Outcome Evaluation of the National Institutes of Health (NIH) Director's Pioneer Award (NDPA), FY 2004–2005

Final Report

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Executive Summary

Overview of Study

The National Institutes of Health (NIH) launched the NIH Director's Pioneer Award (NDPA) in fiscal year (FY) 2004 "to support individual scientists of exceptional creativity who propose pioneering approaches to major contemporary challenges in biomedical research" (NIH 2004). The NDPA program grew out of concerns that the traditional NIH peer review process had become overly conservative, and the belief that NIH required specific means to fund high-risk research.[1] On the premise that great ideas are driven by individuals, and not necessarily by work plans, the program sought to find researchers who have the skills and creativity to take productive risks. The NDPA is a novel program that gave grantees extreme flexibility in how they could use the $2.5 million in direct costs provided to them through the grant.[2]

The NDPA represented a new way of funding biomedical and behavioral research for the NIH and, at the time it was launched, it was viewed by many as an experiment (NIH 2004; Culliton 2006). As such, there has been keen interest in understanding the outcomes of the experiment. The NIH commissioned the IDA Science and Technology Policy Institute (STPI) to undertake an evaluation of the short-term outcomes of the NDPA program. Because the program was experimental, so too is this evaluation; the goal of this outcome evaluation was to develop a valid set of measures that could be used to evaluate this program as well as other high-risk, high-reward (HRHR) programs in the future.

The high-level study questions that drove the evaluation were:

(1) Did the NDPA awardees conduct pioneering research with the NDPA funds?

(2) What are the spillover effects of the program?

In response to the first high-level study question, most experts agreed that the research funded by the NDPA was pioneering. While awardees did not believe their proposed research would have been funded through traditional mechanisms, some experts (about one-third) stated that the research outcomes could have been achieved using traditional mechanisms.

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[1] From interviews with NIH staff and NIH (2004), Risky Business (2004), and Brenner (1998).

[2] The NIH created the DP1 mechanism for the NDPA program to give awardees flexibility in how they use the funds awarded to them through the NDPA grant.

In response to the second high-level study question, our analysis found that most unfunded applicants who responded to the study's survey were able to pursue their NDPA-proposed ideas. In terms of broader changes at NIH and in the scientific community, a number of programs to support innovative research have been established since the launching of the NDPA. NIH staff indicated that the NDPA led the way for other innovative programs within NIH.

The STPI study team used four major data sources to answer the first high-level study question. The applications and progress reports informed our assessment of what had been proposed and helped us track, to the extent possible, the research progress of the awardees. STPI conducted in-depth interviews with the awardees to further assess progress of the research and to understand the outcomes of the award from the perspective of the awardees. Bibliometric analyses were performed on the publications of the awardees, including all their publications as well as those that specifically cited the NDPA funding. A virtual expert panel review was held in which experts assessed the "pioneeringness" of the accomplished research and provided insight into whether the awardees pursued their original proposed research or other high-risk research. This evaluation confirmed the literature's statement that there are no push-button or mechanical ways to assess whether research is pioneering.

Two additional data sources—a survey and interviews—informed the second high-level study question. We surveyed the unfunded applicants over the first four years of the program to understand the outcomes of their proposed ideas. Interviews were held with NIH staff to understand the additional effects of NDPA on NIH, and with staff of two other HRHR programs to understand the effect NDPA had on their design and implementation

The design for this study was primarily cross-sectional. Although we collected information on unfunded applicants, we were not able to make comparisons between the awardees and this group or another group of researchers because of the small number of awardees. The intent of the study was to develop measures for pioneering research that could be collected in future studies.

Literature Review

The concept of "pioneering" research is one that is not well-understood, and thus a literature review was performed to inform the study design and to look for markers that may help operationalize pioneering research.

The term "pioneering" is not widely used in the literature. We found no consensus in the literature as to what constitutes "creative," "innovative," "potentially transformative," or "pioneering" research, in part because these are social constructs.

Funding agencies are using these terms but do not explicitly define what they mean or explain how they compare to "traditional" research.

In terms of how to measure this type of research, most evaluations in the literature relied on expert judgment, although some empirical research attempted to draw a link between certain bibliometric measures and expert assessments of creativity.

The literature review informed our use of an expert panel and helped us determine our choice of bibliometric analyses. In addition, a typology of research risks and research rewards were used in this evaluation to further categorize the risks and rewards present in the NDPA-funded work.

Overview of Research Performed under the Pioneer Award Program

The NDPA funded a diverse set of researchers conducting a variety of HRHR research projects. Of the 22 awardees in the first two years of the program, eight had never been a principal investigator on an NIH R01 award, and two had never applied to the NIH for support of any kind. The awardees proposed to undertake research projects that differed from their previous research in several ways, roughly split between three categories. Some proposed to move their past research to focus on problems of biomedical or behavioral relevance. Some proposed a broader and more ambitious research agenda that tied together much of their past work. Finally, some proposed to undertake tests of a new and controversial hypothesis, work that would require resources beyond other mechanisms at the NIH for collecting preliminary research. In some cases, the awardees stated that they specifically came up with the idea once they heard about the NDPA solicitation; while the majority had held the idea previously but had not applied for support or were not able to have it funded through traditional mechanisms.

The NDPA was part of the high-risk research initiative and it funded projects that could be considered risky in a variety of ways. Experts were asked to characterize the types or risks present in the research according to a typology developed by Rita Colwell (2003), former director of the National Science Foundation. Characterizations were not mutually exclusive; and most projects exhibited multiple types of risk. Using this typology, the 22 expert panels identified that the projects were "high-risk" along at least one measure, specifically:

- Eight expert panels stated their project presented a conceptual risk—that fundamental ideas underpinning the work were at odds with the prevailing wisdom.
- Nine expert panels stated the project presented a technical risk—that the research required equipment, techniques, or approaches that either had not been proven or were assumed to be extraordinarily difficult.

- Eleven expert panels stated the project presented an experience risk—that the research was in an area outside the investigator's previously demonstrated areas of expertise.
- Fourteen expert panels stated the project presented a multidisciplinary risk—that the research entailed an unprecedented combination of disciplines or involved viewing the project from an unfamiliar multidisciplinary perspective.

Research Progress

All awardees felt their proposals would not have been funded through traditional mechanisms because of their risky nature, and most awardees were positive about the types of research the NDPA allowed and how it differed from research possible under traditional grants. The most common view was that the NDPA represented a more natural approach to research, in that it gave the investigators the freedom to follow the research where it took them, instead of applying implicit incentives about following the specific aims set out in a traditional NIH proposal.

Many awardees felt the award allowed them to take a long-term view of their research and thus take risks that wouldn't be advisable in a shorter term research grant. Many awardees also felt that the size and flexibility of the award allowed them to spend more time in the laboratory; they were able to do this both because they did not have the pressure of finding additional funding and because the NDPA allowed expenditures for administrative assistants and other personnel not typically permitted under other research grants.

However, not all the awardees pursued the research proposed in their applications. This was perhaps unsurprising given the nature of the risks inherent in the projects pursued, and the flexibility given to awardees in how they chose to use the NDPA funds. When asked about their research progress, two thirds of the awardees said they had reached their goals for one or more of the projects they proposed in their applications. Approximately one third said that aspects of their research had failed, and about one third said that research they actually pursued with the award had been an evolution from what they had originally proposed, either because of research failure or because of events taking place outside of the laboratory. Most of those researchers whose research evolved pursued other high-risk projects, while a few abandoned their projects to pursue work more closely aligned with projects they had been working on prior to receiving the NDPA. Some awardees stated that although they hadn't yet reached the goals for their project, they had always thought that the research would take longer than five years. A few stated that the progress on their research was actually faster than they had imagined it would be.

Pioneeringness of Accomplished Research

The accomplished or potential results of the NDPA-funded research were categorized by the expert panels into five, non-mutually exclusive types. This typology is one created by Heinze et al. (2007) in a study of creative research outcomes.

- Seventeen expert panels concluded that the research could result in the formulation of new ideas or theoretical concepts
- Thirteen expert panels concluded that the research could result in the discovery of new empirical phenomena
- Ten expert panels concluded that the research could result in the synthesis of existing disparate ideas
- Nine expert panels concluded that the research could result in the development of a new methodology
- Four expert panels concluded that the research could result in the invention of novel instruments
- One expert panel felt none of these outcomes were likely to result from the research.

In addition to assessing the potential outcomes of the research, the expert panels were also specifically asked to what extent they agreed that the accomplished research was pioneering. At least two out of the three experts on a panel strongly agreed that the research was pioneering for 14 of the 21 awardees examined. In two cases, two out of the three experts on a panel moderately agreed that the research was pioneering. In four cases, there was disagreement across the panel, and in one case, all three experts on the panel strongly disagreed that the research was pioneering.

For this study, creativity is measured using bibliometric methods as a proxy for pioneering research. Bibliometric measures that have been used as proxies for creativity include productivity, collaboration and brokerage, interdisciplinarity, and impact. The findings from the bibliometric analyses did not show an agreement with the expert panel assessment that the research was creative/pioneering. This could be because this outcome evaluation is an early review of outcomes (coming at the end of the funding cycle), so it is too soon to measure outcomes using bibliometric analysis. In addition, bibliometric analyses do not capture the full picture of an individual's research and cannot distinguish between failures due to a lack of research activity and failures due to attempt of research and finding the research project to be unfeasible. In addition, given the diversity of the sub-fields of biomedical and behavioral research represented, the range of types of projects undertaken, and the non-publication based outcomes that were found through interviews, it appears that bibliometric analyses are not on their own a method for assessing pioneeringness of the research, at least at this near-term stage.

Value of NDPA to NIH Portfolio

The question of what value NDPA adds to the NIH portfolio is a difficult one to objectively measure in an evaluation with a non-experimental design. Experts were asked, based on the research they reviewed, as to what extent they agreed with the statement that the NDPA was adding value to the NIH portfolio. Thirteen of the expert panels had at least two members who strongly agreed with the statement; one panel had two members who moderately agreed with the statement; one panel had two members who moderately disagreed with the statement; and six panels had disagreement across the members. In some cases, the experts noted the small number of awardees or their lack of knowledge about the program.

Other Effects of the Pioneer Award Program

A survey of unfunded applicants from the first four years of the NDPA was undertaken as part of this evaluation to understand the outcomes of those ideas that were proposed to, but not selected by, the NDPA. The response rate for the survey was slightly less than 50 percent, although the demographic distribution of the respondents was statistically similar for most characteristics (race, ethnicity, seniority, research area, and doctoral degree) except gender, where the number of females in the respondent pool was found to be slightly greater than would be expected based on the gender distribution of the entire unfunded applicant pool.

Of the respondents, approximately three out of five reported they would not have submitted their NDPA proposed idea to the NIH if the NDPA had not existed, and over 90 percent of respondents felt their idea was very risky or of medium risk. Despite not receiving NDPA funds, more than 80 percent of survey respondents said they were still able to pursue their proposed ideas at least partially, and nearly a quarter of respondents said they were able to pursue the idea in its entirety. The majority of respondents who pursued their NDPA-proposed idea indicated that they used other grants and institutional funds, or donated their time to work on the idea. An analysis of scoring data showed that those unfunded applicants who went on to receive other funding had higher scores on their NDPA application than those who did not receive other funding. Regardless of having been able to pursue their idea or not, most respondents reported having important career developments since the time of their NDPA application.

A review of programs that are designed to support innovative research at the NIH and in other federal agencies and foundations was also performed as a part of this evaluation. Representatives from all of the programs within NIH and two programs outside that appeared to be similar to NDPA were interviewed to assess to what extent they were influenced by NDPA. Interviewees of programs outside the NIH confirmed that the program designs had been influenced by the NDPA's design. Within the NIH, interviewees felt that the NDPA was part of a larger change within NIH to fund high-risk

research and that their programs were reflective of that larger change rather than a direct cause of the NDPA. Nevertheless, interviewees did say they felt the culture of the NIH towards funding innovative research was changing as a result of the NDPA and other high-risk programs.

