EVALUATING THE SELECTION PROCESSES FOR THE NIH ROADMAP NANOMEDICINE INITIATIVE NANOMEDICINE DEVELOPMENT CENTERS

Executive summary

Introduction

In late 2006, the Science and Technology Policy Institute (STPI) at the Institute for Defense Analyses (IDA) began an evaluation of the processes through which the National Institutes of Health (NIH) Nanomedicine Development Centers (NDC) program selected the eight current Nanomedicine Development Centers (NDCs), four centers awarded in 2005 and four more awarded in 2006. During the course of this evaluation, STPI conducted a series of interviews with NDC program participants and stakeholders in addition to performing longitudinal content analysis of application documents to assess the feasibility and necessity of a broader, more in-depth evaluation of the NDC selection processes implemented to select the first two cohorts of NDCs.

In addition to the practical goal of assessing the feasibility and necessity of further evaluation, the analytic goal of this study is to identify which aspects of the selection process facilitated the solicitation and identification of applications best suited to meet the objectives of the NDC program. This evaluation includes an analysis of the use of Flexible Research Authority (FRA)1[1] to select NDCs, which enabled program officials – collectively referred to as the Nanomedicine Implementation Project Team (NIPT) – and their Extramural Consultant Group (ECG) to interact with applicants and extramural reviewers at numerous points during the application process, in ways very different from standard NIH processes and practices.

The NDC program is part of the NIH Roadmap for Medical Research (now known as the NIH Common Fund) and is the focus of the NIH Nanomedicine Roadmap Initiative. The mission of the program is to enhance understanding of the operations of molecular structures, processes, and networks as they occur within living cells, by cataloging patterns of interactions between molecules and larger structures. Eventually, it is expected that this understanding will lead to the development of general (i.e., not specific to a particular type of cell, but applicable across a range of tissues) nanoscale tools that enable the construction of synthetic biological devices for, among other purposes, cell repair or the detection and destruction of infectious agents. Despite this emphasis on the manipulation of nanoscale biological structures for medical purposes, the analytic focus of each NDC is the biological system, not a particular technological approach or set of approaches, since multiple technologies will probably be used in resolving particular biomedical problems.

From the NIH perspective, key organizational characteristics that might help NDCs to attain the ambitious scientific, technological, and clinical goals of the NDC program include:

- A center comprised of scientists from multiple fields and disciplines, including but not limited to physicians, biologists, engineers, computer scientists, and mathematicians.

[1] Use of FRA was introduced after program officials had already begun to plan the competition for selection of the first cohort of NDCs.

- Interaction across the NDCs to ensure resource efficiency and scientific complementarity.

While these attributes certainly are required, they are not sufficient to ensure the pursuit of the progressive, high-risk research the NDC program envisions. Accordingly, the NIPT implemented a highly interactive selection process for both rounds of competition which was designed to generate novel center proposals emphasizing progressive thinking.

Table 1. NIH Nanomedicine Development Centers

Award year	Center	Lead institution
2005	Center for Protein Folding Machinery	Baylor College of Medicine
2005	National Center for Design of Biomimetic Nanoconductors	University of Illinois – Urbana-Champaign
2005	The Cell Propulsion Lab	University of California – San Francisco
2005	The Nanotechnology Center for Mechanics in Regenerative Medicine	Columbia University – Morningside
2006	Nanomedicine Center for Nucleoprotein Machines	Georgia Tech Research Corporation
2006	Phi29 DNA-Packaging Motor for Nanomedicine	Purdue University
2006	The Center for Cell Control	University of California – Los Angeles
2006	NDC for Optical Control of Biological Function	University of California – Lawrence Berkeley National Laboratory

Findings in brief

The empirical findings from this report are presented in full in Sections 3 through 8 of the full report and are summarized below. Because this study is based predominantly on interview data, there are many quotations throughout the report. The questions that elicited these various quotations were open-ended and carefully crafted so as not to lead, while adhering to the rules of validity and reliability[2].

