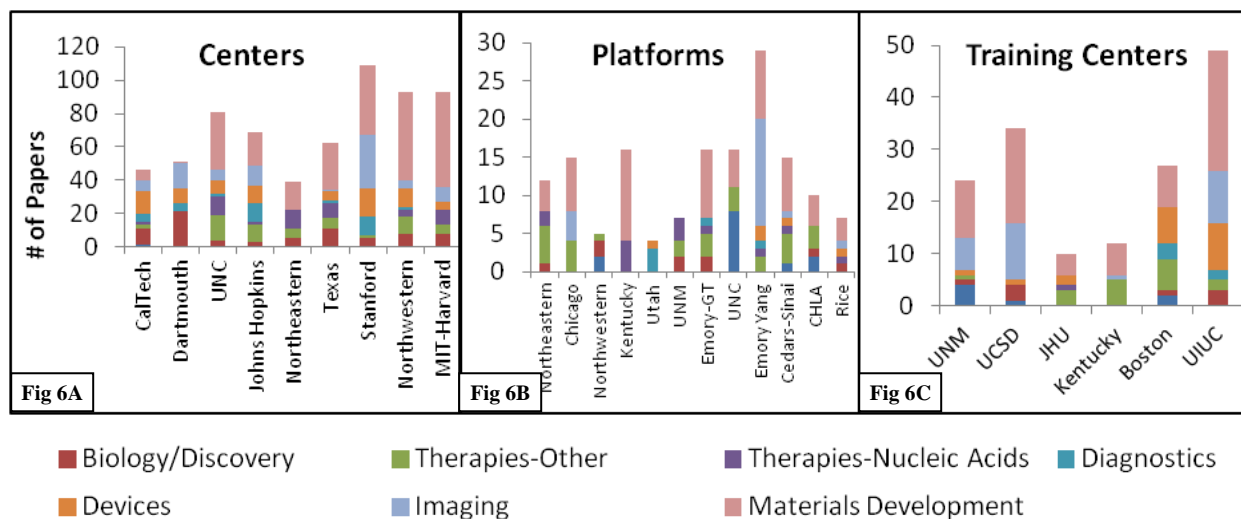


■ Clinical ■ Basic or Pre-Clinical ■ Review/Perspective/Opinion

Papers describing clinical trials, work with clinical samples or Good Laboratory Practices (GLP) and pre-Investigational New Drug (IND) studies were considered “Clinical.” Other papers, including those detailing biodistribution, pharmacokinetics/pharmacodynamics (PK/PD) or toxicity work in animals were considered “Basic or Pre-Clinical.”

Papers were also sorted into the following sub-categories to identify their topical area of focus: Biology/Discovery, Therapies-Drug, Therapies-Nucleic Acids, Therapies-Other, Diagnostics, Devices, Imaging, or Materials Development. Papers could be assigned only one main category but could be labeled with more than one sub-category.

The "Biology/Discovery" label refers to biological research including target and biomarker identification, epidemiological studies and studies of cell mechanics and chemistry. When the development of a vehicle was detailed for delivery of specific drugs or for nucleic acids, the categories "Therapies - Drugs" or "Therapies - Nucleic acids" were used. The "Therapies-Other" label refers to work on delivery vehicles for which cargo was unspecified or to work on therapeutic modalities besides drug or nucleic acid delivery (e.g. hyperthermia). The "Diagnostics" label was used for work in which a diagnostic or prognostic application was outlined or tested. This work is in almost all cases device based, although some materials development is included. The "Devices" label was used for work on instrumentation microfluidics, implantable and *in vitro* diagnostic devices. If the device was developed towards a particular end, such as imaging or diagnostics, the work was also categorized as such. The "Imaging" label refers to work on contrast agents, development of new imaging modalities, and software or algorithm development. Typically, additional labeling as "Diagnostics" was not added, although this application of the work can be generally assumed. The "Materials" label was used for work on materials development and characterization, such as physico-chemical characterization and studies of biological interactions with the materials, including biodistribution and PK/PD. If a particular application for a material is tested in the work, such as use in a device or as an imaging or therapeutic agent, the work was also categorized as such.

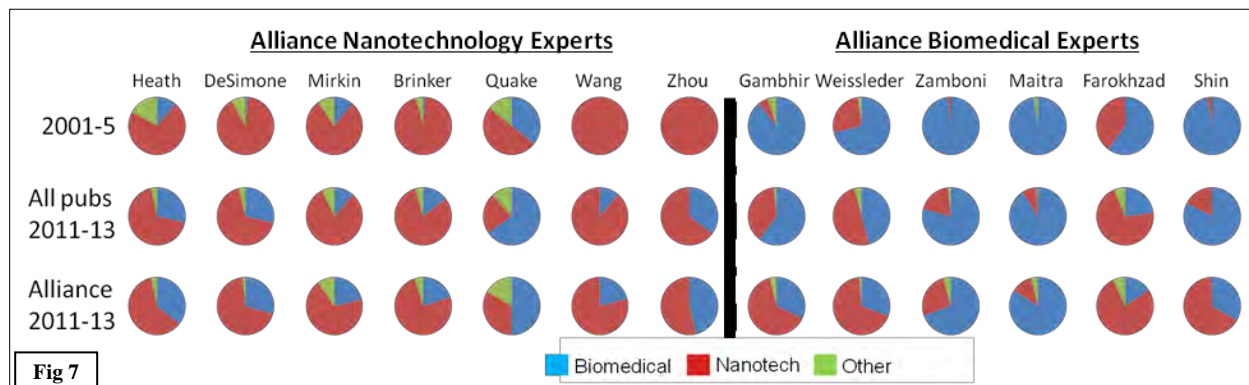


Individual award breakdowns for publications in different topical categories are illustrated in Figure 6A-C.

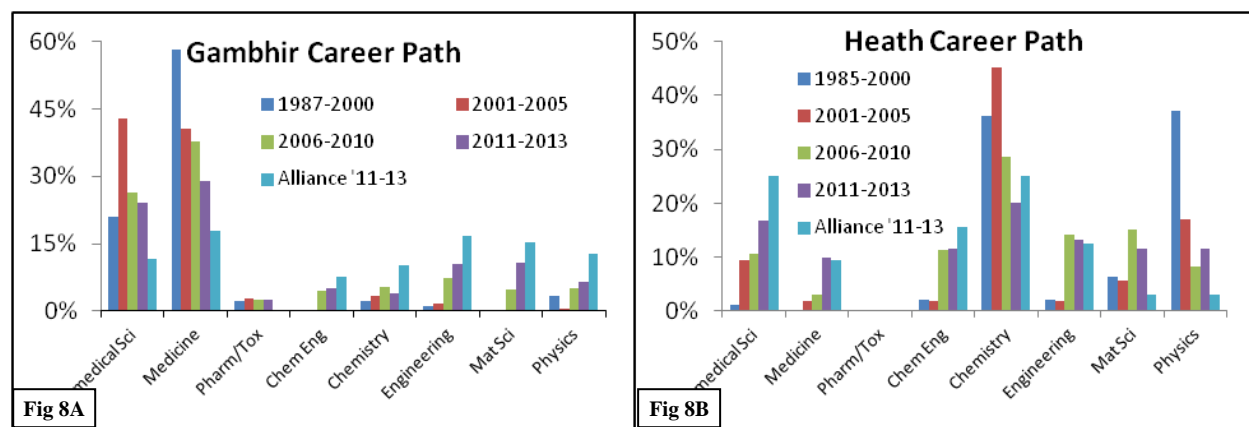
Investigator Topic Evolution- Diversification of Publication Topics by Alliance Investigators

The influence of an interdisciplinary research environment should be reflected in the publication record of the associated investigators. The Alliance program set out to bring together experienced nanotechnologists and biomedical researchers to forge collaborations, but also to facilitate a shift in the career path of the associated investigators. To examine this, the publication record of Alliance principal investigators and project leaders were extracted from the OCNR EndNote publication database and filtered through Scopus analytics. A part of this

analytical pathway identifies the topic(s) of the papers published which can be tracked longitudinally.