Overall Assessment

This evaluation measured the short-term outcomes of the NDPA, focusing on the research conducted by awardees funded in 2004–2005.The evaluation showed the diversity of the types of risks and rewards in the research funded through the NDPA, and the variety of outputs and outcome emerging from the NDPA. While the NDPA-funded project was found in a few cases to be infeasible, and the research was abandoned, the majority of the awardees pursued their originally proposed ideas. The majority of experts agreed that the accomplished research was pioneering. Most experts stated the NDPA is adding value to the portfolio of NIH programs.

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1. Introduction

A. Overview of the NIH Director's Pioneer Award Program

The National Institutes of Health (NIH) Director's Pioneer Award (NDPA) was initiated in fiscal year (FY) 2004 "to support individual scientists of exceptional creativity who propose pioneering approaches to major contemporary challenges in biomedical research" (NIH 2004). The NDPA program grew out of concerns that the NIH traditional peer review process had become overly conservative, and the belief that NIH required specific means to fund high-risk research. [1]

The NDPA was the flagship program of the NIH Roadmap for Medical Research, a framework of NIH priorities designed to optimize the NIH research portfolio and to improve the current state of biomedical and behavioral research through the funding of specific programs.[2] In particular, the Roadmap Initiative aimed to establish programs which specifically promoted high-impact, cutting-edge research, which often did not fall into the interest of a single NIH institution or center. As such, an implicit goal of the program was to change the culture of NIH to be more innovative and to encourage the development of other high-risk funding programs.

The NDPA was designed to support highly innovative research. Based on the premise that great individuals—not just great research plans–result in groundbreaking ideas, the new program aimed to award "investigators who demonstrated the skills and creativity to take productive risks and specifically encouraged researchers working in fields that have not traditionally been supported by NIH" to apply.[3]

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[1] From interviews with NIH staff and NIH (2004), Risky Business (2004), and Brenner (1998).

[2] The NIH Roadmap for Medical Research is one of the programs under the NIH Common Fund. *See* NIH website, "About the NIH Roadmap," accessed May 18, 2011, http://commonfund.nih.gov/aboutroadmap.aspx.

[3] *See* NIH website, "2005 NIH Director's Pioneer Award Program Opens," *NIH News* (January 10, 2005), accessed May 19, 2011, http://www.nih.gov/news/pr/jan2005/od-10.htm.

The selection process for the NDPA substantially differed from that of traditional funding mechanisms at the NIH.[4] NDPA provided individual researchers with $500,000 in direct costs for each of the five years of the award, totaling a $2.5 million award. Between FY 2004—2008, 2,877 individuals have applied to the program, some applying in multiple years, for a total of 3,520 candidacies, and seven cohorts of awards have been granted for a total of 98 individual awardees (Lal et al. 2011).

At the time of its inception, the NDPA was markedly different from typical grant mechanisms at the NIH. Unique features of the program included a brief application that did not require the statement of specific aims (a hallmark of traditional NIH grants), and a review process which was conducted without discussion among reviewers, instead of through a traditional study section where reviewers are brought together to discuss proposals. Proposals were required to be for a new project—one that differed from the applicant's previous research focus[5]—Rather than using the standard NIH merit review criteria, proposals were evaluated on three primary review criteria: the significance of the problem, the qualifications of the investigator, and the suitability of the project for the NDPA mechanism.[6] The differences in terms of the amount, duration, and flexibility between the NDPA and NIH traditional funding mechanism, R01, are examined in Table 1. Compared to the average R01 grant, the NDPA provides a greater amount of funding per year; provides funding over a longer duration of time,[7] and does not require a project budget for how the funds will be allocated.

The NDPA was administered through the NIH Office of the Director (OD), and awarded only a small number of researchers across a range of scientific disciplines; this aspect of the program differed from traditional funding, which is generally restricted to the research area of the Institute or Center providing the funding. Compared to R01 awards, the NDPA was designed to be a more flexible grant than the R01, with no specific aims nor a detailed budget required.

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4 A detailed review of the program selection process can be found in Lal et al. (2010).

5 "To be considered pioneering, the proposed research must reflect ideas substantially different from those already being pursued in the investigator's laboratory or elsewhere." *See* NDPA Program Description, https://commonfund.nih.gov/pioneer/.

6 The review criteria were slightly different in the first year of the NDPA: (1) innovation/creativity; (2) intrinsic motivation/enthusiasm/intellectual energy; (3) potential for or actual scientific leadership; evidence of, or potential for, effective communication/educator skills. The criteria were modified in FY 2005 and remained consistent at least through FY 2008, when STPI ended collecting data on the NDPA process.

7 A total of 42% of all NIH awards are funded for 5 years; however, the average is 3.7 years. (*See* NIH website, "Research Portfolio Online Reporting Tools (RePORT)," accessed May 18, 2011, http://report.nih.gov/.)

Table 1. NDPA vs. R01 funding: amount, duration, flexibility

	NDPA	NIH R01
Funding Amount	$500,000 per year	Average of $300,000 per year
Funding Duration	Five years guaranteed	Three to five years, funding period may be shortened after grant is awarded
Flexibility of Funding	No budget required	Detailed budgets required

Source: FY 2004 NDPA Program Notice, NIH Research Portfolio Online Reporting Tools. (See http://report.nih.gov/).

B. Overview of Outcome Evaluation

Because the NDPA program design was significantly different from prevailing models of NIH funding, the OD commissioned the IDA Science and Technology Policy Institute (STPI) to conduct an outcome evaluation to assess whether the short-term outcomes of the program were consistent with its original goals, and evaluate the impact of the NDPA on NIH and its funding of high-risk research. To address NIH's request, this outcome evaluation focused on answering two core study questions:

1. Did NDPA awardees conduct pioneering research with NDPA funds?
2. What are the spillover effects of the program?[8]

To answer these study questions, the outcome evaluation focused on the short-term outcomes of the 22 awardees from the first two years of the program. The evaluation used a case study method to answer the first study question, relying on four major data sources: semi-structured interviews with the awardees; their applications and progress reports submitted to NIH; bibliometric analyses of the publications produced by the awardees; and an expert panel that reviewed research summaries and a small set of publications chosen by the awardees. For the second question, the data sources above were supplemented with interviews with NIH staff and a scan of innovative programs within and beyond NIH. Further details on the methodology of the evaluation are provided in Chapter 3. An Evaluation Advisory Committee composed of program stakeholders and other leadership at NIH with expertise in program evaluations oversaw the evaluation, and the evaluation itself took place over the period of June 2008 through February 2011.

[8] Our original study question was "What are the spillover effects of the program on the awardees, their students, and their institutions, on the unfunded applicants, and on the NIH?" Based on our pilot interviews, we found that we could not consistently obtain information about the effect of the NDPA on students and institutions. For the effect on unfunded applicants, we conducted a survey of unfunded applicants (*see* Chapter 7).

C. Outline of Report

The report is organized as follows. Chapter 2 contains an overview of the literature review on the topic of creative science and scientists; the review was performed prior to developing the evaluation design and study questions. The evaluation design and methodology are described in Chapter 3. Chapters 4 through 6 primarily focus on the first study question. Chapter 4 provides the perspective of the awardees on the two high-level study questions, and is supplemented with external data (such as funding information) where possible. Chapter 5 gives an overview of the bibliometric analyses that were performed as part of the study. Chapter 6 describes the experts' assessment of the research funded under the NDPA.

Chapters 7 and 8 relate to the spillover effects of the program, with Chapter 7 giving an overview of the survey of unfunded applicants and Chapter 8 listing the programs that have been established at the NIH and beyond that appear to have linkages with NDPA. Chapter 9 summarizes the findings of the evaluation and provides a few key recommendations.

Appendix A provides a list of indicators of pioneering research (A-1) and researcher's career (A-2), Appendix B provides the awardee interview protocol, Appendix C provides short research summaries of the 22 awardees from the first two years of the award, and Appendix D presents the questionnaire for the Survey of Unfunded Applicants.

2. Literature Review

A. Introduction

The purpose of the literature review was to look for methods and approaches that could inform the design of this outcome evaluation of the NDPA program. The NDPA Program Notice stated that goals of the program were "to support individual scientists of exceptional creativity who propose pioneering approaches to major contemporary challenges in biomedical research."[9] Thus, this literature review describes how terms related to pioneering research have been defined and operationalized in the literature.

B. Defining "Pioneering" Research

The term "pioneering" is not widely used in the literature. Thus, other markers are examined to assess if they could be used to help operationalize pioneering research.

Multiple terms, including "creative," "high-risk, high-reward," and "transformative" have been used interchangeably to describe innovative research in the literature and in documents of R&D funding programs.[10] For instance, the National Science Foundation (NSF) uses "potentially transformative" as a criterion in all solicitations, while "creative" and "innovative" appear in both the NIH Director's Pioneer and New Innovator Award program documents. The Office of the Director of National Intelligence's Intelligence Advanced Research Projects Activity (IARPA) describes all of its research as "high-risk, high-payoff."[11] Although it is clear that there are many terms used, there has been little clarification in the literature on the relationship between the terms or if they are in fact used to describe the same concept. The following sections provide short overviews of these terms, from the literature and from program evaluations, with a brief discussion on the nuances that appear among them. Since there is not one accepted definition, the literature provides the foundation for defining "pioneering research" using multiple yet overlapping definitions. Each is defined in turn.

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[9] *See* NIH Director's Pioneer Award Program Notice, January 3, 2005, available online at http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-05-021.html.

[10] Program leaders consider innovative research to be high risk, potentially high reward research (HRHR). We will use the terms innovative research and HRHR interchangeably.

[11] *See* IARPA website, "What is IARPA?" accessed February 28, 2011. http://www.iarpa.gov/whatis.html.

Innovative: In the literature on innovation in science, "innovative"[12] has traditionally been defined as being related to, but distinct from, creativity (described below). Amabile et al. (1996) defines "innovation as the successful implementation of creative ideas within an organization." Researchers often see innovation as the *usage* or *diffusion* of creative ideas.

High-risk: The term "high-risk" research has not been well-defined, although it is commonly used in R&D funding program language. The High-Risk, High-Reward (HRHR) Demonstration Oversight Group (DOG), comprising senior NIH officials, defined high risk high reward research as "research with an inherent high degree of uncertainty and the capability to produce a major impact on important problems in biomedical/behavioral research" (Austin 2008). The DOG elaborates further that the "HRHR definition has 2 independent components:

- First consideration must be "capability to produce high reward/impact (…more than solid, incremental science)
- If project is high reward/impact, then consider level of risk"

In a speech in 2003, Rita Colwell, former head of the National Science Foundation, put forth a typology of high risk projects in the context of research funding portfolios: a project could be risky because (Colwell 2003):

- The ideas underlying it are at odds with prevailing wisdom (conceptual risk)
- It requires the use of equipment or techniques that have not been proven or are extraordinarily difficult (technical risk)
- It is being undertaken by a scientist who has not demonstrated expertise in the area (experience risk); or
- It involves a unique combination of disciplines (multidisciplinary risk)

It is noted that this is not a measure of the level of risk, but rather a categorization of types of risks.

Transformative: This term has been used in official NSF documents. According to the NSF definition, "Transformative research involves ideas, discoveries, or tools that radically change our understanding of an important existing scientific or engineering concept or educational practice or leads to the creation of a new paradigm or field of

[12] Many definitions of "innovation" apply to the transition from laboratory to market. *See* Stone et al. (2008). NIA research focuses on earlier stage research that still must undergo several more research steps before being scaled up for commercialization. Hence the literature is leaner for describing innovation at these earlier stages.

science, engineering, or education. Such research challenges current understanding or provides pathways to new frontiers."[13]

Creativity: Of the terms identified above, creativity is the most commonly used though no single authoritative definition or description of creativity exists. Simonton (1997) defines creativity as "the output of ideas that are both original and adaptive." Alternatively, Ochse (1990) incorporates the idea of utility and originality into his definition of creativity and includes the production of an object or idea in his definition. Finally, Amabile et al. (1996) expand upon both of these definitions by asserting that creativity involves heuristic (encouraging discovery of solutions) rather than algorithmic tasks or thinking.