The results from the interviews and content analyses demonstrate the NDC program to be "unique" for the NIH, with mixed effects regarding the above parameters for selection process effectiveness. It is important to note that the presentation of these findings is empirical – based entirely upon what was reported during interviews and what the content analyses detected. Further, no quantitative decision rules were used for inclusion or exclusion of

[2] Interview questions are considered "valid" when there is congruence between the question and the concept it is purported to ask about; interview questions are "reliable" when they are interpreted consistently across the interviewer and interviewees. See Singleton Jr., R.A. and B.C. Straits *Approaches to Social Research Third Edition*. Oxford: Oxford University Press, 1999.

particular findings. In other words, both unique and common perspectives are included. Indeed, such richness of data is the primary advantage of qualitative case evaluation.[3]

Adherence to original plans and expectations

As mentioned above, the extent to which implementation of the NDC selection processes adhered to initial plans and expectations is not a major concern due to the use of FRA and the attendant flexible nature of NIPT officials' initial plans and expectations. Nevertheless, the structure for implementing the NDC selection processes was premeditated and clear, and implementation steps were performed according to plans. However, initial expectations concerning what precisely was to occur during each phase of the selection processes were considerably less clear. This was especially the case during the first round of competition. In interviews with members of the NIPT, the general expectation was that the first round process would be highly interactive, soliciting novel center proposals that rely more on progressive thinking than conventional center proposals (e.g., for the NIH P50). The findings for proposal novelty are reviewed in brief below.

Interactivity

The NDC selection processes were highly interactive when compared to standard NIH processes and practices. Of the participants and stakeholders interviewed – including members of the NIPT, the ECG, as well as applicants and extramural reviewers – all described the interactions as "unique" and "frequent." However, not all of the interactions were perceived as constructive, but rather as instructive and some even described specific interactions (i.e., at the Concept Development Plan [CDP] meeting) as "contentious." Specifically, most of the applicants and reviewers interviewed did not feel that their input was heeded by the NIPT, despite the stated intention by the NIPT to do so. In contrast, NIPT and ECG members generally felt that both the applicants and extramural reviewers did not understand the goals of the NDC program, specifically the goal of novel, "out of the box" proposals with a vision of how the knowledge gained could be applied clinically. Perhaps most important, the interviews and content analyses did not demonstrate that the interactions had a major impact on the scientific, technical, and clinical foci, or the goals and experimental approaches, of the proposed centers. Accordingly, although the NDC selection processes were highly effective at facilitating interactions, these interactions did not always have clear and consistent outcomes.

Program coverage

Measuring program coverage almost always relies on a reliable idea of who does and who does not comprise the target population. Due to the breadth and newness of the concept of

[3] It is important to note that in a qualitative case study, statistical inferences need not and cannot be made. For example, the perspective of one NIPT member could be of greater insight and value to the program than a common (and perhaps contrary) perspective shared across all extramural reviewers. Accordingly, the findings in this report are presented as-is. When they are interpreted in later sections of this Executive Summary, weight is given to the perceived evaluative value of the perspective and not to the number of interviewees supporting that perspective. However, some highly "valuable" perspectives may be shared across numerous interviewees.

"nanomedicine," however, the target population is sufficiently broad to defy definition per discrete disciplinary boundaries. A majority of those interviewed felt NDC program coverage to be adequate, for both rounds of competition. When asked whether areas of science and engineering that they thought promising avenues of inquiry for nanomedicine were absent from the application pools, most responded that program coverage was adequate.

Novelty of the applications

Whether the NDC selection processes are considered to have elicited (a) applications responsive to the call for progressive proposals relying less on preliminary data and more on creative thinking or (b) applications quite similar to those elicited by conventional selection processes seems a matter of perspective. When asked about the novelty of the applications, the members of the NIPT and the ECG interviewed reported the application pools from both rounds of competition to be comprised of relatively novel proposals. When asked the same question, many of the extramural reviewers interviewed responded differently, stating that a large proportion of the proposals, including some of those awarded NDC funding, could have been funded via conventional mechanisms. However, these reviewers did not comment directly on the novelty of the scientific and technical aspects of the applications, but rather focused on the feasibility of the management of the centers. In some instances, ECG members interviewed similarly reported that they felt some of the proposals could have been funded through conventional mechanisms.