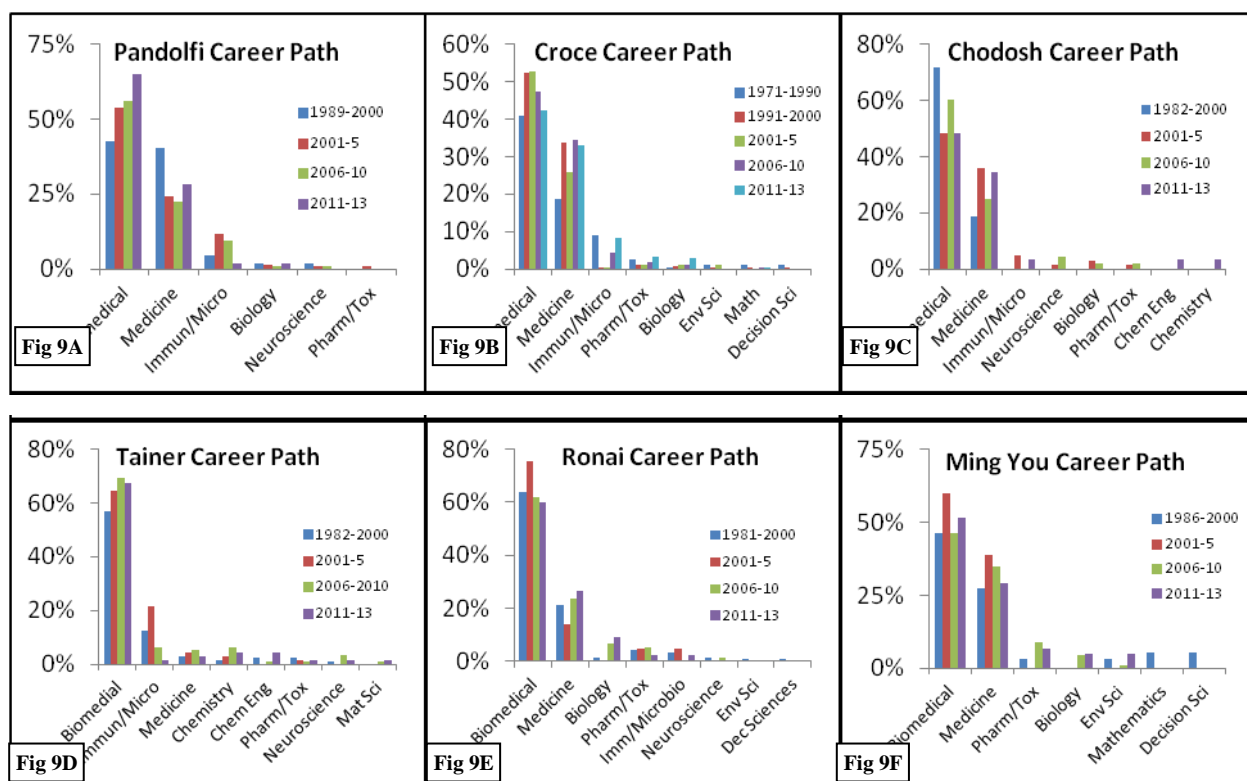
In Figure 7 the topics of multiple Alliance investigator publications were manually collated into “biomedical” (e.g. biochemistry, genetics, medicine, pharmacology), “nanotech” (e.g. material science, chemical engineering, mathematics, physics) or “other” categories. In the top row it is clearly demonstrated how these investigators began their careers publishing almost exclusively in either nanotechnology or biomedical fields before they were supported by the NCI Alliance. The second row shows how their publication records shift significantly to a more interdisciplinary profile after they received Alliance support. Emphasizing the importance of the Alliance in these topical shifts, the third row shows exclusively the topics of the papers produced by these investigators that were supported by the Alliance funding. Their Alliance-associated paper topics show the relevance of this affiliation in driving interdisciplinarity.



In an attempt to demonstrate that the topical evolution of Alliance investigators is not simply exemplary of a typical successful investigator’s career path, a contrast was generated by comparison to leading NCI researchers. Using NIH Project Reporter, the six investigators with the most NCI awards were similarly profiled. In Figures 8A and 8B, non-collated publication topic graphs are shown of two representative Alliance investigators, Jim Heath (PI CalTech Center; a chemist who co-discovered fullerenes, his research interests have diversified to solid-state quantum mechanics, nano-electronics, and systems biology described through microfluidic arrays) and Sam Gambhir (PI Stanford Center; a physician scientist whose career interests have always focused on cancer imaging, he has integrated nanotechnological techniques to

innovate high resolution intravital microscopy and molecular endoscopy). It can be readily seen in these graphs how their publication record gradually shifts from where their careers started toward interdisciplinarity. Importantly, both these scientists were supported in Phase I of the Alliance (2005-10) as well, which is where the initial large shifts in topics are observed.

To contrast, the six most highly funded (by number of awards) NCI investigators from 2010 were similarly examined for their career paths: Pier Pandolfi (Harvard University; 5 R01, 1R37, 2 U01); Carlo Croce (Ohio State University; 4 R01, 1P01, 1U01); Lewis Chodosh (University of Pennsylvania; 4 R01, 1U01); John Tainer (Scripps Institute; 5 R01, 1 P01); Ze'Ev Ronai (Sanford-Burnham Institute; 4 R01, 1 P01); and Ming You (Medical College of Wisconsin; 5 R01). Figure 9A-F shows how these highly-funded NCI investigators have remained in much more siloed career paths.



It is not the insinuation of these data that there is “one good model” for achieving impactful cancer biomedical research. Indeed these six leading NCI grant recipients profusely publish manuscripts of high impact as measured by citation count and number of publications (data not shown). Rather, it is the assertion of Figure 7 that Alliance supported cancer nanomedical research is an avenue to develop the careers of creative scientists who will become comparably productive through achieving multidisciplinary.

Impact Efficiency Analysis

Figure 4 provided rough insight into the impact of the Alliance awards as measured by citations. In an attempt to provide a quantitative comparison between awards that would normalize publication quantity and quality respective to the cost of research, the “Impact Efficiency” metric was developed:

$$IE = \frac{10^{12} (\text{pubs}_p)(\text{cites}_p)}{(\text{cost}_p)^2}$$

where cites_p is the number of citations; pubs_p is the number of publications; cost_p is the total cost over a given period (p) of time. Or $(\text{cites}/\$100,000) * (\text{pubs}/\$1,000,000)$.

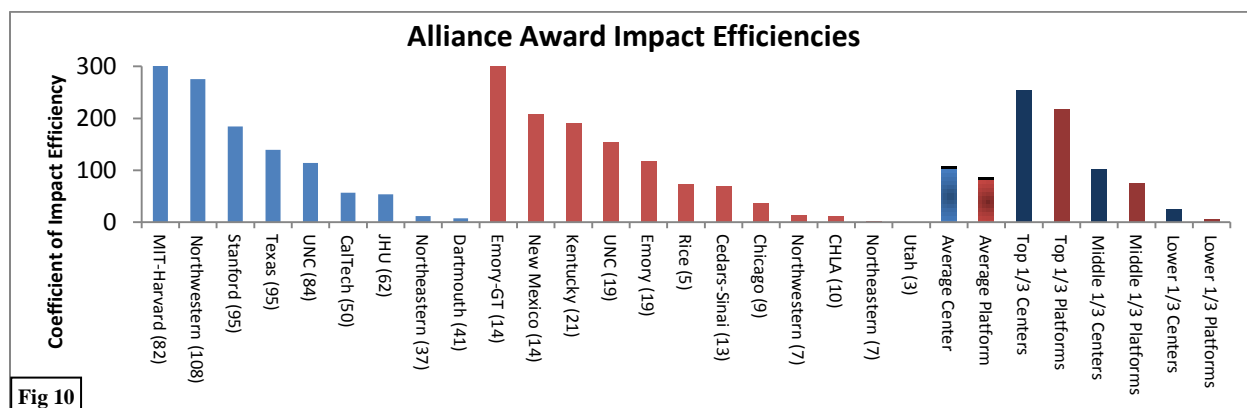


Fig 10

In Figure 10, the Impact Efficiency is calculated for individual Centers and Platforms, as well as for award averages. These data are readily collated into tiers of thirds (right panel of Fig. 10) showing that Centers have consistently higher impact efficiency than Platforms of the Alliance.

In an effort to describe Alliance output with reference to other NCI programs, publication quality and award Impact Efficiencies were calculated for a variety of relevant control groups for publications from 2011-2013 (NCI Integrative Cancer Biology Program centers [ICBPs], NCI Designated Cancer Centers of institutions with Alliance Center awards [AA-CCs], NCI *In vivo* Cellular and Molecular Imaging Centers [ICMICs], NIH RoadMap Initiative Nanomedicine Development Centers [RM-NDCs], and the second Phase of the NHLBI Programs of Excellence in Nanotechnology [Phase 2 PENS]). Note: RM-NDCs used data from the first three years of those grants and the awards were of varying length and some had expired prior to 2013.

