PROGRAM EVALUATION PANEL REPORT
NCI ALLIANCE FOR NANOTECHNOLOGY IN CANCER (ANC)

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Executive Summary

1. The Evaluation Panel felt that the NCI Alliance for Cancer Nanotechnology (ANC) has been highly successful in nanomedicine for the cancer field and translating these advances towards clinical application. This is considered the leading nanomedicine program in the world.
2. The Evaluation Panel felt that the design structure and program management of the NCI Alliance for Cancer Nanotechnology was highly innovative and clearly promoted the critical need to implement best practices in translational research, including GLP and GMP.
3. The Panel identified the Nanotechnology Characterization Laboratory (NCL) and Translation of Nanotechnology in Cancer (TONIC) as elements of the Alliance that were particularly important in facilitating the ongoing and future success of the program.
4. The Evaluation Panel felt that the research accomplishments of the Alliance, both technical and translational, including leveraging of research resources across academic and industry (TONIC), clearly could not be achieved through multiple R01 research grants.
5. The Evaluation Panel identifies education and training of graduate students, postdoctoral fellows and young scientists (the Pathway to Independence Awards) as a main positive outcome of the Alliance in the development of the cancer nanotechnology field and establishing a suitable professional community.

6. The Evaluation Panel identified multiagency collaboration through the National Nanotechnology Initiative as an important factor in the rapid development of cancer nanotechnology field and fundamentally new multidisciplinary approaches at the intersection of physics, engineering and medicine.
7. The main high level recommendations are:

a. NCI support for the Alliance should be maintained, but the organizational structure of the network may need to be modified in the future to emphasize pre-clinical research and the complexities of translating and optimizing methods into clinical trials
b. Alliance research resources such as NCL and the bio informatics resources may need to have a greater emphasis to serve as a resource for the broader R01 grant community, and the clinical trial community such as the NCTN, in addition to the Alliance network.

Charge to the Panel

The review panel was convened to evaluate the performance of the NCI Alliance for Nanotechnology in Cancer with particular emphasis on the following questions:

1. *Alliance supported research:*
   a. Does Alliance supported research address important issues in basic, translational and clinical cancer research?
   b. Are there gaps in the Alliance research portfolio?
   c. How successful has the Alliance been in establishing and supporting an inter-disciplinary model of research? Does this model produce effective collaborations, and do these collaborations provide added value for discovery and translational research?
   d. Is the field of cancer nanotechnology contributing to lasting improvements in cancer research and clinical practice? What was the role of the Alliance program in enabling this progress?

2. *Clinical translation and commercialization:*
   a. How successful are Alliance researchers at clinical translation and commercialization of their technologies? What role do the Alliance network and activities play in this success?
   b. How successful are Alliance efforts in fostering partnerships between academia and industry? What is the value of these partnerships? Which Alliance efforts have been most effective?
   c. Is the Alliance supporting development of standards and public datasets for nanomaterials and nanoscale devices and their widespread adoption? Is the Alliance improving access to information and data on nanomaterial properties and characteristics through public databases?

3. *Training in cancer nanotechnology*
   a. Do Alliance training programs support creation of a cohort of multi-disciplinary researchers capable of applying nanotechnology tools to critical problems in cancer research and clinical oncology?

4. *Does the Alliance program appropriately balance support for discovery research in cancer nanotechnology and promotion of clinical translation of nanotechnology? Should this*

balance be improved or reconsidered in future NCI initiatives in cancer nanotechnology? In preparing for the future, how should NCI prioritize its nano activities?

The panel was provided with an extensive set of materials detailing Alliance activities and output. These included:

- Program accomplishments report
- Table of IND/IDE applications
- Table of Challenge Projects
- Summary of coaching activities
- Report on Cancer Nanotechnology Training Center outcomes

Panel Review Process

Each panel member was requested to review all the information provided, in addition to supplying more detailed feedback on his/her area of expertise. This information was sent to the report coordinator (D. Buxton) who compiled a draft final report. This was circulated to the panel for additional comments and changes, and the final version was sent to Dr. Farrell via e-mail on December 5th, 2013. A teleconference was held between the Review Panel and NCI staff members on December 9th to review the original report. In light of the responses received the report was edited to address questions that had been answered by NCI and resubmitted to the panel members for review. The final report was submitted to NCI on December 18th, 2013.

Report.

1. Alliance supported research:

a. Does Alliance-supported research address important issues in basic, translational and clinical cancer research?