Successes and challenges

Based on the empirical findings summarized above, the processes used to select the first two cohorts of NDCs were effective in that they facilitated high levels of interaction amongst participants, solicited center proposals that some (though not all) program stakeholders perceived to be novel, and gained wide participation across the biomedical community. However, with each of these successes came challenges. The most formidable of these challenges relate to divergence between the NDC processes enabled by FRA and long-standing NIH culture. Other challenges are typical when coordinating scientists and engineers from across institutions and disciplines to foster research and development in a new field of inquiry.

Convincing applicants and extramural reviewers to deviate from standard NIH practice

The first round saw much resistance by the applicant pool to both the structure and the expected outputs of the NDC selection process. Applicants in receipt of planning awards did not cooperate with one another as intended (i.e., approach other applicants to consolidate efforts and form larger or realigned teams). Instead, they viewed one another as competitors. Moreover, applicants during the first round were resistant to the idea of generating center proposals with a reduced emphasis on preliminary data and findings, but rather on progressive, "out of the box" thinking. Even after reassurance from NIPT officials, many applicants did not trust that the extramural reviewers would score favorably proposals without preliminary data and findings.

Indeed, many of the extramural reviewers reported that they scored the applications based on the demonstrated feasibility of the proposed science, regardless of whether or not the application constituted the progressive thinking encouraged by NIPT officials. This resistance occurred despite numerous tactics designed to facilitate a different approach to the reviews,

including preliminary teleconferences amongst NIPT officials and reviewers, written instructions for the reviewers, and the direct intervention of NIPT officials and ECG members during the review meetings.

Coordinating a "network" of NDCs

Coordination of the NDCs into a collaborative network of centers was not a central goal of the NIPT at the time of the competitions and was not a formal review criterion during either round. However, mention of such coordination was included in the Request for Applications (RFA) during both rounds, and the Concept Development Plan meeting during Round 1 included a breakout session on organizing a network of NDCs. Moreover, each of the eight applications awarded NDC funding included language addressing how the proposed center would coordinate within a broader network of NDCs. This language was drafted prior to learning which proposals were to receive funding and, accordingly, constitutes little more than a general and non-binding commitment to interact with other NDCs, independent of their respective scientific, technical, and clinical foci. Further, neither the extramural reviewers nor the NIPT and ECG members interviewed reported that such coordination was a major consideration when selecting the awardees during each round of competition. Finally, each of the NDCs is comprised of investigators from multiple institutions that are not co-located – a substantial coordination challenge (intra-NDC rather than inter-NDC) in its own right. Meaningful collaboration across the current population of NDCs will require programmatic oversight and managerial engineering beyond the center selection processes.

Clarifying what constitutes "nanomedicine" in the context of the initiative

Since inception of the NDC program, significant progress has been made in reaching consensus as to what constitutes "nanomedicine" for this initiative amongst NIPT officials and ECG members. However, some of the NIPT officials and ECG members interviewed still do not agree with the language used to solicit NDC applications. Further, some extramural reviewers and applicants expressed confusion over the definition used in the solicitation. Due to the interdisciplinary nature of this emerging field and due to the goal of simultaneously cataloging nanoscale biological patterns and developing nanoscale tools for clinical application, arriving at a universal definition of nanomedicine is not necessary or even achievable in the short run. But there is room for rendering more explicit the preferred balance of biological research versus tool development, as well as the timeframe from these activities to clinical application.

Conclusions and recommendations

The NDC program implemented two center selection processes (i.e., Round 1 in 2004-2005, Round 2 in 2006) that were highly interactive, solicited center proposals emphasizing progressive thinking towards development of the field of nanomedicine, and gained wide coverage across the biomedical community. An intangible outcome of the selection processes was a degree of consensus over what "nanomedicine" means, at least within the NDC program and perhaps more broadly for the NIH Roadmap for Medical Research. Therefore, on all accounts of process effectiveness, the NDC program may be considered effective.

With these successes came some challenges, most notably the challenge of persuading applicants and extramural reviewers to deviate from standard NIH process and practice. These challenges were difficult if not impossible to avoid insofar that NIH culture is long-standing. NIPT officials, with the help of the ECG, were proactive through every phase of both funding competitions to ensure that the NDC applications adhered to program goals and were not

"typical" of proposals elicited by conventional mechanisms (e.g., R01, P50). That, from the perspectives of the extramural reviewers interviewed, some of the applications resembled more conventional applications should not be viewed as a failing of the NDC selection processes, but rather more broadly (and fairly) as a function of the newness of the processes used to solicit center proposals for this new area of scientific and technical inquiry.

