Summary of Responses to the Request for 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 exits" 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-facetted 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."