The consensus from the panel was that the Alliance has been highly successful in developing nanomedicine for the cancer field. When the Alliance was initiated in 2004, a convergence of scientific interests from the materials science, engineering and chemistry fields with the medical, biological, and pharmaceutical sciences in the application of advances in nanoscience created considerable excitement regarding the potential applications that would bring improved healthcare. Globally there has been significant investment in the hope of building on the emerging platform of basic science to realize these objectives, but achievements against these goals have generally been viewed as modest in terms of added value and delivery of nanotechnologies that are close to bringing improved healthcare (*1*).

In contrast, the Alliance has not only supported important issues, but also enabled a paradigm shift in cancer research, opening the way for new nanoscale approaches not available before the program started. The main progress is in creating a science and engineering foundation in knowledge, physical infrastructure and human resources for treating cancer and developing several avenues for translational research and connections to clinical research. This is the leading nanomedicine program in the world, changing the basic approach from statistical clinical observations toward molecular and subcellular research. The synergism with the National Nanotechnology Initiative (NNI) has played an important role in initiation of the project and in

collaborations thereafter. While publication metrics tell only a part of the story for a program with translational goals, the total of nearly 1000 publications emanating from Phase 2 of the Alliance is impressive. While publications reporting on clinical trials or studies using patient samples comprise only ~7% of the total, the translational successes of the Alliance are probably better represented by Appendix B of the Program Report, which documents forty-three human studies being carried out as clinical trials or IRB-approved studies, and an additional eight clinical trials that were enabled by the NCL.

The success of the Alliance has benefited from:

- A clear overarching focus on cancer and specific clinical goals throughout, and the establishment of the multidisciplinary Centers of Cancer Nanotechnology Excellence working on projects at the interface of the core scientific expertise of the participants with a specific technical focus. The Alliance Challenge Projects provide an opportunity for cross Center Collaboration.
- Focused objectives in the basic, translational and clinical research projects with PhD and MD Co-PIs, with each Center given the goal of bringing "at least one project to the clinical trial stage by the end of the five year funding period."
- The overarching approach to the Alliance management and coordination, coupled with the early establishment of the NCL has been of pivotal importance to the success. Together these initiatives have helped to mentor/support the Centers/Projects and accelerate the basic research advances towards the translation phase - the key goals stated for the ANC second phase funding.

The panel highlighted specific research examples that they felt to be of particular importance and representative of the Alliance successes:

Basic Research

- Combination of PRINT particles with spray-assisted Layer-by-Layer deposition, providing opportunities for development of combination therapy (*2*). Developed through a Challenge Project collaboration
- Trigger-controlled protein-producing nanoparticles, providing the potential for on-demand delivery of therapeutics in vivo (*3*)
- Reporters for molecular imaging of the extracellular microenvironment (*4*)
- Development of safe biodegradable nanoparticles with features enabling penetration of mucus (*5*) and other extracellular barriers (*6*)
- Nanoworms carrying synthetic peptide libraries for non-invasive detection of proteases by measuring cleaved peptides in urine (*7*)
- Use of spherical nucleic acid nanoparticle conjugates for silencing antiapoptotic signaling as an RNAi-based therapy for glioblastoma (*8*)

Translational and Clinical - Therapeutics

- Development and clinical translation of a targeted polymeric docetaxel-containing nanoparticle for treatment of patients with solid tumors - Phase I Bind-014 (*9*)

- Phase I trial of BP-100-1.01 Liposomal Grb-2 antisense oligonucleotide in patients with leukemias (NCT01159028)
- Enhanced Raman-based colonoscopy using SERS nanoparticles as molecular imaging contrast agents - in clinical evaluation (*10*)

Translational and Clinical - In Vitro & In Vivo diagnostics

- Scanometric microRNA array profiling of prostate cancer markers using spherical nucleic acid-gold nanoparticle conjugates (*11*)
- Use of a micro-NMR platform for rapid, multiplexed analysis of human tumors (*12*)
- Sarcoma imaging with cathepsin-activated fluorescent probes in animal models and translation into clinical trials (*13*)

The Alliance has also made significant contributions to the field by sponsoring workshops bringing together leaders in the field, for example the 2012 workshop addressing "*Challenges and Key Considerations of the Enhanced Permeability and Retention Effect for Nanomedicine Drug Delivery in Oncology"* (*14*). Alliance-sponsored review articles, for example "*Best Practices in Cancer Nanotechnology: Perspective from NCI Nanotechnology Alliance"* (*15*), also provide invaluable information to assist researchers inside and outside the Alliance with key information to facilitate translation.

b. Are there gaps in the Alliance research portfolio?