In the context of scientific research, Heinze et al. (2007) developed a typology of creative research outcomes that include:

- Formulation of a novel idea (or set of ideas) that could instigate a new cognitive frame or advance theories to a new level of sophistication
- Discovery of new empirical phenomena that could stimulate the generation of new theories
- Development of a new methodology, enabling empirical testing of theoretical problems
- Invention of novel instruments that could instigate new search perspectives and research domains
- New integration of formerly disparate ideas into general theoretical laws enabling analyses of diverse phenomena within a common cognitive frame

Commonly agreed upon definitions of innovative research and its synonyms in the literature are lacking. Only a fraction of the literature has focused on innovation and creativity in science and engineering. There is evidence in the literature that terms such as innovative and creative are social constructs: an agreed upon, or implicit, idea or set of measures coming from within a community. Sternberg (1990) states that creativity is community-specific and acknowledges that the characteristics of creativity in the humanities may differ from the sciences. Simonton (2003) asserts that input from the respective communities are necessary to develop the definition. Thus, as evaluators, one may have look to more specific, empirical measures that have been used to define "innovative research." These measures are described in the next section.[14]

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[13] *See* NSF website, "Definition of Transformative Research," accessed May 18, 2011, http://www.nsf.gov/about/transformative_research/definition.jsp.

[14] This supports the proposed approach to use expert review to assess the innovativeness of NIA-funded outcomes.

C. Empirical Measures of "Pioneering" Research

There have been studies and evaluations in recent years that have provided some empirical measures of creativity and innovativeness (summarized in Table 2). While some of these measures are not based on underlying theory, they prove to be more functional than the definitions given in the literature for the purposes of this feasibility study.

Table 2. Summary of recent evaluations of "pioneering" research programs or scientists

Authors	Year	Program/Group Evaluated	Examples of Measures Used	Comparison Group Used
Pion and Cordray	2008	Burroughs Wellcome Career Award in the Biomedical Sciences (CABS)	Faculty in top-25 ranked institutions in NIH funds Principle investigator on NIH R01 or other NIH grant Age at first R01 Publications Total articles Articles in top-ranked journals Average citations per article	Non-awardees of the CABS program, matched using Propensity Score Analysis
Heinze and Bauer	2007	Nominated Creative Scientists in Nanotechnology	Overall productivity Citation rates Degree Centrality Integration Score	Peer scientists with the same publishing frequency
Azoulay, Zivin, and Manso	2009	Howard Hughes Medical Investigators	Publications in top percentiles of citations Nobel Prizes won Elected to National Academy of Sciences or Institute of Medicine Trained an early career award winner Novel keywords tagging publication	R01 MERIT Awardees, Early Career Award Winners, weighted using Propensity Score Analysis

1. Publication-based indicators

***Productivity*:** Simonton (2003) argued that creative scientists are more productive than their peers, but that they also publish a higher number of ignored works. He posits that the likelihood of a researcher's peers finding his or her work creative is a probabilistic consequence of quantity. Under this model, the total number of publications can be used as an indicator for creativity. Heinze and Bauer (2007) tested this hypothesis

and found that the total number of publications appeared to be a significant predictor of creativity. They claimed, however, that this operationalization is overly simplistic and suggested that other indicators, such as measures of impact, are preferred.

Impact: In addition to productivity, researchers have found impact to be an indicator of creativity. Most commonly, impact is operationalized using citation rates (Heinze and Bauer 2007; Azoulay, Zivin, and Manso 2009). Evaluations of programs similar to NIA, such as HHMI, have used this as an indicator of creativity/innovativeness. An alternative to citation counts is the h-index, a bibliometric indicator that has risen in popularity since its introduction in 2005 (Hirsch 2005).[15] The h-index is a combined measure of the productivity and impact of a scientist. The h-index captures the career-long achievements of a researcher in the sense that it is insensitive to un-cited or lowly cited papers as well as to one or several highly cited papers. Several variations on the h-index have been used, some of which are discussed in Appendix A. Journal Impact Factor, a measure of the extent to which articles in a journal are cited, may be used to characterize the potential exposure of an article published in a specific journal.

Brokerage: Another indicator of innovativeness is brokerage. Brokerage is defined as a measure of an individual's connections to other scientists. The theory is that people with more connections to distinct social networks are considered brokers and hypothesized to have more innovative outputs since they are exposed to more diverse ideas (Burt 2004). Heinze and Bauer (2007) consider this theory by examining the association between the number of disparate authors and groups brokered by a researcher and his or her citation rate. They find that the connection of isolated researchers is a stronger predictor of creative work than number of co-authors alone. This finding suggests that brokerage promotes creativity.

***Degree Centrality*:** Degree Centrality refers to the size of a researcher's network. This variable has been operationalized by Heinze and Bauer (2007) as the size of a scientist's co-authorship network in any three-year time period. They found that degree centrality does not predict a creative event, but does correlate with the number of author-level citations.

Multidisciplinarity/Interdisciplinarity: As defined by Heinze et al (2007), one dimension of research creativity is multidisciplinarity. While there is little clarification in the difference between multidisciplinarity and interdisciplinarity in the literature, in general, they both refer to the number of disparate bodies of specialized knowledge (Porter et al. 2007; Wagner et al. 2011). In terms of publication data, interdisciplinarity may be analyzed via either (1) cited references of a publication set (the body of

[15] A scientist has an h-index h if h of his or her Np papers have at least h citations each and the other (Np – h) papers have fewer than h citations each.

knowledge drawn from), (2) the publication set itself (body of knowledge), or (3) works citing the publication set in question (body of knowledge citing).

NDPA Outcome Evaluation Use of These Metrics. The NIH Director's Pioneer Award outcome evaluation conducted bibliometric analyses using the above metrics as proxies for innovativeness (Lal et al. 2011). These measures include productivity, creativity, impact, and collaboration. The analyses provided interesting information about the awardees, but conclusive results about the innovativeness of the research were not evident, perhaps because the evaluation is only 5 years out from the receipt of the award.

2. Non-publication-based indicators

Awards: Some evaluative research has used awards to supplement publication-based measures as indicators of innovativeness. For instance, Azoulay Zivin, and Manso (2009) studied elections to prestigious scientific societies, also known as metrics of scientific excellence, as an indicator of creativity.[16] Although not often used in applied work, Simonton (2003) suggests a comparison of honors and awards listed on researchers' curricula vitae to measure creative impacts. Simonton identifies four categories of awards: (1) international recognitions, such as the Nobel prize, (2) national recognitions, such as election to the National Academy of the Sciences, (3) discipline-specific honors, such as the Distinguished Scientific Contribution Award of the American Psychological Association, and (4) society-level recognitions, such as 'fellow' status within a society.

Lab-level indicators: Another non-publication-based indicator of innovativeness is the number of students and fellows trained at a researcher's lab that go on to win Pew, Searle, Beckman, Packard, and Rita Allen scholarships (Azoulay, Zivin, and Manso 2009). This indicator is hypothesized to be an indicator of innovativeness, since more innovative labs can attract higher quality students. This indicator, however, has questionable validity and causation because the trainees' achievement may be caused by both the lab head's creativity and/or the students' own creativity. This caveat is acknowledged by Azoulay et al.

Patents: The last indicator of creativity used in applied evaluation research is patent activity. The two most common measures used are patent counts and patent citations. Previous studies have found that patents are granted by the most productive individuals in research (Stephan et al. 2007) and that patents are preceded by a flurry of scientific publications (Azoulay, Ding, and Stuart 2006). Patents, however, are typically only

[16] Azoulay et al. acknowledge, however, that a lot of the members of these societies are previous HHMI members and therefore might skew results.

pursued in situations in which the research may have commercial value, and thus may not have the same interpretation across various fields.

D. Expert Review to Identify Innovative Research

In addition to the use of publication and non-publication indicators of innovative research identified in the literature, the use of consensual assessment techniques, or expert review, is another method described in this study.

Consensual assessment technique is a method that relies on the subjective judgments of appropriate observers, often experts, to determine whether a research product is creative (Amabile 1982). The Committee on Science, Engineering, and Public Policy, a joint committee across branches of the National Academies,[17] corroborated Amabile's conclusions in identifying expert review as the most effective means of evaluating federally funded research programs in comparison to economic-impact studies, and bibliometric analyses on publication and patent data (National Academies 1999). The committee discussed three forms of expert review which could be valuable for program evaluation: (1) quality review, which judges the quality of the scientific research, (2) relevance review, which judges the relevance of the research to the agency's mission, and (3) benchmarking review judges the international leadership status of the United States in the context of a program.[18]

Grant and Allen (1999) used a novel expert review approach to compare Wellcome Trust Showcase awards with a sample of standard project grants to assess the whether the grants were risky, novel, speculative, adventurous, and innovative on a 5-point scale. The evaluators selected ten research summaries; five from each group, from 40 summaries. These 10 summaries were then sent to the 48 members of the expert panels, which potentially could have yielded 12 reviews per project. In fact, each summary was reviewed by an average of 7.7 panel members. The authors stated this method, which they called a "masked randomized trial," eliminated much of the systematic error that might have occurred using standardized expert review, thus making the results more robust.

In 2008, a Working Group on Peer Review of the Advisory Committee to the Director of NIH recommended that NIH shorten the length of the application and "engage more persons to review each application…optimally 4 or more" (NIH 2008).

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[17] The Committee on Science, Engineering, and Public Policy is a joint unit of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. *See* the Committee on Science, Engineering, and Public Policy website at http://sites.nationalacademies.org/pga/cosepup/index.htm.

[18] The use of expert review supports Sternberg's statement that creativity is a community specific concept (Sternberg 1990).

The Working Group left the actual number of expert reviewers ambiguous, so Kaplan, Lacerta, and Kaplan (2008) conducted a statistical analysis to provide guidance on the optimal number of expert reviewers. They had 10 short proposals scored by an average of 48 reviewers. They then conducted a sensitivity analysis and found that "funding decisions will vary widely with the number of reviewers in considering proposals that are closely scored." They noted that the length of the application affects how many reviewers can be used for scoring; the shorter the application, the more reviewers that can be used. They conclude that the NIH peer review process should be designed to meet statistically significant criteria.[19]

E. Summary

The literature does not provide a definition of "pioneering," which motivated the use of closely related terms in the literature such as "creative" and "high-risk high-reward" in this study. In addition, typologies of risks and rewards were found through the literature. Based on our review of the literature on the use of expert review, we decided that it was one method for determining whether research is pioneering, supplemented by other methods. Due to the growing body of literature on publication-based bibliometric measures related to creativity and creative research, we decided to test bibliometrics measures as proxies for pioneering research.

[19] A STPI statistician did not agree with the Kaplan, Lacerta, and Kaplan (2008) analysis, stating that the sample sizes are inappropriately small, highly selective, and susceptible to bias. There is a tradeoff of providing a more-in-depth proposal that fewer experts can review than a shorter proposal reviewed by many reviewers, perhaps not expert in the proposer's field.

3. Evaluation Design and Methodology

A. Overview

This chapter presents the design of the short-term outcome evaluation of the NDPA program. First, we introduce a logic model—a graphical representation of the program's inputs, activities, outputs, expected outcomes and any external factors—of the NDPA, and then the challenges inherent in evaluating a program of this nature. Next, the unique features of evaluation design and the study questions that drove the evaluation are described. Finally, the relevant data sources and collection methods used to answer the study questions are presented.

