MIDCOURSE REVIEW OF THE NIH NANOMEDICINE ROADMAP INITIATIVE

Nanomedicine refers to highly specific medical interventions at the molecular scale for curing disease or repairing tissue. The NIH Nanomedicine Roadmap Initiative was envisioned as an ambitious ten-year program with three strategic objectives: (1) to apply quantitative approaches toward an understanding of the design of biomolecular structural and functional pathways at the nanoscale, (2) to use this information for the creation, design, and application of biocompatible molecular tools to restore function to cells and systems in vivo, and (3) to adapt these tools for specific clinical applications.

Because the field of Nanomedicine is still in an embryonic state, the immediate goals of the Nanomedicine Initiative are two-fold: to speed the acquisition of the fundamental knowledge, and to create the community of scientists—biologists, chemists, engineers, and clinicians—necessary to make nanomedicine a reality. To achieve these goals, the initiative developed a national network of Nanomedicine Development Centers (NDCs) that conduct novel, multidisciplinary research focused on characterizing the engineering design principles of molecular assemblies that serve as molecular machines carrying out critical physiological functions at the cellular level. Once defined, these design principles would eventually allow scientists to develop tools and nanoscale components that function in cells to repair damage and cure disease. The existing NDCs focus on a range of model systems such as: (1) “smart” cells that have designer guidance systems for targeted delivery of drugs or cellular repair machinery, (2) photo-activatable ion channels for curing blindness associated with various retinal diseases, and (3) design and delivery of chaperonins, protein folding machines that will rid cells of misfolded proteins that lead to diseases such as Alzheimer’s Disease and Huntington’s Disease. Eight NDCs were established following two rounds of Requests for Applications (RFAs) in 2005 and 2006. Using the Flexible Research Authority (FRA) granted by Congress to enhance NIH Roadmap activities, the NIH created the Nanomedicine Initiative Project Team (NIPT) to manage and oversee the initiative, and to work closely with each NDC, providing input and guidance. Because the FRA gave the NIH a great deal of flexibility and authority, the NIPT also provided competitive and non-competitive supplements to the NDCs to spur additional activities and to keep the programs focused on the goals of the initiative.

In April 2009, in conjunction with the 3rd Annual Awardee Meeting for the NDCs, the NIH held an early Midcourse Review of the program in Bethesda, MD. Principal Investigators (PIs) from all eight NDCs were invited to address questions about the structure, management, and direction of the initiative. In addition to hearing from the PIs, the Midcourse Review Panel held meetings with members of the NIPT, and met in closed session for discussions.

There was unanimous agreement in the Midcourse Review Panel that the NIH Nanomedicine Roadmap Initiative is a transformational program that is meeting its goal of synergizing multiple disciplines to focus on a specific biomolecular pathway or question in each of the eight NDCs. Each NDC is supporting a unique and creative, high-risk high-impact approach based on excellent basic science. Within a short timeframe, each center was able to recruit a multidisciplinary team of investigators from different institutions that are developing and applying nanoscale technology to address cellular and subcellular processes in biological systems. The multi-institute approach within each center is one of the great strengths of this program. The complexity of the problems addressed by the NDCs require such a diversity of expertise ranging from surface chemistry to pediatric medicine as examples that the NDC mechanism provides a formal structure for such interactions to occur.

Another key strength of this program is the availability and the use of the FRA by NIH to establish a strong working relationship between the NIPT and the centers, with the NIPT leadership maintaining oversight of the network and having the flexibility and authority to use supplements to recognize scientific merit and to support the scientific and programmatic needs of specific NDCs. By having a small team of NIPT members in close consultation with each center, the program was able to respond quickly to needs, and also urged changes when necessary. The panel thought that the guidance, recommendations and decisions made by the NIPT to this point have been useful and appropriate. In particular, the funding decisions that have been made thus far show that the NIPT has recognized the NDCs that are achieving the program's goals. A prime example is the Pathway to Medicine (PtM) supplements that encouraged centers to identify and form collaborations with clinical investigators working on conditions that might have a direct benefit from the technology being developed. While the PIs found this degree of oversight unusual, they agreed that the interest and guidance provided by the NIPT was important to their progress. These communications underscored NIH's expectation that each NDC should integrate planning for biomedical applications as early as possible, and to translate novel technologies to clinical use.

The Panel also recognized the innovative way the NIPT has ramped up the network: (1) by offering two rounds of RFAs to select the best applications; (2) by providing baseline funding to each center followed by opportunities to obtain supplemental funding targeting specific goals; and (3) by providing intense oversight and guidance. Thus, while the projects are all scientifically ambitious and high risk, which is expected, the program has pushed the basic scientists to include clinicians to their research. Overall, the significant interactions with the NIPT offer a unique and positive way to keep the Nanomedicine Initiative on track to meet its eventual goals.

All panel members noted the high quality of the science supported by the program and the importance of the multidisciplinary education being created. The NDCs are providing a new way of thinking about and approaching novel therapies, and are grooming the next generation of biomedical researchers to think and move comfortably across diverse scientific and medical disciplines. Finally, as a trans-NIH endeavor, the NDC program is unique in its ability to involve a long list of institutes within the NIH whose staff officers serve on the NIPT.