In general the Alliance research portfolio was considered to be comprehensive and well-balanced. The panel did however identify some areas that may merit strengthening:

Basic Research Expertise

- Chemistry plays a key role in the interface between nanotechnology, cancer biology and clinical practice, and encompasses many sub-disciplines, including colloidal chemistry, supramolecular and synthetic macromolecular chemistry, and all aspects of organic chemistry including carbohydrate, lipid and protein/peptide. Complex engineered nanostructured surfaces require carefully controlled surface functionalization using many of these components and linking chemistries, and almost all nanopharmaceuticals and theranostics are complex multicomponent systems. To arrive at effective and safe nanopharmaceuticals this expertise is needed at the outset. Early validation of methodology for characterization of critical features of these complex systems is essential in order to avoid performing biological experiments with poorly characterized and/or impure materials. NCL has provided important support in this area, but the research teams might benefit from inclusion of collaborations at the outset to do more.
- Pharmaceutical sciences are key enablers for transfer of nanopharmaceuticals from lab to clinic. The Alliance would benefit from greater use of quantitative methods to measure pharmacokinetics and biodistribution at the whole body and cellular level, including biosystems research and quantitative imaging. Related areas include consideration of metabolism and long-term fate of all components, as well as issues relating to pharmaceutical formulation and product development. It is often the academic community that develops the innovative methods that underpin later industrial development. Although

NCL has also made important contributions in this area, inclusion of these competences at the earliest stages in each research team would increase productivity.

- Image Guided Drug Delivery (IGDD) is an important research area to be further explored. While some NCI programs are addressing physical standards for image guidance, the scale of research work and related standards for PK/PD studies needs to be greatly increased and validation studies to show that the drug on the nano platform reaches the target.
- There is a growing realization that dysfunction of endocytosis and intracellular trafficking is very important in cancer, especially as most of the discussed nanosystems are designed to hijack these pathways. Additional expertise in this area could be helpful.
- The portfolio has a relatively low emphasis on cancer prevention – per appendix B none of the caNanoPlan milestones on “Nanotechnology and Cancer Prevention” are being addressed by the Alliance.
- The use of nano technologies for cancer risk is an important research area to explore further, but with a clear realization that the methods must meet minimum interventional requirements for subjects that have no symptoms as yet. Some nanotechnologies have the potential of being low cost and thus amenable for large cancer risk studies, particularly in underdeveloped countries.
- Modeling and simulation in addition to informatics is well positioned to support design of nanostructures.
- Establishing user facilities within the Alliance or in collaboration with National Nanotechnology Infrastructure Network (NNIN), Network for Computational Nanotechnology (NCN) or other established tool oriented user facilities could enhance diversity of tools and techniques available to the Alliance researchers.
- Ethical, legal and societal aspects (ELSI) aspects should be included in overall discussions of impact of nanotechnology among Alliance investigators.

c. How successful has the Alliance been in establishing and supporting an inter-disciplinary model of research? Does this model produce effective collaborations, and do these collaborations provide added value for discovery and translational research?

There was a consensus that the Alliance has clearly promoted new interdisciplinary collaborations. The CCNEs, with the ability for cross-Center collaboration, provide an excellent model. The Panel did have questions about how the CCNEs are managed post-award to ensure all partners contribute in a timely way to the original work-plan. The creation of the Alliance network, bringing together a variety of modalities of center/platform/group/individual support, and organizing informatics and Nanotechnology Characterization Laboratory as cross-domain service to researchers was felt to be a valuable approach. Also, the interaction with other NNI programs and centers has involved perspectives, tools and methods from various other areas such as synthesis and characterization of nanomaterials (developed with support from NSF, NIST, DOE, DOD, NASA) to environmental and toxicity issues (sponsored by FDA and EPA).

The Alliance grants are designed to provide synergy, but even so funding seems modest in relation to the diversity of the portfolio coupled with the high expectations of delivery to clinical stage - developing 'specific' innovative technologies that can actually be commercialized and used to bring "a paradigm shift" in patient care is really challenging. It is thus even more impressive that Centers of Excellence/Projects have been so successful in terms of promoting interdisciplinary

collaboration, capacity building and translation. The North Carolina CCNE led by Joseph DeSimone was put forward as an exemplary case of combining these elements, including commercialization potential.