B. Program Logic Model

A logic model can be used to visually describe the inputs, activities, outputs, outcomes, and external factors that represent a given program. A logic model is not intended to provide all details on a program, but instead focuses on those key aspects that are likely to influence any observed outcomes. The logic model in Figure 1 focuses on two different levels of the NDPA—at the level of the individual investigators (both awarded and non-awarded researchers) and at the level of the NIH as a whole.[20]

In the first column on the left, the inputs of the program are given. In the NDPA program, the amount and duration of the award along with its flexibility (no detailed budget is required, and awardees may choose to change projects throughout the award period) are notable. Another input worth noting is the awardee, who was selected through a review process designed to advance individuals who display the creativity to undertake bold approaches to biomedical and behavioral science. The idea that the awardee proposed for the NDPA is likely to be of a high-risk nature, and can be categorized using the Colwell typology discussed in the literature review. At the NIH level, the program has set forth its desired inputs and outcomes through the explicit goals of the program given in the RFA.

The activities expected to be observed at the awardee level include conducting the proposed research, as well as other unexpected research avenues (given the flexibility of

[20] The logic model was informed by the logic model presented in: Bhavya Lal, Amy Marshall, Elizabeth Lee, Adrienne Zhu, Mary Beth Hughes, and Stephanie Shipp, Mario Nuñez and Jamie Doyle. 2011. Process Evaluation of the National Institutes of Health Director's New Innovator Award Program: FY 2007–2009.

the award), submissions for follow-on funding, and the formation of new collaborations. At the NIH level, the different selection procedures used by the NDPA can be considered an activity. Also, the annual NDPA symposium during which previous awardees are brought together to hear the announcement of new awardees, to present posters on their ongoing research, and to generally build a community of Pioneers is considered a key activity of the program.

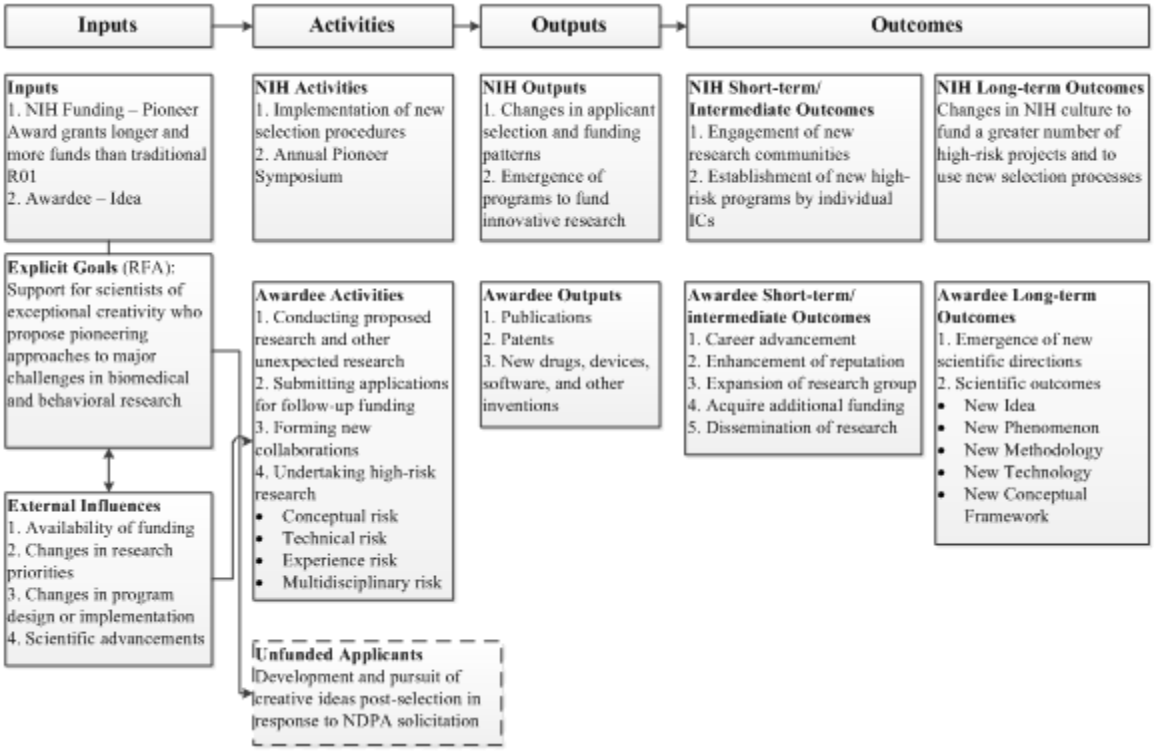

Figure 1. NDPA program logic model

The outputs seen from the NDPA program appear at first glance to be similar to those observed from traditional funding programs. The awardees are expected to publish their findings, to produce research developments such as new drugs, devices, software, and other inventions, and to patent those inventions if appropriate. However, the nature of those outputs may be expected to be more pioneering in the ways discussed in the literature review (such as a higher productivity rate, a larger impact, a higher integration score, etc.). At the NIH level, there is the expectation that new programs designed to fund innovative research will be developed and that funding patterns as a whole at NIH will change.

At the NIH level, short-term outcomes of the program should include the engagement of new research communities and the establishment of high-risk programs by the individual Institutes and Centers (ICs), and in the long-term, the program should inspire changes in NIH culture around supporting high-risk projects and the use of new selection processes. For the individual awardees, outcomes of the NDPA include career advancement,

enhancement of reputation, expansion of their research group, additional funding, and dissemination of research. In the long term, new scientific directions are expected to emerge as a result of the awardees' research, as are the creative research outcomes proposed by Heinze et al. (2007). Lastly the unfunded applicants are expected to develop and pursue the creative ideas they proposed to the NDPA.

C. Challenges of an Outcome Evaluation of the NDPA

There are several challenges when conducting an evaluation of a program like the NDPA. First there are no commonly agreed upon markers of what makes research or a researcher "pioneering." Thus, this evaluation of the NDPA relies on multiple methods as discussed in the literature review, to provide an overall assessment of whether the work conducted under the NDPA was in fact, "pioneering." Second, the award was designed to give the awardees ultimate flexibility in how the funds were used; due to this flexibility and the heterogeneous nature of the proposed projects, no single research trajectory that could be measured in a standardized fashion is expected to be observed across all the awardees. Third, the evaluation is occurring shortly after the first cohort of awardees is ending their funding period—a phase of time too short to be able to observe any fundamental shifts in science if they were to occur as a result of the program. Finally, because of the small number of awardees, and the dissimilarity between the NDPA and traditional research project grants at NIH, it is difficult to make comparisons between the Pioneer awardees and a comparison set of researchers. All of these presented constraints when the evaluation design was being formulated.

D. Outcome Evaluation Design

Given the constraints discussed above, the design selected for this outcome evaluation was primarily a case study method, (which includes multiple components—descriptive data analysis, interviews, and expert review). A comparison of publications and citations, 5 years before and after the receipt of the NDPA, are examined using bibliometric analysis.

Study questions were proposed along two main high-level interests of the program. These features are discussed below.

1. Study Questions

The primary study question for the outcome evaluation focuses on the main goal of the NDPA program:

(1) Did NDPA awardees conduct pioneering research with NDPA funds?

This study question hinges on the definition of "pioneering" which, as was found through a literature review, has no standardized measure. The assessment of whether the research is pioneering requires an in-depth understanding of the research performed.

The second study question aims to capture additional effects of the NDPA, which extend beyond the research outcomes:

(2) What are the spillover effects of the program?

This study question attempts to determine how the NDPA affected the awardees research and career trajectory. This question also addresses how the NDPA affected the greater scientific community, including the unsuccessful applicants, who were not funded by the NDPA, and the NIH as a whole.

2. Cross-Sectional Design

The NDPA program represented many "firsts" at the NIH, and the concept of pioneering is difficult to measure. Based on these features, along with the small number of awardees, it was determined that a cross-sectional approach be used for the evaluation, without a comparison group. A quasi-experimental design was deemed to be neither feasible nor desirable for this phase of the evaluation because of the difficulties in comparing the small number of awardees and the unique characteristics of the pioneers and their research.

3. Case Study Method

Because of the complex nature of defining pioneering and the flexibility of the award itself, the case study method was chosen as the approach to answering the study questions. A case study is "an empirical inquiry that investigates a contemporary phenomenon within its real life context, especially when the boundaries of phenomenon and context are not clearly evident" (Yin 2003). Case studies are used when an evaluator believes that context is important to understanding the outcomes observed—which is the case for evaluating the NDPA research.

The 22 case studies for this assessment were derived from four data sources. The first source was analysis of the awardees' applications and progress reports to develop a research summary; the second was interviews with each of the awardees to understand the context of the research progress and outputs; the third was a bibliometric analysis of all the awardees' publications, and an analysis of their publications that acknowledged the NDPA was conducted separately;[21] and the fourth was an expert review of three publications chosen by the awardees. These sources are described in further detail below. Documentation of the case studies are presented in a supplement to this report, "Outcome Evaluation of the National Institutes of Health (NIH) Director's Pioneer Award (NDPA), FY 2004–2005: Case Studies."

[21] Use caution when making conclusions based on analyses of awardees' publications that acknowledged the NDPA. Standardization of funding acknowledgements across journals could not be guaranteed, nor could the frequency at which awardees acknowledged the NDPA as the funding source of the research be verified.

E. Data Collection and Methodology

As mentioned, multiple sources of data were used to conduct this outcome evaluation, as it was important to capture unique aspects of the research conducted by awardees, and the potential effects of the NDPA program. STPI completed the data collection process in October 2010. The main sources from which data were collected are explained in the following subsections.

1. Awardee Applications and Progress Reports

The applications (consisting of the proposed research essay, letters of reference, and curricula vitae) and annual progress reports of the 22 awardees from the first two years were examined. Based on these data sources, a one-page research summary was developed for each awardee (Appendix C). The awardees were asked during their interviews to review these summaries and correct any errors. These research summaries were provided to the expert panel, as explained below.

2. Awardee Interviews

A primary source of data regarding research outputs were the interviews conducted with awardees. STPI developed an interview protocol (Appendix B) and sent invitations to each of the 22 awardees from FY 2004 and 2005. Interviews were conducted by phone with 9 awardees, and onsite interviews were conducted with 12 awardees.[22] Onsite interviewing involved traveling to the research institution of the awardee and visiting their laboratory. Interviews conducted in-person gave an opportunity for interacting with students and laboratory personnel, and for assessing the culture of a creative research environment.

The following topics were covered in the interview protocol:

- description of research,
- progress and outputs,
- funding, and
- effects of the award.

Interviews with the awardees were approximately two hours in length, and interviews conducted in-person were longer, as attending members of the STPI team toured the research facilities, and engaged with students and lab personnel. A total of 21 interviews were completed between February 2009 and February 2010.[23] A list of the awardees and when they were interviewed is shown in

[22] OMB Clearance 0925-0606, expires 11/30/2012.

[23] Although several attempts to schedule an interview were made, Stephen Quake (2004) was never interviewed.

Table 2, and the interview protocol is presented as Appendix A.