While the average publication from any of these awards is comparable across all the programs in terms of citations (Figure 12A), it is evident when cost and publication count are incorporated into a measure of Impact Efficiency, the Alliance Centers and Platforms are demonstrably valuable investments (Figure 12B).

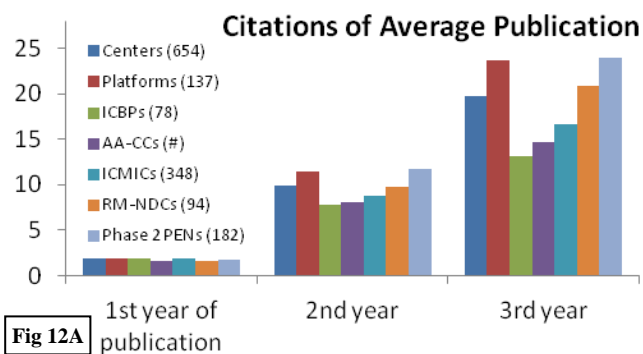


Fig 12A

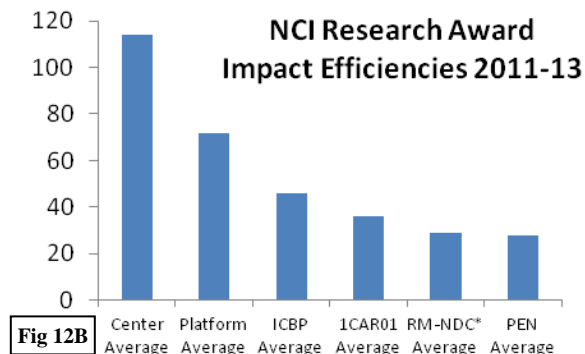


Fig 12B

Quantitative Data Conclusions

The goals of the Alliance program have been to form an efficient network of cancer nanotechnology investigators that enables multidisciplinary team research to achieve highly innovative science as well as advancing novel cancer interventions. Through a variety of approaches the data in this assessment indicate the importance of maintaining funding dedicated to nanotechnology initiatives, the productivity of the Alliance program, and the overall efficiency of Alliance centers in impacting their fields of research.

Bibliometric data demonstrated the high level of publication output in many diverse research categories by the Alliance on average across all award types. Notably, the Centers were unique in producing clinical data (including clinical trials, IND submissions, or GLP). Regardless, the quality of publications, as measured by citation accumulation, also rated very highly when compared to other NCI-funded centers and R01 grants. When coupled to award cost, Alliance Center and Platform productive efficiency over 2011-13 were the highest of award types examined. While funded by the Alliance, many investigators published in fields new to their career paths (physician scientists adopting nanotechnology and nanotechnologists working in biology). Importantly, this diversification of the investigators' publication record reached beyond their Alliance funding reflecting bona fide adoption of multidisciplinary trajectories. These data assert that the Alliance program has met or exceeded its goals as described in its RFAs.

By coupling a portfolio analysis with the bibliometric data, it becomes clear that the continued targeted support of nanotechnology through the Alliance program is important for maintaining the further growth of this field. Nanotechnology-themed applications to the Parent R01 FOA announcement have doubled since 2008. While scoring for these applications has also improved over this span, they still tend to score poorer than non-nanotechnology controls. Furthermore, the interdisciplinary Alliance Training Center program was very successful at drawing new scientists to NIH support. However, since their funding in 2009, no cancer nanotechnology training center has been funded through the Parent T32 or R25 FOAs.

In the sections that follow, through expert interviews and input from the broader cancer nanotechnology community, these quantitative metrics are supported by the qualitative inputs.

II - Summary of Responses to Expert Interviews

Nine leading researchers in the field were asked to participate in phone interviews about the program. Three of the nine interviewees were members of the NCI Alliance for Nanotechnology in Cancer and the other six were not funded by the program but still familiar with the cancer nanotechnology field. The interviews were administered by an expert evaluator from NCI who was external to the Office of Cancer Nanotechnology Research; the protocol for the interviews is detailed in Appendix B. The responses by and large reflect a very positive impression of the role NCI and the Alliance have played in developing the cancer nanotechnology field. Still there are multiple suggestions on how these efforts can be improved in future iterations of NCI support for this field. Below is a summary of what was learned through those conversations.

Cancer Nanotechnology Research

Q1: What do you feel are the most important advances to date in the field of cancer nanotechnology?

The following advances were mentioned:

- Therapeutics, Drug Delivery, Clinical Development
- Targeting of Therapies
- Imaging
- Nanoparticles
- Diagnostics
- Reducing toxicity of therapeutics
- Medical devices
- Promoting scientific collaboration across fields

Nearly all respondents stated that the Alliance was crucial for these developments to occur.

Q2: How important are federal programs supporting specific fields, such as cancer nanotechnology, to introduce new fields of research?

Nearly all of the respondents stated that the Alliance has been quite instrumental in promoting cancer nanotechnology research. Federal programs are essential because the private sector is very risk averse and will not normally “take chances” on this type of research “cross-pollination.” Also “team science” is less likely to occur without federal involvement. Large center NIH grants are needed; typical R01s are unlikely to foster such collaboration. Without the Alliance program, basic research in this area would be limited. Even when this area is mature, NCI will still be needed to maintain the momentum. On the other hand, one respondent pointed out that some of the serendipity of research can be muted by having an overarching program like the Alliance – it might be better, in some cases, to let the research process occur without the management (or structure) of a federal program.

Q3: Many nanotechnology funding opportunities in cancer have focused on translation. Has progress been satisfactory?

Nearly all respondents mentioned that there have been promising activities in the translation component, but there is a way to go here. There is a gap in knowledge regarding toxicity and the “terrain” in which cancer nanotechnology occurs. For example, it is challenging to apply pre-clinical models to solid tumors. The respondents advocated for more translational work, but not at the expense of basic research. Both are considered to be highly important.

Q4: What do you think are the research and translational priorities for nanotechnology cancer research for both the short term and long term future?

- Basic science on distribution pathways of metabolism and degradation
- Intracellular pharmacology
- Early diagnosis of cancer
- Management of cancer
- Matching the right patient to the right drug
- Drugs and quality of life (toxicity)
- The dissemination process of nanoparticles
- Matching particle types to tumor types
- Barriers that prohibit drugs from reaching tumors
- Normalizing the microenvironment so that treatment can be targeted
- Nano-intersection with “-omics” data
- Early detection
- Phenotype
- Multiplex detection

Q5: Please describe the engagement of the clinical community in cancer nanotechnology in general, and your research in particular.

There have been some quite notable drug approvals (e.g. Abraxane, Doxil, Daunoxome) so the clinical community has clearly been engaged. However, there is still some ground to cover in this. Some of the barriers to engagement include:

- Lack of understanding of the tumor microenvironment
- Lack of a “common language” between clinical community and nano researchers
- Oncologists tend to prefer the newer drugs, while the older drugs that are subjected to a nanotech-created system could do quite well.
- Some clinicians think that nano applications are “toys” and do not work (general bias against this.)
- Still waiting for more clinical trials to complete so that community knows nanotech will work

Q6: What do you think would be the best model or models of supporting and conducting nanotechnology research in the cancer context over the next 5-10 years (e.g., projects involving single vs. multi-laboratory efforts; small teams vs. large teams; single institution efforts vs. multi-institution collaborations; focused vs. broadly multidisciplinary projects; investigator-initiated projects vs. large dedicated centers, etc.)?

Overall, nearly all respondents noted that this work needs to be collaborative (i.e. multiple laboratories, multiple institutions, large centers, and multidisciplinary). One respondent cited the collaborative “Stand Up to Cancer” model as exemplary. The centers benefit from the NCI “stamp of approval.” However, some cautioned about geographic barriers (i.e. sharing resources) and the lack of a common language among disciplines. One respondent cautioned against larger groups of researchers because of the difficulty of management – too many “middle managers” can limit progress. Also, it is important to not try to focus on too many areas of research. Another respondent stated that the research teams should come together without too much structure – more organically (example of “requiring a chemist” for a research team was cited, regardless of the work being conducted.)

Q7: What positives and negatives do you see in building multi-institution collaborations?

Sometimes multi-institution collaborations can be difficult to manage. They may interfere with the ability to conduct more improvisational research. In some cases, sharing resources may be limited by geographic factors. For example, some are limited in sharing nanoparticles.