The Alliance Challenge Projects provide an additional mechanism for promoting inter-disciplinary partnerships with internal and external partners, including translational activities such as scale-up of nanomaterial production, GMP production of nanomaterials, and pre-IND activities. Challenge projects are funded from restricted funds, approximately 5% of the total award amount. Thirteen of sixty-four Challenge projects funded to date have included partners from outside the Alliance, although in the most recent round of funding only three of twenty-one projects included external partners. External partners also do not receive funds from the Alliance as a result of the partnership. Given the rapid changes in the field and availability of new technologies, greater flexibility in bringing in new partners and providing funding to them through subcontracts should be considered.

d. Is the field of cancer nanotechnology contributing to lasting improvements in cancer research and clinical practice? What was the role of the Alliance program in enabling this progress?

While it takes time to introduce new technologies, first generation nanomedicines and diagnostic devices are already beginning to make important contribution in the clinic. Progress is certainly accelerating with the increasing number of nanopharmaceuticals/imaging agents, companion diagnostics and devices under clinical evaluation and entering the market. The Alliance program has led to systemic improvements in the investigative approaches (subcellular, molecular medicine) in both foundational and applied research methods. While the Alliance funding cannot be used for clinical trials, upstream projects leading to clinical trials are required in each Center (such as leading to Investigational New Drug and Investigational Device Exemption status to FDA), leveraging with partners (such as through the Translation of Nanotechnology in Cancer consortium and dissemination of standardized protocols and best practices) have been required. After three years of Phase II, there are 17 related clinical trials for therapeutics and five devices and instruments have started clinical trials or IRB approved studies. Benchmarked against other NIH or NCI research networks for translational or global efforts in this arena, the Alliance has been very successful in accelerating translation of really novel technologies from the early prototype stage to clinical translation (e.g. Aurolase, PRINT Nanoparticles).

2. Clinical translation and commercialization: How successful are Alliance researchers at clinical translation and commercialization of their technologies? What role do the Alliance network and activities play in this success?

Ultimately in order for nanotechnology to have a meaningful impact, tangible results need to be evident in patients. Metrics of IDE/IND submissions as well as open clinical trials during this period are particularly important. This round of the Alliance was conceived as a translational research program, and the Centers of Cancer Nanotechnology Excellence in particular were expected to aggressively pursue clinical application and commercialization of developed technologies.

Each center was expected to have at least one IND or IDE submitted to the FDA by the end of the funding period. Several of these research efforts, for example in vivo investigations include the use of both physical devices and molecular probe(s), and are thus treated as "combination products" by the FDA. Thus, one important translational goal and metric for success for the Alliance is to seek IND approval from the FDA for a "combination products", clearly a very difficult goal to reach. The Alliance network design has in several ways uniquely positioned itself to meet this goal. For example, the development of a network-wide research environment across the academic centers, where good laboratory practice (GLP) is implemented and good manufacturing practices (GMP) are envisioned and shared are critical to reach this goal. The NCL, a unique facility worldwide, has clearly served as a critical resource. Alliance funding cannot be used specifically to fund clinical trials, but it was the intent that Alliance funds were used to leverage support for nanotechnology clinical trial from other funding sources. The Alliance has also attempted to improve the likelihood of clinical success by assisting investigators by providing access to industrial representatives, through forums and panels at Alliance sponsored meetings and through the Translation of Nanotechnology in Cancer (TONIC) consortium.

In order to measure the success of the clinical program attention was paid to the quantity and quality of IND/IDE submissions and clinical trials, the ability to leverage outside funding and the evidence that the Alliance was able to facilitate communication and disseminate information. Based on a high level review of the Alliance reports, it is readily apparent that an extensive exchange of knowledge and best practices has been encouraged across the research centers and has resulted in several IND applications, either submitted or planned, as reflected in the extensive list of ongoing Phase 1 and Phase 2 clinical trials (Appendix B). This is a remarkable achievement by the Alliance members, industry partners, and NCI program management, especially considering the limited time period of the program. The research efforts of Alliance members are often initially at the concept level or early pre-prototype stage. By comparison, IND's would typically take 5-10 years for a technology at a mature prototype stage, under R01 funding.