Table 2. NDPA awardee interview schedule

Pioneer	Institution	Year Awarded	Date Interviewed
1. Junying Yuan*	Harvard Medical School, Dept. of Cell Biology	2005	February 2, 2009
2. Sunney Xie*	Harvard, Chemistry Dept.	2004	February 2, 2009
3. Steven McKnight	UT Southwestern Medical Center, Dept. of Biochemistry	2004	June 4, 2009
4. George Daley	Harvard Medical School, Dept. of Biological Chemistry & Molecular Pharmacology	2004	June 26, 2009
5. Homme Hellinga*	Duke, Biochemistry Dept.	2004	July 16, 2009
6. Erich Jarvis*	Duke, Neuroscience Dept.	2005	July 17, 2009
7. Thomas Rando*	Stanford Med School, Dept. of Neurology and Neurological Sciences	2005	July 27, 2009
8. Pehr Harbury*	Stanford, Biochemistry Dept.	2005	August 18, 2009
9. Karl Deisseroth*	Stanford, Dept. of Psychiatry & Dept. of Bioengineering	2005	August 19, 2009
10. Mike McCune	UCSF, Dept. of Biopharmaceutical Sciences	2004	December 31, 2009
11. Clare Waterman*	NHLBI, Lab of Cell and Tissue Morphodynamics	2005	January 20, 2010
12. Nathan Wolfe	Stanford, Dept. of Human Biology	2005	January 22, 2010
13. Titia de Lange*	Rockefeller, Dept. of Cell Biology and Genetics	2005	January 27, 2010
14. Larry Abbott*	Columbia, Dept. of Physiology and Cellular Biophysics	2004	January 27, 2010
15. Derek Smith	Cambridge, Dept. of Zoology	2005	February 1, 2010
16. Giulio Tononi	UW Madison, Dept. of Neuroscience	2005	February 1, 2010
17. Chad Mirkin	Northwestern, Dept. of Chemistry	2004	February 3, 2010
18. Leda Cosmides	UC Santa Barbara, Dept. of Psychology	2005	February 12, 2010
19. Rob Phillips*	CalTech, Dept. of Applied Physics	2004	February 22, 2010
20. Holly Cline*	Scripps, Depts. of Cell Biology and Chemical Physiology	2005	February 23, 2010
21. Vicki Chandler	U Arizona, Dept. of Plant Sciences	2005	February 24, 2010
22. Stephen Quake**	Stanford, Dept. of Bioengineering	2004	—

* Interviewed in person. ** Not interviewed.

† In 2007, Waterman accepted a position to head the Laboratory of Cell and Tissue Morphodynamics at the National Heart, Lung, and Blood Institute at the National Institutes of Health. While she had to relinquish her NDPA funds, she has continued her work on developing the cytomechanical system proposed in her NDPA application.

The awardees' assessments of their own research and the NDPA as a whole are presented in Chapter 4.

3. Survey of Unfunded Applicants (SUFA)

Part of understanding the spillover effects of the NDPA was to explore how participating in application process affected NDPA applicants, As a result, a survey was conducted to track unfunded applicants (SUFA) (Appendix B) focused on career developments of the individuals who were not awarded, and the progress, if any, in pursuing their NDPA-proposed idea. Invitations were e-mailed to the unfunded individuals who submitted full applications to the NDPA program in FY 2004—2007.[24] Repeat applicants were asked to respond based on their most recent application.

The survey was open for twelve weeks,[25] with e-mail reminders sent every two weeks. Out of the 1,096 total unfunded individuals from FY 2004-2007, 526 completed the SUFA, for a response rate of 48 percent. However, 34 unfunded individuals could not be reached at all; in some cases, e-mail addresses could not be found, and in others, the individuals were deceased or on extended medical leave. Thus, the overall response rate out of the 1,062 individuals with valid e-mail addresses was approximately 50 percent. The response rates by year are shown in Table 3.

Table 3. Survey of unfunded applicants response rates by competition year

Fiscal Year	Completed Surveys	Unfunded Individuals	Unreachable Individuals	Reachable Unfunded Individuals	Response Rate
2004	63	164	11	153	41.2%
2005	96	190	7	183	52.5%
2006	162	314	8	306	52.9%
2007	205	428	8	420	48.8%
Total	526	1,096	34	1,062	49.5%

Source: Survey of Unfunded Applicants.

The low response rates are consistent with previous attempts to survey unfunded applicants. Abt Associates' pilot version of the SUFA (launched in 2007 as part of the feasibility study of the NDPA outcome evaluation) yielded a response rate of 34 percent.[26] Many unfunded individuals expressed annoyance at being asked to complete multiple surveys, because they did not know the difference between the SUFA and the

[24] Only unfunded applicants from FY 2004-2007 were invited to complete the survey. This was intended to allow sufficient time since application submission, to adequately capture research/career developments.

[25] The survey was open for two weeks longer than was originally designed, in the hopes of increasing the response rate.

[26] For the Abt pilot SUFA, survey invitees were 500 randomly selected applicants from FY 2004 and 2005. Applicants were incentivized by a $20 donation to one of three charities for each completed survey (Abt Associates 2007).

NDPA applicant survey from the process evaluation of the first five years of the program Lal et al. 2010).

STPI analyzed the demographics of the SUFA respondents to determine whether the individuals were representative of the entire unfunded applicant pool. The SUFA respondents generally matched the unfunded applicant pool in race,[27] ethnicity,[28] seniority,[29] research area,[30] and doctoral degree[31] distribution, but the number of females in the respondent pool was found to be slightly greater than would be expected based on the gender distribution of the entire unfunded applicant pool.[32] STPI focused its analyses primarily on descriptive, combined-year results. The results of the SUFA are presented in Chapter 7.

4. Expert Review

An expert review was conducted to determine whether and how the NDPA-funded research was pioneering. The goals of the expert review were to assess the impact of the work conducted under the Pioneer Award, and to provide insights regarding the effects of the NDPA program. During the awardee interviews, the awardees were asked to suggest three to five prominent investigators (consisting of both supporters and critics) in their research field who could potentially serve as expert reviewers of their work done under the NDPA. STPI also requested awardees submit three publications representative of their Pioneer research.

Individuals referred by the awardees as potential experts were first checked for conflicts-of-interest, which included collaboration or co-authorship,[33] before being invited to participate in the expert review. In cases where awardees did not refer potential experts, or when the referred individuals were collaborators with the awardees or declined to participate, STPI sought additional experts in the research field and invited them to participate. These individuals were identified using the Howard Hughes Medical Institute (HHMI) website and BiomedExperts, and were sometimes suggested by individuals referred by the awardees, but who had declined to participate. There are 330 HHMI investigators who were chosen based on their reputation for their creativity and

[27] χ^2=6.69, df = 5, p = 0.245

[28] χ^2=3.11, df = 1, p = 0.078

[29] χ^2=0.009, df = 2, p = 0.995

[30] χ^2=16.7, df = 9, p = 0.053

[31] χ^2=3.71, df = 3, p = 0.294

[32] χ^2=4.96, df = 1, p = 0.026

[33] Individuals who were invited to participate in the expert review were also asked to notify STPI if they had a conflict-of-interest with the Pioneer they were asked to evaluate.

productivity.[34] BiomedExperts is an online community that connects biomedical researchers to each other through the display and analysis of the networks of co-authors with whom each investigator works to publish scientific papers.[35] It provided a good source of experts by subject area.

Three experts were used to assess the research of each of the awardees from FY 2004—2005, for a total of 63 experts (3 experts per 1 awardee).[36] A feedback form was developed for the expert reviewers to characterize the Pioneer research, and to assess the effects and value of the NDPA program. Experts who committed to participate were sent a research summary describing the Pioneer activities, three publications from the NDPA project, the NDPA Program Notice from the year of the award,[37] and the feedback form to record their assessment of the Pioneer project. Following submission of the completed feedback form, phone interviews were held with selected experts, either because they requested to submit additional feedback, or to clarify answers on the feedback form.

The results of the expert review are provided in Chapter 6.

5. Interviews with NDPA Program Leadership and Other NIH Staff

Interviews were conducted with program leadership to inform the design of this evaluation. NIA leadership provided a history and an overview of the program planning and implementation. They also provided access to application data and progress reports for each of the awardees, which was used to assess their progress, and informed the research summaries written for the experts to review.

Interviews were held with NIH staff involved with other innovative research programs, either within the OD or one of the other 26 NIH ICs. The purpose of these interviews was to understand how, if at all, their programs had been influenced by the NDPA. The results of those interviews informed the presentation of material in Chapter 8.

6. Publication Databases

Based on a literature review, bibliometric indicators for characterizing research were identified. STPI used Web of Science, an online database that contains detailed

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[34] *See* HHMI website, "HHMI Investigators," accessed May 18, 2011, http://www.hhmi.org/research/investigators/.

[35] *See* BiomedExperts website, "BiomedExperts: Your Scientific Match Point," accessed May 18, 2011, http://www.biomedexperts.com/.

[36] An expert review was not arranged for NDPA research of Clare Waterman-Storer (2005), as she relinquished the award mid-term in 2007 after accepting an intramural research position at the NIH.

[37] The Program Notice was included to provide a reference for the experts when answering questions regarding the goals of the program.

citation records for academic publications, to gather the data necessary for the bibliometric analyses conducted in this evaluation.[38] The awardees' full publication records were downloaded from the database, and were then refined into two categories:

- The first included all journal articles published five years before and five years after receiving the NDPA—these publications are referred to as the awardees' "full publication set" throughout this report
- The second category included articles which cited the NDPA in the funding acknowledgments.

Bibliometric analyses were conducted on both categories of publications, for all 22 awardees. These analyses are presented in Chapter 5.

7. Web-Based NDPA Materials

To inform the discussion of the origin and purpose of the NDPA, publicly available program materials, including the Request for Applications (RFA) and web profiles of the NDPA awardees were used. Program Announcements were used to inform the expert reviewers of the program goals. All NDPA materials were retrieved from the NIH program website.[39]

F. Summary

The outcome evaluation of the NDPA faced several challenges due to the unique nature of the program and the short-term nature of the evaluation. The design selected for this phase of the evaluation was non-experimental, based primarily on case studies of the 22 awardees from the first two years of the program. Study questions centered around two main areas: (1) did awardees conduct pioneering research with NDPA funds? and (2) what were the spillover effects of the NDPA program? Case studies of the awardees were supplemented by interviews and expert review; these case studies helped to address both study questions. A survey of unfunded applicants and interviews with NIH staff were also used to assess additional spillover effects to answer the second study question.

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[38] Web of Science data were used (in lieu of NIH IMPAC II data) to facilitate analysis of interdisciplinarity.

[39] *See* NIH website, "NIH Director's Pioneer Award Program," accessed February 28, 2011, http://nihroadmap.nih.gov/pioneer/index.aspx.

4. Awardees' Assessment of Awardees' Research

A. Overview

This chapter is based largely on the interviews performed with the 21[40] Pioneers, although it also relies on external information, such as funding data available through NIH's IMPAC II database. It is broken down into five main sections: prior to receiving the NDPA and the NDPA-proposed idea; the research activities accomplished under the NDPA; the research outputs; the research outcomes; and spillover effects of the program.

B. Prior to NDPA and NDPA-Proposed Idea

1. How many of the awardees were new to the NIH?

One of the goals of the NIH and the Coordinating Committee involved in planning the launch of the NDPA was to attract individuals who in the past had typically not applied to the NIH for funding (Lal et al. 2010). Of the 22 awardees in the first two years of the program,

- Eight had never received an R01 from the NIH. Of these eight,
  - Two had never applied to the NIH for support
  - Three had applied for but never received NIH funding
- Two had NIH K-awards prior to applying to the NDPA.
- Seven had received exactly one R01 before receiving the NDPA.
- Seven had received more than one R01 before receiving the NDPA.

2. How did awardees come up with NDPA-proposed ideas?

Interviews with the awardees revealed that the majority had the idea that they proposed for the NDPA before the solicitation for the program was announced. These awardees explained that they had already had the idea or had developed a technology before they wrote the proposal, and applying to the NDPA provided the opportunity to utilize their tools or try and realize their hypotheses. A few awardees, however, stated

[40] We were not able to interview Stephen Quake; therefore, this chapter refers to 21 interviews. When we were able to obtain information from other sources, results are presented for 22 awardees.

that they actually were motivated by the program's announcement to come up with new ideas. Several Pioneers provided explanations::

> *"One way in which the Pioneer [program] immediately paid off is that if you dangle that amount of money in front of somebody, it induces new thinking. I wanted [the award], so I thought I needed to come up with an idea that is outside my own area of investigation but still…something that the panel would believe I could do. So, I started thinking and thinking and came up with this new direction for my lab. Once I started writing it up, I realized it was a really good idea. I became really excited about it and decided I wanted to do it, NDPA or not."*
>
> *"My lab and I talked about what would be an interesting problem, what is a Pioneer-ready project—big, challenging, interesting—and this is what we came up with."*
>
> *"When I wrote my project for the Pioneer Award, I was quite excited because I had never had a chance to really express what I really would like to do in terms of a project in a grant proposal. That got me thinking a little bit more creatively just by writing it; even if I had not gotten the award."*

3. How did the NDPA-proposed ideas differ from previous awardee research?

By reviewing the awardees' NDPA applications, their publications before the award, responses during awardee interviews, and expert comments, three codes were generated to characterize how the awardees' proposals were different from the foci of their previous research.[41] Compared to their research foci before the award, the awardees proposed to:

- *Apply previous research methods and ideas to new biomedical issues* (9 awardees). Some of the awardees applied their previous research to biomedical issues that were new to them. This result is not surprising, considering that NIH requested investigators to propose projects that were different than their previous research, yet also applicable to biomedicine. Outreach to investigators in fields not traditionally funded by NIH also contributed this type of content change.
- *Broaden the focus of their research to a grander systems level (7 awardees).* Another way in which awardees changed their research focus for the NDPA was by broadening the scope of their previous research projects.