Q8: The 2010-2015 Alliance had inter-Alliance collaboration mechanisms, or Challenge Projects, built-in to push for inter-institutional collaboration. This amounted to 2-3% of the parent grant's direct costs. There have been mixed views on this mechanism of supporting collaborations. While some researchers found this format supported collaborations, others did not find this mechanism to be as effective as it could be. What has your experience been? What could be done to improve it?

Several respondents were unfamiliar with the Challenge Projects. For those who were, there were several comments. One respondent stated that geographic barriers are a factor regardless of the support mechanism. Another respondent mentioned that these provide flexibility. Others gave mixed views, stating that the best way to encourage interaction is to have more PI meetings. Yet another stated that funding is not enough to have a real impact. More funding would be needed to make an impact.

Q9: Have you experienced any barriers to accomplishing your project's goals and strategies?

Some mentioned that timelines were a bit unrealistic. Another mentioned that he has been working on an analysis of tumors to identify combination therapies and needs to obtain drugs from drug companies. He is having trouble doing this and would like NCI to help facilitate. Budget cuts were mentioned and these are especially problematic for young

scientists. Some also mentioned the lack of a common language among scientists of different disciplines. Similarly, one respondent mentioned that it has been difficult for her (a chemist) to connect to those doing medical research at the same university. Another mentioned the difficulty of working with solid tumors with nanotech and the need for better animal models. A respondent who works for a private sector firm stated that better metrics for determining economic success of Alliance projects are needed.

Q10: How has your program handled pitfalls and gaps in the translation of research to the clinic?

Some respondents mentioned that the nanotech work might still be a bit advanced for clinical applications, although this is greatly dependent on the type of work (for example, tumor cells in blood research is more aligned with nanotech.) FDA needs to be more involved and engaged (could NCI help?) but the NCL is helping a great deal with translation and is very promising. Currently, the amount of funding to support preclinical toxicology work is more than NCI can provide, but (again) the NCL has been a big help by providing a systems perspective. There is resistance in the clinic to nanotech cancer research but NCI could help by providing more education to clinicians. Also, as mentioned above, the lack of nanotech research on solid tumors is problematic – could NCI emphasize this area more?

Q11: Besides increasing funding, what do you think NCI should do to increase the amount or value of your interactions with industry, to promote commercialization or the clinical translation of your research?

Nearly all of the respondents are concerned about this issue. There is a lack of business experience among scientists, so NCI is definitely needed to bridge the gaps. NCI should make strategic programmatic investments where industry sees value. Could NCI arrange industry partnerships (like is done in academia?) CCNE program staff could meet with industry to promote commercialization. Also, NCL should be used to its full potential. (One respondent stated that NCI should not be involved in this function -- commercialization should happen naturally.)

Q12: Have you interacted with the Nanotechnology Characterization Laboratory?

Of those respondents who have dealt with (or heard of) the NCL, all were quite positive about their experiences. Their function of providing additional data provides additional oversight. NCL makes commercialization more feasible. The emphasis upon toxicity and characterization is very helpful. It would be helpful if NCL communicated the results of its work more broadly and work more extensively with the pharmaceutical industry.

Training

Q1: What particular needs or requirements are specific to training students in cancer nanotechnology as compared to training scientists in other areas?

- Ability to form coalitions with others
- Good communication skills
- Flexibility
- Ability to cross-train and work in a multi-lab environment and across disciplines
- More willingness for those trained in cancer biology to learn engineering (the reverse has not been that problematic)
- Material scientists willing to learn about the tumor micro-environment
- NCI funding is essential

Q2: What role do training programs have in improving the overall research environment and research value at their institutions?

- Heavily promotes multidisciplinary science (biology, engineering) and overall collaboration
- NCI training programs provide a model for others at the universities
- Increases the body of knowledge
- Ultimately provides great economic benefits for society
- Provides a stable source of funding for the universities and stability for graduate programs
- Outcomes of training have included research conferences and workshops

Q3: How do you attract trainees to assure multidisciplinary in your training effort?

- NCI training, by its nature, encourages a multidisciplinary focus
- Trainees are put into small teams with other scientists
- The research needs of the university attract those who want to do multidisciplinary research
- Projects that we do are, by design, multidisciplinary in nature
- We discuss flexibility with trainees when we interview them.
- PI exposes trainees to different areas of science
- Seminar series, co-mentors (different fields), lots of research collaborations, and the placement of engineering students in biomedical labs.

Q4: What effect do you think training programs focused on cancer nanotechnology have on students in terms of intellectual and career development?

Respondents mentioned that most of their students are working in some form or fashion in the nanotech arena, oftentimes regarding biomedical issues (if not cancer specifically.) Many have taken academic positions (in some cases – medical schools) or national labs, some have joined start-up firms, and some have joined established private sector firms (e.g. pharma, biotech.) More maturation of the field is needed before more join established private sector firms.

III - Summary of Responses to the Request of Information

A Request for Information (RFI) on the Directions and Needs for Cancer Nanotechnology Research and Development (NOT-CA-13-017) was developed by the Program Office and posted on the NIH Office of Extramural Research's Grants and Funding website on September 12, 2013. The last RFI response was received on December 15, 2013. The RFI can be found in Appendix C.

The purpose of the RFI was to gain feedback, comments, and novel ideas from interested members of the cancer nanotechnology community, other relevant segments of scientific communities, and the American public on the field of cancer-relevant nanotechnology including its support by NCI. The RFI was advertised to the nanotechnology cancer community including cancer researchers, clinicians, students and other interested members of the community so that they could share their perspectives. The RFI was divided into three areas: Areas Relevant to Nanotechnology Research, Areas Relevant to Training in Nanotechnology and Areas Related to Commercial Development of Nanotechnology-based Approaches. Participants were also welcome to comment on any other aspects of cancer-related nanotechnology that they felt were appropriate.

We received 31 separate responses to the RFI made up of a total of 76 participants. This group was made up of three members of industry, 26 students and 47 faculty members. The majority of the responders were members of the Alliance.

Overall the respondents had many suggestions for where the field of cancer nanotechnology should progress scientifically, programmatically, in training and in translation and commercial development. Their feedback gave the program office insight as to what a wide group of individuals of different career levels felt would benefit the area, as well what barriers need to be overcome in order to successfully advance the field.

Areas Relevant to Nanotechnology Research

Advances that are the most important to date in the field of cancer-relevant nanotechnology and progress towards clinical applications. Current and/or potential contributions of nanotechnology to answering the big topics in cancer biology. (Topics A1 and A2)

Overall respondents were very enthusiastic about the developments in the field of cancer nanotechnology to date. Advances in basic understanding of how nanomaterials interact with biological environments, new methodologies which have pushed the field forward, as well as the evolution of specific challenges in using nanotechnology to image, reach and treat cancer cells were all mentioned in response to this topic.

- Many respondents felt that the advances made in nanotechnology delivery based platforms were most important to the progress towards *in vivo* clinical applications.

- They also felt that “nano-enable diagnostic platforms will become more clinically relevant; they inherently undergo „less-complicated“ regulatory pathway as compared to emerging nanovector drug delivery systems.”

The nanotechnology advances which have made it into clinical trials were of course mentioned as examples in this area. The “later stage clinical trials ... for gold nanoparticles,” as well as the “therapies and imaging agents currently used in the clinic, including Abraxane, Doxil, other liposomal drugs, Tc-silver colloid, iron oxide nanoparticles, and polymer conjugates” are examples of the success the field has had in translating research into clinical applications.

Theranostics were met with mixed enthusiasm. Some respondents felt that the development for “programmable nano-particles for [both] diagnosis and treatment” was an important advance in the field. However others didn’t think that the promise of theranostics has been met yet. “Multifunctional, theranostic (therapeutic + diagnostic) nanoparticles look very attractive in theory but their clinical development appears to be very difficult in the near future.”

The ability of nanotechnology to target tumors and address undruggable targets were viewed to be particularly important:

“Other tools for the internalization of foreign materials (from small molecules to macromolecules) into cells *in vitro* and *in vivo*, potentially targeted to specific organelles or tissues, will allow the induction of specific molecular changes to biological systems and the facilitation of model development.”

Another area with many responses to how nanotechnology has or will have impact on cancer biology was the field’s ability to work synergistically with the genomic and proteomic fields of research. Using nanotechnology to act on the results of these two disciplines has great potential.