Clinical work can be broadly divided into therapeutics, imaging and diagnostic devices. Alliance supported therapeutic trials can be divided into several broad areas, including trials designed to enhance the activity of approved chemotherapeutic agents, gene therapy studies, and studies on enhancing siRNA delivery. In addition plans have been made to eventually move into facilitated delivery of tyrosine kinase inhibitors. Those that are chemotherapy based are the furthest along and are moving to large trials. This appears to be the area that would most likely to move to FDA approval. PK/PD analysis of these studies has clearly supported the impact that nano delivery has on drug availability. These studies are less "sexy" but are very important to continue to move the field forward. It will be very important to determine the clinical impact of both the camptothecin and docetaxel based trials. Positive studies will rapidly accelerate this technology into a wide variety of small molecules, but there is some caution after the CRLX101 study failed to meet its primary endpoint. Gene therapy studies and the use of nanoparticles to facilitate siRNA delivery is not as far as along clinically, although there remains significant work in these areas. It is important to see additional clinical activity in these areas over the next several years as a means to jump-start these more complicated therapeutic modalities.

There have been a very significant number of IND/IDE's filed in the area of imaging. This is clearly an area of significant importance and should be strongly supported. The work may not be as far along as some of the chemotherapy-based trials but there promising results in both breast

imaging as well as in virtual colonoscopies. These positive results in breast cancer led to initiation of a Phase 1 trial sponsored by the UNC Lineberger Comprehensive Cancer Center in collaboration with NCI (NCT01773850). The trial is expected to be completed in January 2015 following recruitment of ~100 patients. The goal of the study is to compare the confidence level of radiologists evaluating patients using the carbon nanotube based device compared to conventional mammography. Trials such of these are very important and are an example of strong industry/academic/government collaborations.

The pathway to approval is very different for technologies that are not used *in vivo.* Multiple trials are underway that use Alliance supported devices to monitor activity in clinical trials. This is an area that needs continued support, but the utility can only be understood once the clinical activity of the investigational agents is demonstrated. This seems like an area that continued support should be provided because the need is great, but the costs may not be as significant.

There is no doubt that the emphasis on translational research is having its desired impact in the clinical arena. The number of IND/IDE's, clinical trials and evidence of leveraged funding is significant. It will be very important in the future however to demonstrate the next step and move the promising array of technologies beyond the research state and onto the FDA approval list. The Alliance is working hard to provide both the tools and collaborative opportunities to make this happen.

b. How successful are Alliance efforts in fostering partnerships between academia and industry? What is the value of these partnerships? Which Alliance efforts have been most effective?

The Alliance centers provide a critical mass of committed investigators that operate in an "open science" or precompetitive space. The latter "open science " efforts include the implementation of trans-center working groups, including collaboration with other NCI initiatives at the division and program level. Such goals and rationalization are consistent with NCI's major investment in research networks for biological research, such as the TCGA, and clinical trials networks (NCTN). The extensive outreach to over 70 companies interested in the translation and dissemination of nanotechnology to address the cancer problem, is very impressive. In addition the operational design of the Nano Alliance Centers and research sites by NCI program staff, including for example, enhanced collaboration between centers, has played a critical role in ensuring the basic and clinical research timelines are met and that important cancer problems are targeted.
This management design has thus created a framework to develop and implement a Public Private Partnership (PPP), namely TONIC (Appendix B). This is an excellent example why NCI should support technology research networks, as research framework, if well designed as the Nano Alliance is, attracts leading device and drug industry to join in the partnership. Thus the Nano Alliance is highly leveraged, not only with additional funding at several of the academic sites, but includes industry investment on a large scale, which has clearly resulted in early dissemination of Nano technologies that address important cancer problems. Information provided by the Alliance indicates that $115M in awards was made to Alliance institutions and affiliated companies between September 2010 and June 2013, and in addition there was more than $250M in investments in the most successful Alliance affiliates over the course of Phase I and II of the Alliance. This extensive leveraging will easily exceed NCI's total investment in the Alliance by completion of Phase II. It is difficult to comment objectively across the whole program but it is

clear that there are significant successes as mentioned above and documented in the Report. The industrial partnering/support of ANC related companies such as BIND (recently leveraging partnerships with Amgen, Pfizer and AstraZeneca), Liquidia Technologies, and Integrated Diagnostics is very impressive. However, there is a need to strengthen the bridge to application after Alliance research and preliminary testing.

c. Is the Alliance supporting development of standards and public datasets for nanomaterials and nanoscale devices and their widespread adoption? Is the Alliance improving access to information and data on nanomaterial properties and characteristics through public databases?