Based on the findings and challenges presented above, we provide two sets of recommendations. The first set of recommendations is specific to the NDC program. These recommendations are "ex post" recommendations addressing how NIPT officials may address currently some of the challenges faced during the Round 1 and Round 2 competitions (e.g., the lack of serious consideration of inter-NDC collaboration). The second set of recommendations is relevant to other NIH Roadmap initiatives that may use FRA or implement a program with comparable goals (i.e., an interactive network of centers pursuing a newly defined field of research and development). These latter recommendations are also relevant to the NDC program in the event that it solicits additional NDC proposals with subsequent rounds of competition.

"Ex post" recommendations for the NDC program

These recommendations address how NIPT officials may address some of the challenges faced during the competitions for NDC funding, now that the competitions are completed.

Provide incentive for inter-NDC collaboration

Initially, one of the chief "ex post" recommendations to be included in this report was to facilitate inter-NDC research projects using a program-level solicitation for joint project proposals on topics developed by the NDCs (and not by the NIPT) – requiring each proposal to include personnel from multiple NDCs and to focus on topics of mutual yet complementary interest that further the nanomedicine agenda. Further, our initial recommendation qualified that inter-NDC collaborations should not be mandated.[4] The reasoning for this follows from the first round of competition, when there was little incentive for applicants to heed seriously encouragement from the NIPT to evaluate the potential for collaborations with one another.[5]

[4] Empirical findings from the economics and strategic management literatures on "effective" inter-organizational collaboration in research and development suggest that the structure of these incentives should be "organic" – stemming from the mutual interests of investigators across the NDCs – rather than "top down" and orchestrated in focus and function by the NIPT. In other words, future inter-NDC collaborations should be initiated and implemented with as little programmatic interference as possible.

[5] This is understandable, given that applicants were asked to consider cross-proposal collaborations while the competition was still underway. However, during the second round of competition, there was increased incentive for consideration of cross-center collaborations insofar as there was the first cohort of NDCs (i.e., the four NDCs awarded funding in the first competition) with which to align, viewed by Round 2 applicants as being comprised of potential collaborators rather than competitors.

In 2007, the NDC program implemented such an effort, using the flexibility of FRA as a tool to manage set-aside funds that are allocated amongst the NDCs based on need or on competitive supplements. The request for competitive supplements included specific instructions encouraging inter-NDC collaborations, though proposals were not required to be collaborative.

Develop the meaning of (and broaden consensus over what constitutes) "nanomedicine"

The interviews that constitute the empirical basis of much of this report demonstrate disagreement across participant strata on a number of important issues.[6] Perhaps the one topic for which there was consensus across the participant strata was that there is room for further development of the meaning of "nanomedicine." While during the two competitions for NDC funding, it was beyond the purview of the NIPT to develop a common understanding of nanomedicine outside programmatic boundaries – and while today the NIPT is still obligated only to its constituents within the NDC program and to the broader NIH Nanomedicine Roadmap Initiative – the interview findings demonstrate that a clearer idea (though not necessarily a formal statement or definition) of what constitutes nanomedicine is in demand amongst those involved with the program.

Though the NIPT, with the aid of the ECG, reached consensus over what would be the "official" NDC program line regarding what constitutes nanomedicine and what does not, many individuals from both the NIPT and ECG reported in interviews that there remained "unofficial" disagreement over use of the term. This is not to say that such disagreement was overt or constituted a barrier during the selection processes, but rather that there is further program definition to occur. To this point, both applicants and reviewers expressed confusion over the definition used in the solicitations for NDC applications.

Of course, program definition for new fields of scientific and technical inquiry that span disciplinary boundaries and emphasize translation from the laboratory to the clinic cannot occur simply because one wants it to. The NDC program defined "nanomedicine" at the outset of the first round of competition to the extent possible under the difficult circumstance of defining a new field of inquiry.