[41] This coding is non-exclusive so that an awardee can fall into more than one group (code). Thus there are 23 responses reported by 21 awardees.

- *Conduct new experiments that support their unconventional theories and hypotheses (7 awardees).* Some awardees used the grant to explore an idea they held previously, or came up with specifically for the NDPA, but had not had the opportunity to explore, because of its risky nature.

4. How did awardees assess the nature of the risks in the proposals

The awardees were asked to characterize the risks in their NDPA proposal, following the typology of risk (Table 4). Awardees most often characterized their NDPA proposals as incorporating multidisciplinary risks.

Table 4. Awardees' assessment of the nature of the risks of their proposed research

Pioneer	Conceptual Risk	Technical Risk	Experience Risk	Multidisciplinary Risk	None of these risks
1		X	X	X	
2	X	X	X	X	
3	X	X	X	X	
4	X		X	X	
5	X	X	X	X	
6	—	—	—	—	
7	—	—	—	—	
8		X	X	X	
9	X	X	X	X	
10	X	X	X	X	
11		X	X	X	
12	X	X	X	X	
13	X	X	X	X	
14	X		X	X	
15	X	X		X	
16	X	X	X	X	
17		X	X	X	
18		X	X	X	
19	—	—	—	—	
20	X		X	X	
21	X	X	X	X	
TOTAL	13	15	17	18	0

Source: Awardee interviews.

Note: Dashes indicate that three awardees (6, 7, 19) could not be reached for comment regarding the nature of their risks.

5. What did awardees propose to do with the NDPA?

The aims of the proposed projects were also used to characterize the NDPA proposals. Through an examination of the awardees' application essays, codes were developed to characterize the primary objectives of the proposals. For the NDPA, awardees primarily proposed to:

- Develop a new technology or approach to research that may have multiple applications (10 awardees)
- Test a specific hypothesis or set of hypotheses (6 awardees)
- Pursue an open-ended research objective (6 awardees)

The NDPA-funded projects spanned multiple research areas and awardees hailed from a variety of fields. Due to the lack of a comparison group, it cannot be definitively stated whether the diversity of this set of awardees was greater or less than that of traditional funding mechanisms. Nevertheless, several researchers with backgrounds in physical science, engineering, and behavioral and social sciences were chosen as awardees, which suggests that the characteristics of NDPA recipients may be different than that of typical R01 awardees.

6. Why wouldn't this work be funded by traditional mechanisms?

Awardees stated that they believed their work wouldn't have been funded under traditional NIH granting mechanisms for a variety of reasons. One reason was that the project had no preliminary data or was a novel idea:

> *"So we were basically alone, and certainly, in this idea of really looking at the interface… no other groups were working on it as far as I know."*
>
> *It is something that I would have never proposed to a regular NIH grant panel, because it would be dead on arrival basically. So, at the time that I was developing this hypothesis and doing this research, the funding for it was just sort of like a side type of project that was attached to a main project from my other NIH funding or other types of funding."*

Another reason mentioned was that the project fell between the interests of multiple ICs:

> *"There are a lot of fundamental things in genetics that cross organisms so that part of the hypothesis is not rocket since, but that said, you know, people don't fund this work because it has no home. There is just no way this would have been funded on a standard NIH process."*

Another reason was the awardee wasn't known in the field:

> *"But that means that we often don't have the kind of track record in a particular area. For example, the research we did in. [research area] was published in*

Proceedings of National Academy of Sciences. *It came out to a lot of attention. People were quite interested in it. But, you know, we didn't have a prior track record in that area. Not the kind that you would usually have in order to get the normal kind of funding.*

The project was for technology development was yet another reason given:

"This is an enabling technology that normally wouldn't be funded through a traditional mechanism, because it itself does not have hypotheses to test. It's infrastructure building."

Pioneer awardee Tom Rando explains his work to STPI team.

C. NDPA Research Activities

1. Did the awardees conduct NDPA-funded research differently than other research? If so, in what ways did it differ?

Awardees were asked how their approaches to NDPA-funded research differed from that of their other projects. Out of the 21 awardees interviewed, 14 stated they had always been risk-takers and that the NDPA did not change their approach to research. Examples of what was heard from these 14 awardees are below:

"To me, if ten labs are already studying something, it's almost not worth it to us."

"I think for me, I made some decision that I wasn't going to do anything incremental."

"I've always been an entrepreneur."

Other awardees mentioned that their NDPA work is more high-risk (4/21), and allowed them to think more creatively. Awardees also mentioned (5/21) that compared to their normal research, they approach the NPDA project by thinking about the "big picture," and about the health relevance of their research.

2. What, if anything, did the NDPA allow researchers to do that couldn't be done under traditional mechanisms?

Awardees were also asked about the kinds of activities that they were able to perform uniquely under the Pioneer Award, as opposed to traditional mechanisms of funding (Table 5).

Table 5. Awardee Interview Question: What, if anything, has the NDPA grant allowed you to do that you could not do without it?

Coded Response	Number of Responses
Follow a natural research trajectory (i.e. explore new areas, employ multiple strategies to address one problem, alter the course of their research based on results)	18
Spend more time on lab research (i.e. focus less on teaching, administration, or getting more funding)	13
Take a long-term view of research (i.e. perform longer-term studies, think about their overall research goals)	12
Improve laboratories (i.e. improve facilities, hire new researchers, lab technicians or administrators, purchase new equipment)	6
Undertake resource-intensive projects (i.e. perform large-scale screens or assays, fund research with animals)	5

Source: STPI analysis based on awardee interviews.

Of the 21 awardees interviewed, 18 stated that compared to traditional funding mechanisms, the NDPA allowed them to *follow a natural research trajectory*, that is, they could explore new areas, employ multiple strategies to address one problem, alter the course of their research based on results. Pointing to the flexibility in how NDPA funding could be used, these awardees said they were enabled to change their approaches if they weren't working, pursue interesting results, and employ multiple strategies at the same time. These awardees stated:

> *"Without that money I would have had to refocus and change directions into much more predictable areas… And that basically means that you're doing what can be done, not what you hope could be done."*

> *"It was a large enough amount of money for a long enough period that…I could convince myself that the first strategy was not going to be effective and then…regroup and think of…several different alternate strategies."*

> *"Publish a paper first and then propose it…This is exactly what everybody always says about the NIH… How am I supposed to do that work and publish the paper without income to support the work?"*

The 13 awardees who indicated that the Pioneer Award allowed them to *spend more time on lab research* attributed this to the size, duration, and flexibility of the funding. With the NDPA, these awardees did not need to engage in a constant search for funding or take away time from research to account for how they used their money. These awardees commented:

> *"It gave us and our graduate students the time to do the research because it allowed me [and my graduate students] to teach less so that [we] could focus on the research more."*
>
> *"I can put my intellectual resources and physical resources into doing the science and solving the problems and not into the grant itself."*

Twelve awardees remarked that the duration and innovative aspect of the NDPA enabled them to *take a long-term view of their research*. In applying to the program, awardees were challenged to come up with an idea that was innovative to the scientific community and that could occupy their intellectual interests and resources for at least five years. It forced them to question their research directions and overall goals. These awardees noted:

> *"It is really the first time that anybody is giving me money to do what I really want to do instead of chastising me…I have learned along the way not just my view of the research area, but just how to go about doing science in general."*
>
> *"The big change was that…there was…this window of time…where we could really build a foundation. And that was the goal of the award…to really build something new and different and pioneering that might actually come to fruition in five years, or six years, not next year."*

Erich Jarvis, NDPA Pioneer, in his lab at Duke University.

Six awardees indicated that the NDPA enabled them to *improve their laboratories* because of the larger amount and flexibility. Of these six, some used the money to purchase new equipment and improve their facilities, while others decided to hire new researchers or administrative assistants. The Pioneer Award improved the research environments of these awardees. These awardees stated:

> *"[We] bought the mass spectrometer, but had to lay the foundation the first 2-3 years and now have this great robust tool."*
>
> *"I was able to have this administrative assistant, and on this RO1, the new one, I cannot pay for her."*
>
> *"[Under traditional grants] I have all these people telling me you cannot spend $1,000 to put in shelves so that your gang can do their real work properly because it violates some rule."*

Five awardees used the Pioneer Award funding to *undertake resource-intensive projects*. In addition to being able to fund expensive animal experiments, multiple awardees noted their ability to conduct 'exploratory' screens and assays. These screens provided information on how they should proceed with their research. A couple of these awardees explained that it is difficult to obtain R01 funding for this kind of task, despite its importance for advancing research. Awardees commented:

> *"My award was really a fishing expedition which you can never get funded…to try to ask questions using a couple of different systems."*
>
> *"There would have been no way I would have done the screen."*
>
> *"Our mouse costs are a big drain on our budget."*

Awardees were positive about the ways in which the NDPA changed their approach to and method of conducting research. Compared to R01s, they cited the larger amount, longer duration, increased flexibility, and focus on producing innovative results as influential on their research activities.

3. Was the research successful?

In discussing the current research progress of the NDPA-funded research, assessments of change between the proposal goals and the results of the funding were made. Mutually exclusive codes were applied to interview responses on the current progress of the NDPA research and whether it differed from the proposed research. Results for the 21 awardees who completed the NDPA funding term were as follows.[42]

[42] Clare Waterman gave up her award when she moved to NIH, so her outcomes were not evaluated.

Pioneer awardee Per Harbury shows his lab to STPI team member.

Broad research goals were met or are showing progress (14 awardees):

"In this case because I didn't have a plan, I just said I would like to do this, I really did what I said…it's now the central stuff that we are going to do for the next five years still…We don't know everything, but I think the basic goals were accomplished."

"I think in that regard we sort of exceeded what they wanted to achieve."

"We've got four threads that are going really strong, and each of them is populated by postdocs and students."

"I think we achieved our goal in that we've made really good progress on these things…We've developed new methods that allow us to get a lot of interesting new data quickly…and we're going to keep going."

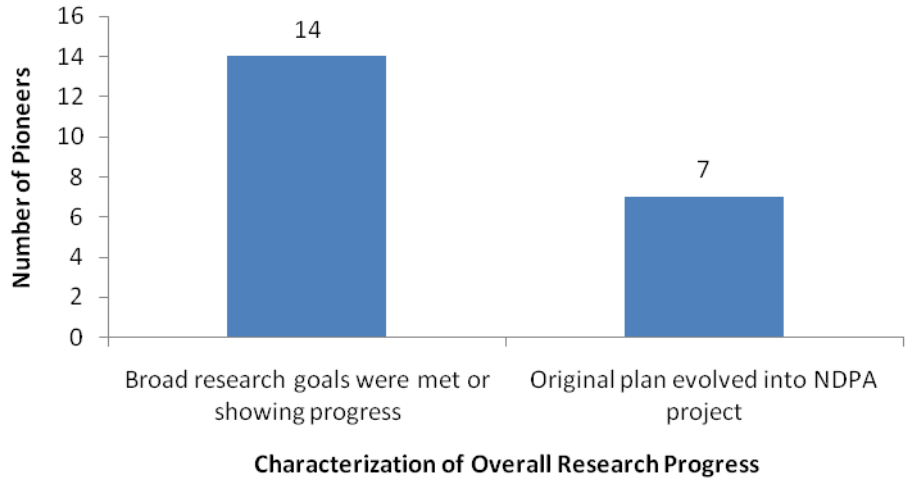
"In the three areas that we approached, we had interesting observations made in the first two and we're more cognizant of the nuances of the third."