The support for nanobio-informatics, in establishing the web portals, caNanoLab and the Nanomaterial Registry are essential for the whole operation and have to be institutionalized by NCI. The NCL has created caNanoLab, a unique database with physico-chemical measurements, in vitro and vivo testing results for the nanomaterials used in cancer research. NCL through its activities and publications has been very important in development of standards/methods and public datasets for nanomaterials. Dissemination of NCL experiences through publications (*16-20*) and through meetings globally has been invaluable. This is an excellent example of research driven informatics as opposed to top down approaches addressed by NCI under the CaBIG initiatives.

3. Training in cancer nanotechnology

Do Alliance training programs support creation of a cohort of multi-disciplinary researchers capable of applying nanotechnology tools to critical problems in cancer research and clinical oncology?

The six Cancer Nanotechnology Training Centers (CNTCs) have a focus on early-career trainees, providing interdisciplinary training to more than 100 graduate students and 21 postdoctoral fellows. Dedicated courses on nanobiotechnology and nanomedicine have been established at UCSD, University of Kentucky and Boston University CNTCs, and the CNTCs are also exploring other innovative approaches to foster interdisciplinary research, including dual mentoring by both research and clinical mentors and the use of network analysis to assess outcoes.

The CCNEs provide additional opportunities for training. The formal requirement of 2.5% the budget for a center to be dedicated to education, training and outreach and 3% for innovative pilot projects are relatively small as compared to the perceived need. The Pathway to Independence Awards is a combination of two year postdoctoral support followed by a three-year independent research in the program. There are seven successful awardees in the Phase II. There are multiple outreach activities to public that have an important impact on general public information and recruiting younger scientists in the field. The established cancer research platforms successfully link science, engineering, biology, and informatics to medicine. It is important that the training and research environment exposes the trainee to all disciplines that would be needed to realize the research to practice and also bring some understanding of translational challenges.

Graduate student trainees from the CNTCs who have received their PhDs have gone on to a mix of postdoctoral fellowships and industry positions. A number of Alliance trainees have gone on to faculty positions. The general sense is that the Alliance is being successful in developing cross-trained researchers, but longer-term metrics will be needed to assess this fully. These metrics should include attempts to assess the relative career success of trainees in the CCNEs versus those trained through the dedicated CNTCs.

4. Does the Alliance program appropriately balance support for discovery research in cancer nanotechnology and promotion of clinical translation of nanotechnology? Should this balance be improved or reconsidered in future NCI initiatives in cancer nanotechnology? In preparing for the future, how should NCI prioritize its nano activities?

Cancer research is a long-term challenge that needs simultaneously a balance between basic research, translational research and clinical trials. Basic research needs to continue in parallel with innovation in future programs. The initial focus on basic research in Phase I and increasingly on system approach and clinical targets in Phase II seems appropriate. The Panel felt that it is difficult to gauge the balance between discovery research and clinical translation without a feeling for relative funding, and numbers of staff/projects being supported in the 2 areas. Data on the level effort (number of people, funding) in different areas from 2005 to 2013 from NCI would facilitate a more quantitative evaluation of the balance. Following receipt of the initial draft report, Alliance staff provided an estimate of the portion of research Center budgets assigned to translational research, which ranged from ~20-35%. Overall, approximately 30% of the funds and personnel for Centers are allocated to projects with a translational goal, which would represent ~20% of the overall Alliance budget. The Panel felt this was appropriate considering the state of the field.

The Alliance has created an excellent foundation for cancer treatment in the U.S. and entire world that has to be continued with a new forward-looking plan to have the return on investment. It is recognized as a global flagship program in cancer and medicine. The core of the Alliance is the CCNEs, the NCL, and TONIC, and retaining these components should have a high priority. It will be important to consider which projects should be closed (either as the basic science is completed or because the technology has been spun out). In the current fiscal climate, with budgets declining in real terms, it will be critical to take a hard look at ongoing and newly proposed basic/discovery science projects to assess which of them really have translation potential. For example, in the delivery vehicles described in Table 1 (Accomplishment Summary), how many of these examples are just nice science, versus how many have the capability to progress and should be supported further to ensure they translate?

In terms of additional focus areas, an increased focus is needed on preventive measures for cancer by food, natural drugs, and other methods. Consider including toxicity and societal implications evaluation in all large centers and projects.

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