The NIPT is now in the position to take advantage of learning from its experiences during the NDC selection processes as well as from learning that has occurred thus far at each of the eight NDCs. The question of what constitutes "nanomedicine" and what does not should be revisited, based on preliminary data sets and findings from the NDCs as well as on input from the ECG, extramural reviewers, and key personnel from the NDCs. A workshop or comparable forum should be held – either as part of a broader workshop or as a standalone event – to discuss further where the nascent nanomedicine "field" is and where it is headed. An

[6] For example, NIPT members felt that the proposals for NDCs were progressive and "out of the box," while the extramural reviewers and some of the ECG members felt that many of the proposals could have been funded using conventional mechanisms. Round 1 applicants reported that the Concept Development Plan (CDP) meeting had little impact on the scientific, technical, and clinical foci of their proposals, while NIPT members maintain that the meeting was necessary to get applicants "on track" regarding programmatic goals and expectations.

output of the workshop should be a programmatic definition statement, to be distributed for comment to a broader audience.

Expand the clinical ties of the NDCs

Initially, one of the chief "ex post" recommendations to be included in this report was to expand the network ties of the NDCs by soliciting outside clinicians to collaborate with NDCs in nanomedicine development and, eventually, nanomedicine trials/testing. The reasoning behind this recommendation was that while the applicant document deliverables included in the content analysis uniformly referenced potential clinical relevance, more often than not the language was quite general with no clear statement of specific clinical applications.

The NDC program has already implemented such an effort. In November 2007, a "Call for Clinical Collaborators" was announced by the NIH Nanomedicine Roadmap. Specifically, the Call requested "letters of interest in collaboration" from clinical investigators.[7] Awardees are expected to "explore opportunities for potential medical applications that build on the science emerging from one or more of the [NDCs]." The NDC program has made approximately $2 million available with which to support three to five clinical investigators through 2009.

"Ex ante" recommendations for future competitions

These recommendations address how NIPT officials may avoid some of the challenges faced during the first two competitions for NDC funding, in the case that subsequent competitions to fund additional NDCs occur. These recommendations may also apply to other NIH programs that may use FRA or be aimed at funding centers with comparable goals in mind (i.e., an interactive network of centers pursuing a newly defined field of research and development).

Increase decision making transparency

Practically all of the participants interviewed who were not members of the NIPT expressed ignorance of the decision rules and methods through which the awarded applications were selected to receive NDC funding. In particular, many of the subset of extramural reviewers interviewed were skeptical that their scores were a major consideration in NIPT officials' final decisions.

Given the unorthodox nature of the selection processes (e.g., not requiring proposals to include preliminary data and findings), it would serve the NDC program well to be clearer in its rules and methods for testing the extent to which proposals meet program goals and criteria. Codified dissemination of administrative differences and differences in review criteria may help offset some skepticism and help to align stakeholders with programmatic goals.

[7] See http://nanomedcenter.org/funding.

Do not expect competitors to cooperate

From a process perspective, the component of the NDC selection processes that stands out as unique was the CDP meeting during Round 1.[8] According to interviews and documentation, one of the purposes of the meeting was for applicant teams to share ideas, to self-identify synergies with other applicant teams, and perhaps even to make formal plans to cooperate (e.g., by combining multiple NDC proposals into a single proposal). This did not occur. All of the applicants interviewed expressed incredulity in response to this goal of the meeting.[9]

This is not to say that future competitions (whether for the NDC program or another NIH program) should not endeavor to develop an interactive network of centers focused on a unified scientific and clinical mission. However, effective research collaborations most often occur when there is mutual interest and the collaboration occurs as an outgrowth of that interest rather than when the collaboration is mandated by a program or policy. Accordingly, it is perhaps unrealistic to expect competitors to engage willingly in collaborative activities before funding has been awarded, unless there is assurance of mutual benefit (e.g., such as those found among firms in some technology-based industries). Therefore, in the future inter-NDC collaborations should be facilitated post-competition (e.g., once the NDCs, like firms in a particular industry engaging in collaborative research and development, are "established" as formal components of the NDC program).