“Nanotechnology in combination with genomics and proteomics could play a major role in elucidating the carcinogenesis process.”

“Nanotechnology has allowed rapid functionalization of genomic discoveries.”

This will be especially useful in cases such as multi-drug resistant cancer cells, “one of the biggest challenges for cancer therapy.”

The use of nucleic acid-based nanotechnologies to act on the “identification of genomic aberrations” as we gain better understanding of the “evolution of genetic mutations, the effect of the cell microenvironment, and the effects of drugs” will be a critical area of discovery. Finally, the massive amounts of data generated by nanotechnology experiments and devices naturally solicit improvements in the fields of bioinformatics and computational biology.

Research priorities for nanotechnology in cancer over next 5 years. (Topic A3)

There were two major themes to the responses to what the research priorities should be over the next five years. The respondents felt that the research priorities should be addressing the basic research needs that are still prevalent in the field as well as an increase the translation of nanotechnology-based therapeutics into clinically relevant applications.

Many respondents commented on the need to better understand the pharmacology of the nanoparticles in the body. This includes “efficacy, mechanism of action, PK, PD, bioavailability,” “distribution, excretion, [and] metabolism” all of which will enable “optimization of the dosing schedule” as well as other clinically relevant factors. Similarly “nanoparticle transport across biological barriers and their modifications in cancer” should be better understood.

It was also suggested that nanomaterials should take cues from the living cell in their design. Creating biomimetic cell-like nanoparticles can result in the “ability to coordinate the functions of nano-sized componentry ... to attain superior functions.” This could allow the nanoparticles to be “adaptive to biological stimuli systems” such as a heterogeneous and evolving cancer cell mass.

Another area in which many were interested was the ability of nanotechnology to play a role in “immunotherapeutic approaches” to treating cancer. There was interest in using “nanomedicines for regulation of effector cells” in order to “boost [the] immune system.”

The toxicity of the nanotechnologies used in cancer diagnosis, imaging and treatment needs to be better understood and improved on. The “reduction of damage to vital organs should be a priority for nano cancer research.” There should be standard tests, both “negative and positive” of the nanotoxicity of these materials. Long-term studies are also needed to “identify possible side effects caused by deposits of non-degradable nano materials, especially inorganic materials.”

The models used to study nanoparticles also need improvement in the next five years. There need to be better animal models, as well as improvement in the choice and type of tumors used in these models. The “selection of tumor model,” such as subcutaneous, orthotopic, or metastatic tumor, need to better match the human disease.

A major component of the ability to translate nanotechnology approaches into clinical applications is the ability to reproducibly generate “large scale production[s] of the nano-materials ... desired.” The ability to “scale-up and manufacturing... [at] reasonable cost” the nanomaterials needed as well as funding for the development of these capabilities is necessary.

Standardization in the field will also help to facilitate translation. “Systematic comparison between various nanovectors in terms of biodistribution, disease loci targeting and

toxicology” is needed to improve the efficiency of translation and clinical development. It was also suggested that “stricter guidelines for *in vitro* work” are needed as well as “standardization of the animal models and cell lines used for research.” There are currently “no established criteria or venue for evaluation of nanodrugs” which is a barrier to efficient translation of new discoveries into clinical approaches.

Finally there was a call from some respondents to approach the next five years in the cancer nanotechnology field in a much more top-down manner. It was felt that having NCI determine more specifically which nanotechnologies, nanostructures or cancer types show the most promise and then “unifying the efforts of many research groups” toward these common goals would allow the program to maximize its gains in those areas over the next five years by allowing the “community to work collectively on some with a proven track record.”

Key factors that can influence progress in the field of cancer-relevant nanotechnology. Main barriers to efficient conduct of research in cancer-relevant nanotechnology. (Programmatic barriers)(Topics A4 and A8)

The ability to foster better relationships between scientist, clinicians and industry members and establish “greater partnerships” and “broad cross-collaboration” among them would help to advance the field. There is a need to improve communication between the relevant research areas of science “such as materials chemistry and preparation, animal models and cancer biology.” For those institutions with both research scientists and medical practitioners there may still be issues with how to improve communication if there are no established networks between them already in place.

Funding was cited as an area that would influence progress in the field. Many respondents felt that the need for translational funding was greatest during the “valley of death” period between current options for government funding and when industry is willing to take over. Increased governmental funding for clinical trials as well as rewarding researchers for their “prior translational research [success]” were two specific areas in which additional funding was felt to have potential significant impact.

Facilitating researcher’s interactions with the approval process within the FDA would help to overcome some of the barriers related to approvals of INDs and IDEs. When researchers interact with the FDA they felt that they had difficulty achieving “compliance with FDA requirements.” In part they felt that this was due to “insufficient FDA’s perception of nanomedicines as special drugs” and in part due to “the current regulatory pathway and the funding & time needed to achieve clinical translation.”

The future role that the NCI (as well as NIH, in general) may or should play to stimulate and/or facilitate progress in cancer-relevant nanotechnology. (Topic A5)

The most common comment in this section was that NCI should support and facilitate the translation of research from the bench to the clinic. Increased support in this area would help

researchers from smaller research groups or those with less experience with industry gain a foothold in the “very competitive ... field” of nanotechnology pharmaceuticals. Respondents asked that NCI do more to support interactions between academia and “small businesses, Big Pharma and patient advocacy groups.”

It was also suggested by a number of researchers that the NCI could help with the translation process in a top-down manner by “streamlining commercial manufacturing steps for nanomedicines.” There should be a set of standards developed so that nano-therapeutics properties can be optimized in areas such as “highly effective tumor-targeting, evasion of the immune system and controlled drug release.” However, there were no suggestions for how these standards should be developed.

A number of respondents specifically mentioned increasing the number of SBIR and STTR grants given to groups working with nanotechnology as an important mechanism to address some of these issues. There was also the suggestion that NCI should be “identifying steps and accelerators for translating cancer nanoscience through the proof of concept stage gates” as a resource to researchers in this area. The NCI should play a “critical role up to IND package development, if not up to Phase I.” It was also recommended that there be specific funding for the clinical trials of cancer nanotechnology available to researchers.

There was also a call for NCI to continue to support basic and multidisciplinary research.

“Funding of early-stage mechanistical studies is required”

Many respondents felt that funding multidisciplinary research groups allowed for the “work to be as flexible as possible” to meet the research needs. Multidisciplinarity includes scientists of different specialties and engineers working together as well clinicians who, as collaborators, are able to “address a relevant clinical need.” In addition to just funding groups who come to NCI already formed, NCI should reach out and help to “initiate collaborations and educate each of the parties on how to bridge the language barriers between them” thereby bringing together researchers “who would not have ordinarily shared the same research sphere/arena.”

Respondents would also like NCI to support resources for the community. Many were very enthusiastic about the NCL and the NExT programs and felt that they “encourage investment in the field [and] are essential in clinical transition and commercialization”. They would also like NCI and NCL to continue to “develop relevant assays” and provide “guidance on biorelevant release testing for ... different nanocarriers.” as well as maintaining “core laboratories open to all local institutes” as well as “centers for ... scaling up of nano drug synthesis, and GMP compliance of synthesis.”

Many respondents would like to see increased support by NCI of various training mechanisms. Funding for medical residents as well as pre-doctoral candidates focusing on multidisciplinary training was one suggestion. There were many who felt the need to

generally support “young scientists in different fields to pursue cancer research by promoting the importance and potentials of nanotechnology” whether through a K99/R00 mechanism or by limiting the applicant pools to mechanisms like challenge grants or pilot grants to junior investigators.

There were many who were very supportive of the current format of the Alliance and felt that “the NCI Alliance of Nanotechnology has been a strong transformative force in cancer treatment and diagnosis during the last ten years.”

Value of various models of supporting and conducting nanotechnology research in the cancer context over the next 5-10 years.(Topic A7)

The most popular model suggested by respondents was large team projects. They felt that working on cancer is a “team effort” and should involve a “robust set of expertise and skill sets.” It was also felt that the investment in centers made a larger impact than similar amounts of funding for “smaller collaborative or an individual effort.” However, many people mentioned that although they supported the large group model, they felt that this was only if the entire group was at one institution or at institutions which were in very close physical proximity to one another, and that once a group got too large or disperse, the extra work it took to organize them was counterproductive.

There was also support for smaller projects where “researchers who work in the small institution are able to more focus in one specific area.” R01-like mechanisms which paired a “nanotechnologist ... with a biologist or clinician” for five years of funding would “allow the time for ideas to reach fruition and allow the necessary parties to communicate.” This also might be a better mechanism to bring young investigators into the field as they are less likely to be able to compete for a large center award.