The Panel agreed that the eight NDCs were not all equally successful in making progress in their research, as well as in meeting the goals of the initiative. Although the panel acknowledged that good science was being done in all of the NDCs, some centers had evolved in directions that are clearly aligned with the stated goals of the Nanomedicine program and others had not. The uneven performance of the centers reflects, in part, the commitment of each center not only to creativity and excellence in basic science, but to establishing strong collaborations, extending outreach to the scientific and clinical communities, and to creating educational opportunities for young investigators in academia. Some centers were successful because they were nimble and understood well the goals of the program, and could therefore respond quickly to new funding opportunities offered by the NIH. For example, with the PtM program, some NDCs responded with ideas and actions that significantly improved the scope of their program while the actions or reactions of other centers actually diluted and diminished their progress.

This difference in success rates is to be expected given the ambitious goals and tight timeframe of the initiative, which requires bold steps and investment in high-risk projects. The panel noted that all of the NDCs have dramatically changed their programs, and all centers are conducting excellent research. One panelist pointed out that meritorious research on molecular and cellular

biology with a focus on nanoscale structures currently conducted in the NDCs could also be funded through other, conventional mechanisms within individual institutes within the NIH.

The leadership of the NDCs expressed concern that close oversight and guidance by the NIH could at times be stressful. Some PIs felt that attempting to meet the NIH's many expectations sent them in different directions and ended up diluting their efforts. They felt that information about new plans and directions from the NIH was sporadic and often required a quick turnaround; they believed that they could have planned a better response had they been given more time. The PIs all felt that the program was under-funded if all the goals were to be met within the given timeframe. Some of these challenges were triggered by changes in NIH priorities, which understandably compelled the NIPT to redirect NDC activities.

Some members of the Panel wondered if it was unrealistic to expect translation of such new technologies within such a short timeframe, and whether by recruiting too many participants, some centers were hindering their management and their ability to be nimble and productive. Finally, the Panel felt that interactions and collaborations between the eight NDCs should be much more robust if the program is to operate as a network as envisioned. In addition to improving collaborations and outreach efforts, many centers shared similar problems and could benefit if they tried to solve them together.

RECOMMENDATIONS

The Panel had several major recommendations for the Nanomedicine program.

1. A new mission statement is needed that states clearly the nature, goals and expectations of this program. This is a transformational program that supports high-risk, high-impact approaches in a new scientific field by building multidisciplinary teams, each focused on developing a unique, innovative approach for addressing biological processes that have hitherto not been addressable. The mission statement should underscore the translational thrust of this program and the active participation of clinician-scientists to develop these technologies for eventual clinical use.

2. NDCs that are less successful and have had difficulties achieving the key goals of the program should be phased out or terminated. The Panel noted that about half of the NDCs fall into this category. This will allow the NIH to fully fund the activities of the centers that are successfully meeting most of the goals of the program.

3. The next competition should be an open call to allow new centers to be recruited into the network. The Panel believes that since the last call for proposals in 2006, many new groups with innovative approaches in this field have emerged. By opening the next RFA to the growing field of researchers, the program could benefit from an influx of new ideas and investigators. Some Panel members felt that the successful NDCs could continue with non-competing renewal applications akin to Merit awards. Others felt that all NDCs should apply anew. The successful centers will prosper in the competition having already built up their program over the past funding periods. The less successful centers should be advised that they would need to change their programs significantly in order to be competitive in the next round of funding.

4. Based on the experience with the existing NDCs, it would be beneficial to the program to fund NDCs in 5 year periods with the assumption that each is eligible to apply for and, if successful, receive a second period of funding for a maximum 10 year funding life. It will

require 10 years of support for an NDC to produce transformative science that may impact future medical practice.

5. Participating investigators should be encouraged to obtain additional funding (spin-off grants) so that new discoveries can progress at a faster pace and continue beyond the 10 year term of the Nanomedicine Initiative. Any confusion over whether spin-off grants are permitted under the terms of this initiative should be clarified.

6. To extend the reach of NDCs, mechanisms to support small applications (e.g., R01's) should be created to allow new research groups to "piggyback" onto the existing NDCs. One possibility is a "Pathway to Science" that mirrors the successful PtM initiative.

7. Outreach to the broader scientific and clinical community and the education of young investigators will be important to bring more attention to this emerging field and its many opportunities. The next generation of biomedical advances will come from scientists and clinicians who are able to move and think comfortably across scientific and medical disciplines. Thus, this program should continue to encourage workshops, courses, and mini-symposia to spread the "nanomedicine" concept.

8. At present, basic science is still the driving force for developing the nanoscale techniques and tools. As the program progresses, the clinical component should expand to highlight the "medicine" part of Nanomedicine. One panelist pointed out that the current emphasis on clinical translation is a step in the right direction. However, success in translation would require additional support for clinical translation infrastructure (such as standardization and robustness of platforms) without which the expectation to have clinical translation valence in 10 years is not realistic.