The original plan evolved into the research they performed during the NDPA period and are currently conducting (7 awardees):

"If a scientist answers that they never had any adaptive management in what they did with their experiments they're lying or they're really being not very creative. We certainly did modify some of the things we did."

"Things that we weren't even planning on doing have kind of expanded further, and taken us in new directions…That's almost been the greatest benefit of the award…we've actually headed in directions that we didn't plan when we wrote this five years ago."

Based on findings from the interviews, it appears that if this research had been funded under traditional mechanisms, there could not have been as many project evolutions over the course of the funding period because of the goal-oriented nature of those types of grants. Furthermore, the projects proposed likely would not have had to change because a plethora of preliminary data is necessary for R01s to be funded. Figure 2 displays information on the research progress of NDPA awardees.



Source: Awardee interviews, NDPA applications, and publication data from Web of Science.

Figure 2. Research progress of the awardees on their Pioneer Award projects?

In the context of research progress, events that occurred to awardees throughout the funding term were coded into categories. Multiple events may have been designated to one awardee:

For example, six awardees said that aspects of their research failed:

"The strategy that…I initially thought of and tried…for the first two years…turned out not to work so well…Then there was that conundrum of at what point do you say okay, this isn't working, and try a new strategy?"

"You could certainly have an interpretation that we failed, but on the other hand I think we've learned some important things."

"We spent so much time and money on that and it didn't get anywhere. That was a mess. We generated lots of data sets and…that was very disappointing."

Five awardees stated that their projects would not be complete in five years:

> *"I proposed an objective that I didn't even think I would be able to achieve in the five-year period…Have I been able to achieve milestones along that way for objective; the answer is yes."*

> *"Not meeting goals was built in almost from beginning, in the sense [that] we set the goals very high and very far. The mantra that we were taught in [omitted] as investigators in making proposals, is to identify a long-term compelling goal, that is twenty years out, and then figure out how to bring it forward in five years."*

Five awardees stated that progress was faster or more successful than expected:

> *"I would say we completed the goals…which [is] pretty amazing…because I look back at the essay and I was…ambitious."*

> *"We more or less fulfilled our objectives within the first 2 or 3 years on the [omitted] part—the progress went better than I thought."*

On the other hand, three awardees indicated that progress was slower than expected:

> *"I always estimate too short a period of time for how long things will take."*

> *"I hoped to have all this work finished about 3 years ago…We are two years behind where I hoped to be, which in reality I don't think is terrible."*

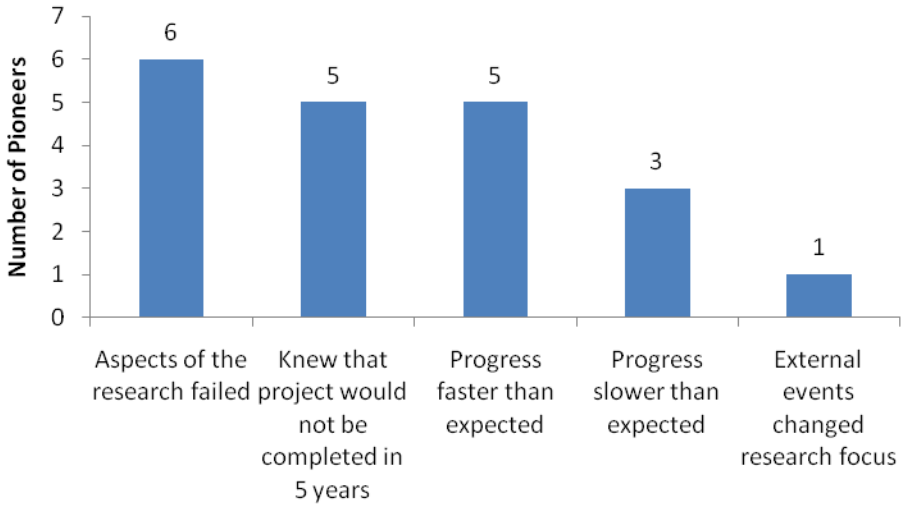
One awardee noted that events outside their control changed their research focus

> *"In a sense [omitted] kind of scooped my entire Pioneer proposal, but it also then allowed us…to really exploit what [omitted] had done and build it into our own system and leverage it and make it even more productive."*

These research events (as coded above) can be traced back to the difference between the program elements of the NDPA and traditional mechanisms discussed in Chapter 1. The failures and projects that experienced slower than expected progress may be attributed to the encouragement of highly risky and ambitious projects in the RFA.[43] Researchers were free to propose pioneering projects that they knew would not be completed in five years because of the flexibility of the funding and lack of a budget in the application. Also, NIH expectations are that more projects might fail to meet original goals set forth in their application due to the high risk nature of the research. For those that experienced faster than expected progress, they had not anticipated the great acceleration of research pace that may have resulted from a large amount of money

[43] Research undertaken using other award mechanisms may also fail. This study does not compare the findings to the success/failure rates of other award programs.

received from the NDPA or, it could have been that the research simply went well. Figure 3 displays information on the research events that affected research progress.



Source: STPI analysis based on awardee interviews, NDPA applications, and publication data from Web of Science.

Figure 3. Research activity events that contribute to overall research progress

Of the seven awardees whose original plans evolved over the duration of the funding period, five indicated that aspects of their research proposal had failed. It is likely that these failures led their goals to change over time because only one of 14 awardees who indicated that their goals were met or showing progress noted that aspects of their research failed. Furthermore, since the interview questions are open-ended, some awardees may have had failures that they did not discuss. The relatively high frequency of failures (6/21) and the possibility for further unaccounted failures seem to indicate that failures and obstacles should be expected, particularly of high-risk research. One Pioneer noted "if you have a high-risk project, you have to have a certain rate of failure…its inherent in the riskiness…Ideally, [the Pioneer Award is] a program that allows you to fail…and still end up making some progress."

In terms of other research activity outcomes, four of the awardees, including those that generally met their research goals, made comments along the lines of "If you do…exactly what you said you would do [over five years], I think there is something wrong. You aren't thinking very creatively."

D. Research Outputs

1. What is the effect of NDPA on publications?

Based on the literature review, it is posited that researchers that publish frequently have a higher likelihood of being designated creative by peers. However, this theory applies to producing a large number of publications over a full research career and may not necessarily be suitable for evaluating publications over the five-year funding period of the NDPA.

Based on interviews, most awardees stated that publication rates are a matter of personal preference. While some awardees stated that they were publishing at different rates than before they received the award, others remarked that their patterns had remained the same. Without feeling the constant demand to publish, some awardees chose to limit their publications to what they perceived as their most impactful science. [44]

> *"I think I've always…published at about the same rate to tell you the truth."*
>
> *"I prefer not to publish a great deal of quantity…I prefer to focus on potentially transformative work."*
>
> *"I think we had a big increase…Last year we published 45 papers."*

Awardees noted that high-risk projects take longer to succeed than less risky projects. Five awardees commented on the varying amounts of time it took for their projects to yield useful results. A few awardees stated that an award period of slightly longer than five years would have been ideal for addressing the type of broad, scientific problems funded by the NDPA. Based on the publication data from Web of Science, the first article attributed to NDPA funding was published in 2007. Most awardees did not have their first NDPA-attributed publication until 2008. Regarding their rates of publication, awardees stated:

> *"I don't think that high-risk research costs any more than low-risk research…It takes longer to get the result that is publishable."*
>
> *"It is probably taking fifty percent longer to get these things published. Because now, I am not concerned…it has got to be published…it takes a longer time to actually do the research…I want to make sure we put more milestones into these projects than we normally would have."*
>
> *"In terms of rate of publication, I'd say it's been harder and slower to break into—the non-human primate work has been harder and slower than I would have imagined."*

[44] More information about awardees publication is presented in Chapter 6.

Some awardees did not have sufficient time to complete their projects or publish their results within the five-year time framework of the award. A few of the awardees explicitly stated that they had not yet published anything related to their NDPA work.

Furthermore, several awardees said that the duration of the NDPA enabled them to focus more on attaining larger research milestones and worry less about publishing incremental results. Awardees who noted this advantage stated that the relief from a persistent need to publish enhanced their creativity and ability to perform high-risk research. For example, awardees stated:

> *"When you have a conventional grant, you don't want those gaps…I do believe there was a gap there. It's hard to see in the CV because…it takes a while to get published and that fills in the hole. I would say there was a period when we were building these wrong models. We never published a paper on those models. We presented them at meetings, and then they turned out to be the wrong way. "*

2. Are awardees publishing in new journals?

Another measure of research output is the impact of journals where awardees published. Changes in where awardees published may indicate a change in the direction, audience, quality, or influence of their research over time. Regarding the journals they publish in, awardees commented:

> *"This is the first time that we've gotten something into Nature."*
>
> *"They are about the same in terms of impact factor, the types of journals that we aim for. It's the audience that differs."*
>
> *"One is in a new journal that I hadn't published in before."*

Since the NDPA encouraged researchers to move into new fields, some awardees commented that it was difficult to begin publishing in these new fields. Awardees stated:

> *"For instance, in cancer I don't have any credibility. I've had those [papers] triaged, and I had never had a paper triaged in my life."*
>
> *"When the Pioneers began walking into this new territory, they might get slaughtered by the indigenous tribes because they don't know where to walk. And that's—in our review process."*
>
> *"Starting to publish in a new field is hard because you don't know the history of how people are thinking."*

Titia de Lange, NDPA Pioneer, in her lab at Rockefeller University.

3. Have any non-publication outputs been produced? What are these outputs?

Several awardees indicated that non-publication outputs also resulted from the NDPA funding and some awardees even noted multiple non-publication outputs. Three awardees mentioned that patents were being filed on their research. One indicated that his new technology was being commercialized, and another explained how labs had asked to use his reagents for their research. Three awardees indicated that the software they had developed was being used by other groups. Three awardees also stated that their methodologies and protocols had been disseminated and were being used by other labs. Two mentioned that they were holding courses and seminars that teach students about their methodologies and research. One explained that the public health applications of his work had been featured in a university textbook.

4. Has the NDPA-funded idea received other funding? If so, through what programs and mechanisms?

The pursuit of other funding is another research activity that awardees likely performed during the NDPA funding period. In their interviews, awardees expressed a fear of "the cliff," or the time at which their NDPA funding would end. Many awardees also decided to file no-cost time extensions to their grants in order to use their NDPA funding over a longer period than the five years, and so some had not started applying for funding yet. Despite their concerns, at the time of interviews, most awardees who had applied for grants were successful at obtaining them to continue their NDPA projects.

Of the 20 awardees who discussed additional funding in their interviews, two had been selected as Howard Hughes Medical Institute (HHMI) Investigators. Similar to the NDPA, HHMI seeks to fund creative investigators and "urges its researchers to take

risks, to explore unproven avenues, and to embrace the unknown—even if it means uncertainty or the chance of failure."[45]

One awardee received the National Security Science and Engineering Faculty Fellowship (NSSEFF), a program similar to the NDPA in purpose and criteria (see Chapter 8).