Regardless of which model respondents supported, all felt that the groups being funded should be multidisciplinary, even those who supported small groups funded by R01s. “Networking with experts in other areas makes researchers have [a] better view of the overall problem” in order to move “therapeutics into clinical trials, joined effort from multidisciplinary teams is highly desired.” It is important to have the “the most knowledgeable and appropriate researchers, given the topic being studied ... involved in a particular project.”

Engagement of the clinical community in cancer-relevant nanotechnology. (Topic A6)

In general the respondents reported that engaging the clinical community was “critical” and “should be encouraged whenever possible” but that this type of engagement is “difficult to achieve” and at this point “there has been insufficient consultation with clinicians.” A number of barriers were discussed as well as some suggestions on how to improve interactions between clinicians and researchers.

There were comments about the divide between basic research and the clinic. Researchers' poor understanding of how clinical problems will affect the design of the nanomaterials they are developing was cited as a result of this lack of communication. Close interaction between both groups will allow for "nanomedicine designs [to] ... be integrated into a workflow paradigm that currently exists" improving the chances of their nanomedicine being adopted by the medical community. Improving the education of clinicians about the advantages of nanoparticle-based drugs as well as informing them about the "nanomedicines [with]... a history as approved drugs and imaging agents" was suggested to improve clinical interest in collaboration.

NCI/NIH role in supporting the interactions between the academic research community and industry, to promote commercialization or the clinical translation of research findings. Types of support that NCI/NIH could provide (funding, access to resources, etc.) that would facilitate translational efforts and path to product commercialization. (Topic A9)

Not surprisingly, the most common response to this topic was for the NCI/NIH to increase funding in order to better support interactions which could improve the rate of commercialization. It was generally felt that "nanomedicine drug product development is perceived in big Pharma as a high risk" and so more funding is needed in the transition of nanotechnology research from government funding to industry funding compared with other more traditional pharmaceutical research. Increased funding which specifically supports interactions between academia and industry were suggested, such as SBIR-type grants which require these interactions. Supplemental grants were also suggested for grantees who are close to commercialization of their products, and so the additional funds could be used to support the transition to industry.

"The NCI/NIH could provide additional funding through grant programs that link academia with industry to promote commercialization and translation. Other funding organizations (e.g., NSF, DoD) have been successful with such a model."

"Perhaps the public-private-partnership (PPP) model should be adopted to advance cancer-relevant nanotechnologies to translate emerging nanotechnologies past the initial "seed" stage of research."

The extent to which you and/or your collaborators have interacted or collaborated with the Alliance for Nanotechnology in Cancer or participated in Alliance supported activities or benefited from that program in any other way. (Topic A10a)

The respondents were very positive about the interactions they have had with the Alliance. They commented on the support in the areas of collaboration, research innovation support, interaction support, their ability to leverage their funding as well as how their relationship with the Alliance has improved their ability to recruit.

“The program does an excellent job of coordinating, highlighting, and supporting multidisciplinary research efforts.”

“Strong interaction with colleagues from different institutions and campuses through Nano Alliance meetings has been very beneficial in generating new ideas, preventing study redundancy, and for comparing studies before publication.”

“The [Alliance Challenge] program enabled the ... lab to interact with scientists of different backgrounds and to establish several interdisciplinary collaborations involving basic scientist and clinicians.”

“The relationship with the NCI Alliance and the NCL [has] allowed us to attract attention by different major and medium sized industrial partners.”

“The CCNE program has provided an amazing opportunity to foster collaborative research in a multidisciplinary manner. Our own research endeavors really highlight this fact.”

“With the Alliance Challenge Programs and other grants each of the researchers of CCNE are involved in, we were able to support individual ideas and leveraged the team effort to make them successful spinoffs of the main grant.”

Your interactions with NCI’s Nanotechnology Characterization Laboratory (NCL) and how these interactions affected the clinical translation of your research.(Topic A10b)

Overall feedback about the NCL was very positive with people indicating that the services offered by the NCL were a valuable addition to the community.

“The NCL is a wonderful resource and should continue to do a great job in supporting the cancer nanotechnology research community.” The NCL is “the best strategic governmental initiative that I came across in my 20 years of industrial drug development.” The NCL’s outreach activities “de-risk Nanomedicine development which will be important for the speed of development of breakthrough drugs in oncology.”

The ability of the NCL to assist smaller research groups as well as all collaborators with the FDA approval process was also a common theme. With the pre-clinical characterization of nanoparticles by the NCL being noted as a significant step towards clinical trials.

The strength of interactions with both the Alliance and NCL has “allowed [one respondent] to attract attention by different major and medium sized industrial partners” indicating the added value of these interactions above and beyond funding the group’s research.

The NCL's outreach to the community was particularly well received with many respondents reporting a very positive experience from attending the Lessons Learned Workshops. Respondents reported the workshop as being "invaluable" and "a highlight of [the] meeting" they had attended. Additionally the development of assays and guidance on different nanoparticle testing was viewed as very valuable to the community.

"Scott McNeil and Anil Patri are excellent resources – they have both been willing to discuss toxicology, standardization, and translation to help out our research studies and have provided many protocols and recommendations."

There were also some comments about ways to improve NCL's services. The resources needed to produce sufficient quantities of nanoparticles of high enough quality to interact with the NCL were a barrier for some respondents. Others felt that the NCL's services should be expanded to include "standardized synthesis of nanoparticles for purchase [which] would help establish standards in the nanoparticle research community." The *in vitro* services were better received than the *in vivo* toxicity studies, with indications that the respondent felt that NCL was not properly equipped to perform the *in vivo* studies to the same level as *in vitro* studies.

Areas Relevant to Training in Nanotechnology

Training needs in the field of cancer nanotechnology and the value of such activities for the development of new research directions. (Topic B1)

Many respondents felt that it was very important that training in the field of cancer nanotechnology be multidisciplinary.

"The different parties must gain a basic foundation in each other's fields in order to begin to communicate and ask the right questions. Nanotechnologists/engineers must receive basic education in fundamental areas of cancer biology and therapeutics (cancer genetics, animal models, therapeutic targets and mechanisms), while biologists and clinicians must learn about the scope of technologies available and their potential benefits."

This type of multidisciplinary training approach allows people to see the "big picture" and gives them the tools for their career to take "a holistic approach to have something actually become clinically available." One respondent commented that "the researcher of tomorrow will need to be multi-faceted in order to stay competitive" which was a sentiment echoed by many others. There were also other suggestions for how best to train researchers in this field beyond scientific topic areas. Understanding the "commercial development of nanotechnology-based approaches" is an important step for successful researchers. This requires that students have a foundation in "the translational aspects of drug/device development with regard to considerations in business, law, finance, and regulatory [areas]." It was also mentioned by respondents that clinical exposure was an important part of this

training in order to “keep students and faculty focused on clinical applications and expectations of their work.”

Another area that was mentioned in this section was the types of funding mechanisms that would be most useful in training. Extending the length of training programs was felt to be useful. There was also support for continuation of the K99/R00 mechanism, as well as a call to include more “physicians/students/MD-PhDs” in the training programs.

The interpersonal contact networks which naturally develop in the multidisciplinary cancer nanotechnology field are also a benefit to the students being trained in this area. Many respondents felt this was an essential part of their student’s training and also of the career development of the faculty involved in the program.

“The [training] program enabled me to interact with clinicians at a local hospital and also introduced me to fellow researchers in different fields that I would not have met otherwise.”

“Providing basic training in different fields enables experts in different fields to more effectively communicate and opens new collaborations. New collaborations open up new avenues of research.”

Effectiveness of various recruitment efforts to attract multidisciplinary trainees to your institution's research and training programs in cancer-relevant nanotechnology. (Topic B2)

On the whole respondents felt that they were able to effectively attract high quality trainees into their programs. They felt that their strengths lay in being able to “show them that strong collaborations exist across departments and between research groups” as well as by showcasing the benefits of the program. Being able to showcase the career trajectories of previous students was mentioned as one highlight that could be used for recruitment and the ability to showcase an interesting multidisciplinary group of potential advisors incoming students can choose from was another.

They also felt that they were able to recruit a “high caliber” multidisciplinary cohort of students, including “students from a variety of fields in biology and engineering” who “wanted to expand their training or develop expertise in cancer-relevant nanotechnology.” One responder commented on their being fewer women than would be optimal to recruit, potentially an issue with the “engineering heavy” group they were recruiting from.