Ensure alignment between programmatic and applicant expectations, continually

The NDC selection processes were designed as step-wise processes (especially during the first competition) to allow applicant teams ample time to develop their proposals for NDC funding. As applicants submitted "interim" (i.e., pre-NDC application) document deliverables, NIPT officials and ECG members evolved their plans and expectations for moving forward in the selection process. While there was frequent and extended communication between the NIPT and applicants throughout, many of the Round 1 applicants interviewed entered the "CDP meeting" phase of the selection process with different expectations than did the NIPT and ECG.

Specifically, in response to the CDPs that applicants submitted during Round 1, the NIPT altered their plans for the CDP meeting. Initially, one of the chief reasons for the meeting was to gather input from the applicant teams as to what the eventual limited competition NDC RFA should look like and to determine if the plans for the RFA were reasonable given the state of the science. After receiving the CDPs, NIPT officials realized that many of the applicant teams still had "missed the point" of proposing progressive research plans that included tough

[8] During this meeting, applicants who were approved to continue in the competition (after submission of a 5-page proposal and, upon approval from NIPT officials, receipt of a $50,000 planning award) met with one another as well as with NIPT officials and ECG members for a two-day workshop.

[9] There were varying reasons for such expressions. First, at the time of the meeting, no one knew which center proposals were to be funded. Many applicants expressed concern over allying with "losing" proposals. Second, the competition was "on" and the applicants did not want to "show all of their cards." Last, the amount of money to be allocated per NDC seemed to applicant teams enough to support themselves, but not themselves in addition to the research agenda of additional personnel from other teams.

challenges and “out of the box” ideas that are usually not funded by NIH. Accordingly, the majority of the discussion during the CDP meeting was spent conveying the goals and intent of the program by members of both the NIPT and the ECG.

Many of the applicants interviewed expressed dissatisfaction with this aspect of the CDP meeting. They went in expecting to help the program develop its mission and identity, but left having had little opportunity to provide such input. Universally across the participant strata, the CDP meeting was described as contentious, though some NIPT officials interviewed reported that the meeting started contentiously but ended amicably. If applicants had entered the meeting with different expectations – for instance, with the expectation of receiving critical feedback on their CDPs and how to align better their ideas for an NDC with the goals and expectations of the NDC program (which is precisely what occurred during the meeting) – the CDP meeting may have been described by applicants as helpful and instructive rather than as contentious. Coupled with the expectation for applicants to develop collaborations with each other during the meeting (see above), from the perspectives of the applicants interviewed, the CDP meeting was disruptive rather than helpful.

Allow more time for process planning

From the outset of the NDC program, and despite the intended interactive nature of the selection processes, there seems to have been insufficient clarity in the communications between the NIPT and applicants and between the NIPT and extramural reviewers. Indeed, most of the above recommendations address in one way or another increasing the transparency of programmatic expectations and decision making so that applicants, reviewers, and the NIPT can continually be “on the same page.” If the above recommendations were combined into a singular meta-recommendation, it perhaps would read “Articulate, and then *re*-articulate, programmatic goals and expectations.”

Perhaps some of the need for “re-articulation” may have been avoided if there had been ample time for process planning. The NDC program was not originally charged with the use of FRA. Once FRA was granted, NIPT officials essentially scrambled to figure out how to use it during program implementation (which was already underway). Many of the NIPT members interviewed reported feeling that the process planning was rushed.

Future implementations could benefit from more time for planning. Some of the extramural reviewers and ECG members interviewed mentioned that they felt many of the NDC applications to be fundable via conventional mechanisms. This is partially owing to long-standing NIH process and practice and therefore not entirely under the control of the NDC program (or any other centers program). However, the observation makes the need for extended process planning and design all the more apparent.

Anticipate the above challenges and then some

Do not expect the process to go perfectly. This report highlights the strengths and challenges of developing a new award selection process within the context of long-standing institutional culture at the NIH. The prevalent NIH emphasis on strong hypothesis driven science based on preliminary findings and arms length peer review is very different from an interactive selection process involving all stakeholders and focused on high risk, “out-of-the-box” proposals. This variance with standing process and practice made it difficult for the NDC

program to win the “hearts and minds” of all applicants, ECG members, and extramural reviewers participating in the program. Other NIH program officials implementing comparable programs soliciting “out of the box” proposals that aim to establish nascent fields of research and development must spend time to anticipate barriers to process implementation at the outset.