Role of training programs focused on cancer-relevant nanotechnology as a step in career development for their participants and possible ways to enhance this aspect. (Topic B3)

This section had many replies from students as well as professors, and overall it was felt that training in cancer nanotechnology programs has a positive influence on trainees’ careers. Many felt that trainees were receiving a “multi-disciplinary education [which] better prepares participants for future careers in nanotechnology.”

“The most important aspect in career development that the [training] program provides is networking opportunities with other researchers. The connections formed from the program enable further collaborative research efforts and potential job opportunities after graduation.”

Respondents commented on how, with their additional training, the “predoctoral and postdoctoral trainees appear to be highly sought after by prospective employers” and that this is due to “their advanced training in cancer-relevant nanotechnology and their comfort level in a highly interdisciplinary environment.” One respondent did caution, however, that there may be some draw backs to an interdisciplinary education.

“While significant emphasis has been laid into interdisciplinary approaches, the acceptability of scientists trained in interdisciplinary fields is still minimum. I was recently in the job market and in spite of strong discussions on creating an interdisciplinary workforce, the reaction of a few interviewers was not positive. Unless strong future is exemplified to the potential investigators before they began training in interdisciplinary field, they will rather take a traditional approach of maintaining strength in the field of their expertise.”

Areas Related to Commercial Development of Nanotechnology-based Approaches

Sources of innovative technologies your company relies on. The degree to which a company’s goals and future products would depend on technology licensing from academia vs. other sources, including in-house research. (Topics C1 and C2)

Primarily the respondents told us that companies’ research is “born out of research projects initiated in an academic setting.” Whether they continued to rely on innovations from academia as their company progressed, or went off on their own for further development depended on the individual companies.

“As a start-up company, our goals and future products are almost completely aligned with the technology we licensed from academia.”

“My company’s goals and future products depend heavily on our ability to successfully license technology from academia.”

“Initially, licensing is the engine; however, in-house research can become more important as the company develops.”

Many from academia mentioned that their technologies have been licensed for use by companies.

Main challenges companies face in undertaking nanomedicine research and development efforts. (Topic C3)

The main challenges that respondents felt companies had in their research and development efforts were issues with funding, dealing with industry members who were skeptical of nanotechnologies potential impact and with customers and regulatory officials who are unknowledgeable about nanotechnologies.

“Nanomedicine research and development efforts, like traditional drug research and development efforts, are lengthy and extremely costly. A company would be taking on a huge risk in beginning to develop such a product.”

“Financial issues are the only one barrier preventing us from bringing the drug to the clinic.”

“The lack of experience by potential customers ... with nano medicine approaches.”

“In general I feel that Nanomedicine drug product development is perceived in big Pharma as a high risk as development timelines and probability of regulatory and technical success cannot be estimated as easy as for the more mature technology fields like small molecule classical development or biologics development.”

Activities or programs NCI/NIH could develop to aid translation of nanomedicines from academia to the commercial sector. (Topic C4)

Many respondents felt that there were specific funding mechanisms which the NCI/NIH could develop to aid in the translation of nanomedicines.

“SBIR-like Pilot grants ... [to] support the link between commercial and academic ... efforts.”

“A specific extension of the [current grant’s] funds with intent to support commercialization in the final phases of the grant”

“Financing the drug development and toxicity studies *in vivo* as per FDA guidelines”

Finally the respondents felt that anything that the NCI/NIH could do to continue to facilitate introductions and collaborations “between academic groups engaged in nanotechnology-based cancer research, small businesses in the Nanomedicine field, Big Pharma and patient advocacy groups” would aid in the successful translation of “late stage programs into the clinic.” One format that was suggested was the development of “academia-industry-NCI partnerships.”

“Commercialization requires tight partnerships between government bodies, universities, entrepreneurs, small and large companies to match new and advanced ideas in the nanotechnology research with accelerated development into the new/better products, based on startups and new companies.”

Your experience with academic and/or federal (governmental) partnerships and the effect of these partnerships on your technology, product, and/or business developments. (Topic C5)

There was generally positive feedback about this topic. It was felt that their interactions with NCI as well as the NCL had a positive impact on their company.

“The relationship with the NCI Alliance and the NCL have allowed us to attract attention by different major and medium sized industrial partners.”

“The academic and federal (governmental) partnerships and the effect of these partnerships have been invaluable, particularly the developing of interactive and productive networks.”

“These [partnerships with academic and federal labs] have helped to more quickly develop our products and technologies.”

Appendix A:

Below are the full names of the grants and grant numbers of each member of the Alliance for Nanotechnology in Cancer along with the abbreviated term used in the evaluation document.

Centers of Cancer Nanotechnology Excellence (CCNEs)	
CalTech	California Institute Of Technology U54 CA151819
Dartmouth	Dartmouth College U54 CA151662
UNC	University Of North Carolina Chapel Hill U54 CA151652
Johns Hopkins	Johns Hopkins University U54 CA151838
Northeastern	Northeastern University U54 CA151881
Texas	University Of Texas Health Science Center Houston U54 CA151668
Stanford	Stanford University U54 CA151459
Northwestern	Northwestern University At Chicago U54 CA151880
MIT-Harvard	Massachusetts Institute Of Technology U54 CA151884

Cancer Nanotechnology Platform Partnerships (CNPPs)	
Northeastern	Mansoor Amiji, Northeastern University U01 CA151452
Chicago	Wenbin Lin, University Of Chicago U01 CA151455
Northwestern	Thomas O'Halloran, Northwestern University At Chicago U01 CA151461
Kentucky	Peixuan Guo, University Of Kentucky U01 CA151648
Utah	Marc Porter, University Of Utah U01 CA151650
UNM	Cheryl Willman, University Of New Mexico Health Sciences Center U01 CA151792
Emory Shin	Dong Shin, Emory University U01 CA151802
UNC	Alexander Kabanov, University Of North Carolina Chapel Hill U01 CA151806
Emory Yang	Lily Yang, Emory University U01 CA151810
Cedars-Sinai	Julia Ljubimova, Cedars-Sinai Medical Center U01 CA151815
Children's LA	Fatih Uckun, Children's Hospital Of Los Angeles U01 CA151837
Rice	Nancy Halas, Rice University U01 CA151886

Cancer Nanotechnology Training Centers (CNTCs)	
UNM	University Of New Mexico Health Sciences Center R25 CA153825
UCSD	University Of California San Diego R25 CA153915
JHU	Johns Hopkins University R25 CA153952
Kentucky	University Of Kentucky R25 CA153954

Boston	Boston University R25 CA153955
UIUC	University Of Illinois Urbana-Champaign R25 CA154015

Pathway to Independence Awards in Cancer Nanotechnology Research (K99/R00)

Wake Forest	Ravi Singh, Wake Forest University School of Medicine R00 CA154006
Colorado	Andrew Goodwin, University of Colorado, Boulder R00 CA153935
UIUC	Andrew Smith, University of Illinois at Urbana-Champaign R00 CA153914
Wake Forest	Aaron Mohs, Wake Forest University Health Sciences R00CA153916
Utah	Mingnan Chen, University of Utah R00 CA153929
UMass	Prakash Rai, Univeristy of Massachusetts, Lowell R00 CA153948
Georgia	Jin Xie, Univeristy of Georgia R00 CA153772

Appendix B:

Below are the interview protocol and questions used for the phone interviews of experts in the cancer nanotechnology field.

CCNE Interview Questions

Hello, is this Dr. _____? My name is _____, and I'm a member of the project team working with NCI to evaluate the Alliance for Nanotechnology in Cancer Program. We greatly appreciate your willingness to answer a few questions about the Alliance Program, the Federal approach to funding cancer nanotechnology research, and your opinion on the state of the field. You have been selected because you are a prominent investigator in the Alliance and have received funding for [provide grant numbers and names]. I want to assure you that your participation is voluntary and that your responses will be kept strictly confidential. We would like you to be totally candid. We will take careful precautions to ensure that your name cannot be associated with your responses. We expect our discussion to take about _____ minutes. Do you have any questions about this, the questions you have received or the consent form? Do you wish to proceed at this time?

If yes: good. We realize that your time is valuable, so let's get started.

If no: Would you like to schedule another time for this discussion? (Try to schedule another time and thank the respondent for his or her willingness to participate.)

Our interview is divided into two sections:

- Cancer Nanotechnology Research
- Training

Cancer Nanotechnology Research

1. What do you feel are the most important advances to date in the field of cancer nanotechnology?
 - a. Do you feel these advances could not have happened without the Alliance?
2. How important are federal programs supporting specific fields, such as cancer nanotechnology, to introduce new fields of research
 - a. How do you feel the NCI Alliance has affected and/or effected the level and quality of nanotechnology in cancer research and clinical development?

- b. Is a program like the NCI Alliance still essential to the advancement of cancer nanotechnology basic and clinical research?
3. Many nanotechnology funding opportunities in cancer have focused on translation. Has progress been satisfactory?
 - a. How balanced is the research portfolio of the Alliance between basic and translational research? Should this balance be shifted in one way or another and why (not)?
4. What do you think are the research and translational priorities for nanotechnology cancer research for both the short term and long term future?
 - a. What „big questions“ in cancer biology might nanotechnology answer?
5. Please describe the engagement of the clinical community in cancer nanotechnology in general, and your research in particular.
6. What do you think would be the best model or models of supporting and conducting nanotechnology research in the cancer context over the next 5-10 years (e.g., projects involving single vs. multi-laboratory efforts; small teams vs. large teams; single institution efforts vs. multi-institution collaborations; focused vs. broadly multidisciplinary projects; investigator-initiated projects vs. large dedicated centers, etc.)?
 - a. Why do you think this is the best model?
7. What positives and negatives do you see in building multi-institution collaborations?
 - a. Has your group (or center) benefited from a multidisciplinary research environment? Does it benefit a group affiliated with a CCNE/center grant to work beyond the walls of that institution?
 - b. Please explain how and provide examples.
8. The 2010-2015 Alliance had inter-Alliance collaboration mechanisms, or Challenge Projects, built-in to push for inter-institutional collaboration. This amounted to 2-3% of the parent grant's direct costs. There have been mixed views on this mechanism of supporting collaborations. While some researchers found this format supported collaborations, others did not find this mechanism to be as effective as it could be. What has your experience been? What could be done to improve it?

9. Have you experienced any barriers to accomplishing your project's goals and strategies?
 - a. What additional support from NCI would help you to overcome them?

10. How has your program handled pitfalls and gaps in the translation of research to the clinic?
 - a. What further programmatic support could NCI offer that would be useful to overcome these gaps?

11. Besides increasing funding, what do you think NCI should do to increase the amount or value of your interactions with industry, to promote commercialization or the clinical translation of your research?

12. Have you interacted with the Nanotechnology Characterization Laboratory?
 - a. Please describe your experience with NCL in relation to achieving the translation of your research.

Training

1. What particular needs or requirements are specific to training students in cancer nanotechnology as compared to training scientists in other areas?

2. What role do training programs have in improving the overall research environment and research value at their institutions?

3. How do you attract trainees to assure multidisciplinary in your training effort?

4. What effect do you think training programs focused on cancer nanotechnology have on students in terms of intellectual and career development?

Appendix C:

Below is the Request for Information (RFI) that was posted for public response on September 12, 2013 (<http://grants.nih.gov/grants/guide/notice-files/NOT-CA-13-017.html>). The RFI was advertised through emails to the general cancer nanotechnology list serve which is open to the public, through posts on the Alliances website (nano.cancer.gov), as well as through emails to the members of the Alliance and the other list serves of CSSI grantees as was deemed appropriate by their program offices.

Request for Information (RFI) on Directions and Needs for Cancer Nanotechnology Research and Development

Notice Number: NOT-CA-13-017

Key Dates

Release Date: September 12, 2013

Response Date: November 1, 2013

Related Announcements

None

Issued by

National Cancer Institute (NCI)

Purpose

The purpose of this Request for Information (RFI) is to gain feedback, comments, and novel ideas from interested members of the cancer nanotechnology community, other relevant segments of scientific communities, and the American public on the field of cancer-relevant nanotechnology including its support by NCI.

This RFI is for information and planning purposes only and should not be construed as a solicitation or as an obligation on the part of the Federal Government, the National Institutes of Health (NIH), and/or the National Cancer Institute (NCI).

Information Requested

The NCI supports the development of nanotechnologies with applications in the diagnosis and therapy of cancer. The Alliance for Nanotechnology in Cancer - a funding program supporting a diverse network of basic and translational researchers - was formed to accomplish this task. Beyond the Alliance efforts, NCI and other Institutes and Centers (ICs) of the NIH support a large portfolio of center awards and individual investigator awards involving nanotechnology.

Biomedical nanotechnology, including cancer-relevant nanotechnology, is widely viewed as a promising and highly innovative field, with a potential for transformative scientific advancements and practical applications. Essential for the realization of this potential is the diversity of

scientists and engineers contributing to research and development efforts in biomedical nanotechnology. Thorough understanding of these aspects, including the perspective of the involved members of scientific community is needed for the optimized planning of future initiatives in the field of cancer-relevant medical nanotechnology.

Specifically, the NCI requests that cancer researchers, clinicians, and other interested members of the community share their perspectives on any applicable/relevant aspects in the following areas:

Areas Relevant to Nanotechnology Research (*Questions A1-A10b*)

- Advances that are the most important to date in the field of cancer-relevant nanotechnology and progress towards clinical applications.
- Current and/or potential contributions of nanotechnology to answering the big questions in cancer biology.
- Research priorities for nanotechnology in cancer over next 5 years.
- Key factors that can influence progress in the field of cancer-relevant nanotechnology.
- Future role that the NCI (as well as NIH, in general) may or should play to stimulate and/or facilitate progress in cancer-relevant nanotechnology.
- Engagement of the clinical community in cancer-relevant nanotechnology.
- Value of various models of supporting and conducting nanotechnology research in the cancer context over the next 5-10 years (e.g., projects involving single vs. multi-laboratory efforts; small teams vs. large teams; single institution efforts vs. multi-institution collaborations; focused vs. broadly multidisciplinary projects; investigator-initiated projects vs. large dedicated centers, etc.).
- Main barriers to efficient conduct of research in cancer-relevant nanotechnology.
- NCI/NIH role in supporting the interactions between the academic research community and industry, to promote commercialization or the clinical translation of research findings. Types of support that NCI/NIH could provide (funding, access to resources, etc.) that would facilitate translational efforts and path to product commercialization.
- If applicable, you are encouraged to share specific experiences you may have had with the NCI/NIH support for cancer-relevant nanotechnology research and its translation from academia to the clinic and/or commercial environment. Examples of the aspects you may wish to address can include but are not limited to:
 - The extent to which you and/or your collaborators have interacted or collaborated with the Alliance for Nanotechnology in Cancer or participated in Alliance supported activities or benefitted from that program in any other way.
 - Your interactions with NCI's Nanotechnology Characterization Laboratory (NCL) and how these interactions affected the clinical translation of your research.

Areas Relevant to Training in Nanotechnology (*Questions B1-B3*)

- Training needs in the field of cancer nanotechnology and the value of such activities for the development of new research directions.

- Effectiveness of various recruitment efforts to attract multidisciplinary trainees to your institution's research and training programs in cancer-relevant nanotechnology.
- Role of training programs focused on cancer-relevant nanotechnology as a step in career development for their participants and possible ways to enhance this aspect.

Areas Related to Commercial Development of Nanotechnology-based Approaches (Questions C1-C5)

- Sources of innovative technologies your company relies on.
- Degree to which a company's goals and future products would depend on technology licensing from academia vs. other sources, including in-house research.
- Main challenges companies face in undertaking nanomedicine research and development efforts.
- Activities or programs NCI/NIH could develop to aid translation of nanomedicines from academia to the commercial sector.
- Your experience with academic and/or federal (governmental) partnerships and the effect of these partnerships on your technology, product, and/or business developments.

Comments on other aspects of cancer-related nanotechnology are also welcomed.

Note: Do not include any proprietary or confidential information.

How to Submit a Response

Responses will be accepted through November 1, 2013. Please mark responses with this RFI identifier NOT-CA-13-017. Responses in electronic formats are preferred and can be emailed to cancer.nano@mail.nih.gov.

All individual responses will remain confidential. Any identifiers (e.g., names, institutions, e-mail addresses, etc.) will be removed when responses are compiled. Only the processed, anonymized results will be shared internally with NIH staff members and members of scientific working groups convened by the NCI, as appropriate.

Respondents will receive an automated email confirmation acknowledging receipt of their response but will not receive any individualized feedback.

Inquiries

Inquiries regarding this RFI should be directed to:

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