One Pioneer was awarded a Grand Challenges in Global Health grant, which is a joint initiative of the Bill & Melinda Gates Foundation and NIH. The goal of the Grand Challenges Initiative is to engage "creative minds across scientific disciplines…to work on [global health] solutions that could lead to breakthrough advances for those in the developing world."[46]

One Pioneer received funding from the Defense Advanced Research Projects Agency (DARPA), a research and development office for the Department of Defense. DARPA's goal is to fund "unique and innovative research,"[47] and it executes its strategic vision by "constantly [searching] worldwide for revolutionary high-payoff ideas."[48]

One awardee received a TR01, Transformative Research Projects Program, grant from NIH. The TR01 grant was "specifically created to support exceptionally innovative, high risk, original and/or unconventional research projects that have the potential to create or overturn fundamental paradigms." A discussion of the differences between TR01 and the Pioneer Award may be found in Chapter 8.

Awardees have also received more general funding from organizations such as: NIH, the Burroughs Wellcome Fund, Human Frontier Science Program, the Packard Foundation, NARSAD, Elizabeth Glaser Pediatric AIDS Foundation, World Health Organization, and the McKnight Foundation.

E. Research Outcomes

1. Types of Rewards

The awardees were asked to characterize the potential or realized outcomes of their work following the Heinze et al. (2007) typology (Table 6). Awardees most often

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[45] *See* HHMI website, "HHMI Investigators," accessed February 24, 1011, http://www.hhmi.org/research/investigators.

[46] *See* Grand Challenges in Global Health website, "Grand Challenges Initiative," accessed February 24, 2011, http://www.grandchallenges.org/about/Pages/Overview.aspx.

[47] *See* DARPA website, "About DARPA," accessed February 24, 2011, http://www.darpa.mil/about.html.

[48] *See* DARPA website, "Strategic Vision," accessed February 24, 2011, http://www.darpa.mil/stratvision.html,

predicted that their NDPA research could result in the discovery of new phenomena (17/21).

Table 6. Awardees' assessment of the nature of the outcomes of their research

Pioneer	New Idea	New Phenomenon	New Methodology	New Technology	New Framework	None of these outcomes
1	X	X	X		X	
2	X	X	X	X	X	
3			X	X		
4	X	X	X			
5	X	X	X		X	
6	—	—	—	—	—	—
7	—	—	—	—	—	—
8		X	X		X	
9	X	X	X	X		
10	X	X	X	X	X	
11	X	X	X	X	X	
12	X	X	X	X		
13	X	X	X		X	
14	X	X			X	
15	X	X	X	X	X	
16	X	X			X	
17	X	X	X	X	X	
18		X	X			
19	—	—	—	—	—	—
20	X	X			X	
21	X	X	X		X	
Total	15	17	15	8	13	0

Source: Awardee interviews.

Note: Dashes indicate that three awardees could not be reached for comment regarding the nature of their outcomes.

2. What are the applications of awardee research to the diagnosis and treatment of disease?

The goal of the NDPA is to encourage pioneering approaches to "major contemporary challenges in biomedical research," with biomedical research defined as "scientific investigations in the biological, behavioral, clinical, social, physical, chemical,

computational, engineering, and mathematical sciences."[49] This section discusses the relevance of the awardees' research to applied health-related fields.

Almost all of the awardees had ideas about how their results could have biomedical implications, even if they themselves were not pursuing these avenues of research. The current health impacts of the awardees' results are in a variety of stages. The awardees explained that:

- They could state the potential long-term applications of their research (6 Awardees)

  "I think our results could eventually lead to…more diagnosis and treatment…I mean this is very long term now."

  "The ultimate goal of my Pioneer Award proposal does not necessarily apply to disease, but the outcome…will be applicable …If we can figure out how to induce these brain circuits in a non-vocal learning species, then that same technology then could be utilized to try to repair brain circuits for speech in humans."

- Discoveries of health-related applications were expected to occur within a ten year timeframe (5 Awardees)

  "We have a program in place here … where we're trying to imagine putting patient-specific cells into patients within a seven year timeframe."

  "I think over the next two to six years it's going to transform it and find a cure to Alzheimer's."

- Studies with implications for disease treatment and diagnosis are underway (6 Awardees)

  "A parallel set of experiments that we are doing is to develop a disease model for autism spectrum disorders…It would be perfect if we could take this method and apply it to…that experimental model."

  "They're going through trials and likely or certainly are going to be part of the research market. They likely will head to therapeutic trials sometime in the next year or two."

  "We published a Parkinson's paper in animal models…It has helped us to guide brain stimulation therapies better. So now, already we have human trials here."

- Their research is already having an impact on disease and public health (3 Awardees)

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[49] *See* the NIH Director's Pioneer Award Program Notice, January 3, 2005, available at http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-05-021.html.

"We knew all along during those five years…that if we were successful that it would have immediate application."

"We had a visiting cogno-behavorial therapist for a little bit and she was finding that the stuff on kin detection was helpful to her in dealing with certain clients."

While their research is in different stages of diagnosis and treatment development, all of the awardees had at least an idea of how their research could have biomedical applications in the future.

Independent of having specific biomedical applications of their research, the NDPA spurred non-biologists to think more about the biological implications of their research. Awardees commented:

"I think many of [the publications] are in very, very highly interdisciplinary journals and some of them have a much greater biological flair than we would have normally published prior to the award."

"We had spent a decade developing tools for [nanotechnology, tools to build structures on the molecular scale]. Many of these tools had been developed with the physical sciences and the semiconductor industry in mind…We thought there might be the ability to begin to use these types of tools to really impact biology."

3. To what extent are other researchers making use of techniques and findings developed by the awardees?

One way to demonstrate the spillover effects of the NDPA is to evaluate the awardees' productivity through their research outputs, as well as the extent to which their work is being transferred throughout the scientific community. As mentioned in this chapter, the work conducted under the NDPA has produced a variety of research developments including textbooks, software, vaccine production, patents and commercialized products.

Through the interviews, it was made clear that many of the awardees' have made sharing their outputs with other scientists a research priority.

"Our philosophy of sharing has been the following: my lab has been a major source of all reagents on mammalian telomeres or antibodies or constructs, or cloned genes, etcetera, etcetera. You can go to our website and follow. There is not really a shopping cart in the website but there could be…, everything is described with indications of how it works."

"Since our initial paper in May 2005, and a number of subsequent papers, we have lot of requests from many people for reagents and also for help in using them. And so, we have sent them to nearly 450 labs worldwide now. Many papers have gotten published from those labs, graduates of the labs, of my lab has gone

onto other institutions, we've start to run courses both at Stanford and at Harvard on this whole optogenetics, we call as optogenetics now."

"The intention of this whole project was to make this something that basically any lab can do."

"I think you're going to see all sorts of new tools that become part of research labs all over the world– we already know we have medical diagnostic tools that are used in hospitals all over the world. And soon we will hopefully have therapies that are used."

"I think the last number was 26 different researchers who have come through the lab for many instances, as much as two to three weeks, who we've trained on the iPS methodology."

"We deliberately released software that has the free and open-source license."

Some awardees have developed coursework at both the undergraduate and the graduate levels, and others are offering training courses to teach other investigators how to use their research tools and techniques. Awardees are sharing everything from their reagents to their research methodology, which has increased their level of collaboration at the national and international levels.

Sharing their techniques and research tools has also forged new collaborations for many of the awardees. Out of the 21 awardees interviewed, 18 mentioned that they were collaborating with other researchers on their NDPA projects, and a few were even collaborating with other awardees. Some of the awardees are exploring the clinical applications of their research, as six awardees (who are not clinicians) mentioned they were either consulting with, or currently collaborating with practicing clinicians on their NDPA projects.

F. Spillover Effects

1. How has the NDPA affected the scientific reputation of the awardees?

Although many of the awardees stated that at the time of receiving the award they had already reached the highest professional level in their careers, others believed the NDPA positively affected their career trajectories and or improved their scientific reputations. Two awardees mentioned during the interviews that their labs and their research fields have experienced increased visibility since receiving the NDPA. Several awardees have enjoyed popular press coverage of their Pioneer research including the *New York Times*, *Wall Street Journal*, *Wired*, *Technology Review*, *The Economist*, *Forbes*, *Discover*, *Scientific American*, *Popular Science*, *Rolling Stone*, and broadcast such as NPR, CNN, ABC, PBS NOVA, BBC News, Google Tech Talks, TED Talks, and

National Geographic.[50] Some awardees mentioned the NDPA also brought additional scrutiny to their work due to the level of funding, and the high-risk nature of the program.

2. How did the NDPA affect the awardee's role as an independent researcher?

When asked whether their careers had changed since the NDPA, many awardees (11/21) said that winning the NDPA did not have an effect on their career trajectory because they had already received tenure or had reached a level where the award would not have an effect. However, two awardees were promoted after receiving the NDPA, and another two awardees acknowledged that their careers had significantly changed after winning the Pioneer Award. The awardees' descriptions of how the NDPA changed their careers are shown below:

> *"Have you seen the movie* It's a Wonderful Life*? I'm the guy standing at the bridge. I have no idea what the lab would be today if we hadn't won the Pioneer."*
>
> *"I left academia to fully pursue research. I wanted a sustainable research career, and the Pioneer made a huge difference."*
>
> *"Having received promotion and tenure, I went from post-doc to full professor and the Pioneer Award was hugely instrumental. I don't know anyone else that it's happened to."*
>
> *"Any awards after NDPA are all related to it, because before we didn't publish much before. I've received tenure this year…and that's rather early after only four years."*

Additionally, two awardees stated that after winning the NDPA, they left a position as a director or other leadership in their institutions to become full-time investigators, and another awardee said the NDPA allowed him/her to focus more on his/her research. Awardees were highly invested in their NDPA projects and winning the Pioneer made allowed some awardees to spend more time as researchers. One awardee mentioned returning to the research bench "for the first time since '97, to show the lab how serious I was about starting this new direction."

G. Summary

The awardees were highly positive about the NDPA program and its outcomes on their research. The proposed projects were diverse; with many different types of risk present in them. Given the nature of the risks inherent in the projects pursued, and the flexibility given to awardees in how they chose to use the NDPA funds, a perhaps

[50] Due to the timing of the evaluation, STPI ended data collection of media coverage in January 2010. However, with continuous dissemination of the awardees' research developments, the Pioneers' research has received additional popular press coverage since we began writing this report.

unsurprising finding is that not all the awardees pursued the research proposed in their applications. When asked about their research progress, two thirds of the awardees said they have reached their goals for one or more of the projects they proposed in their applications. Approximately one third said that aspects of their research failed, and about one third said that research they actually pursued with the award was an evolution from what they had originally proposed, either because of research failure or because of events taking place outside of the laboratory. Of those that evolved, most pursued other high-risk projects, while very few abandoned their projects and pursued other projects that were more closely aligned with projects they had been working on prior to receiving the NDPA. Some awardees stated that although they haven't yet reached the goals for their project, they knew that the research would always take longer than five years. And another few stated that the progress on their research was actually faster than they had imagined it would be.

Awardees provided many examples of non-publication-based outputs that have been accomplished with the NDPA. Most of those awardees who had begun applying for follow-on funding for their projects were successful. There were a variety of spillover effects of the program on the awardees, including enhanced reputation and accelerated career development.

5. Bibliometric Analyses

A. Introduction

For this study, pioneering is equated to multiple related terms, such as creativity. In this section, bibliometric measures (measures of publication and citation data) are proposed as proxies for creativity include productivity, collaboration and brokerage, interdisciplinarity, and impact. (See Chapter 2 for a review of the literature.)

While the quantitative nature of bibliometric analyses gives the appearance of authority in characterizing publication sets, bibliometrics do not capture the full picture of an individual's research and cannot distinguish between failures due to a lack of research activity and failures due to attempt of research and finding the research project to be unfeasible. Furthermore, bibliometric analysis is an evolving and relatively untried field. As such, it is difficult to know a priori if the techniques can be applied to identifying and characterizing pioneering research. Keeping these caveats in mind, we explored the use of bibliometrics primarily as descriptive measures for the purpose of this evaluation. Bibliometrics are most useful when combined with other elements in a multi-method evaluation.

B. Productivity

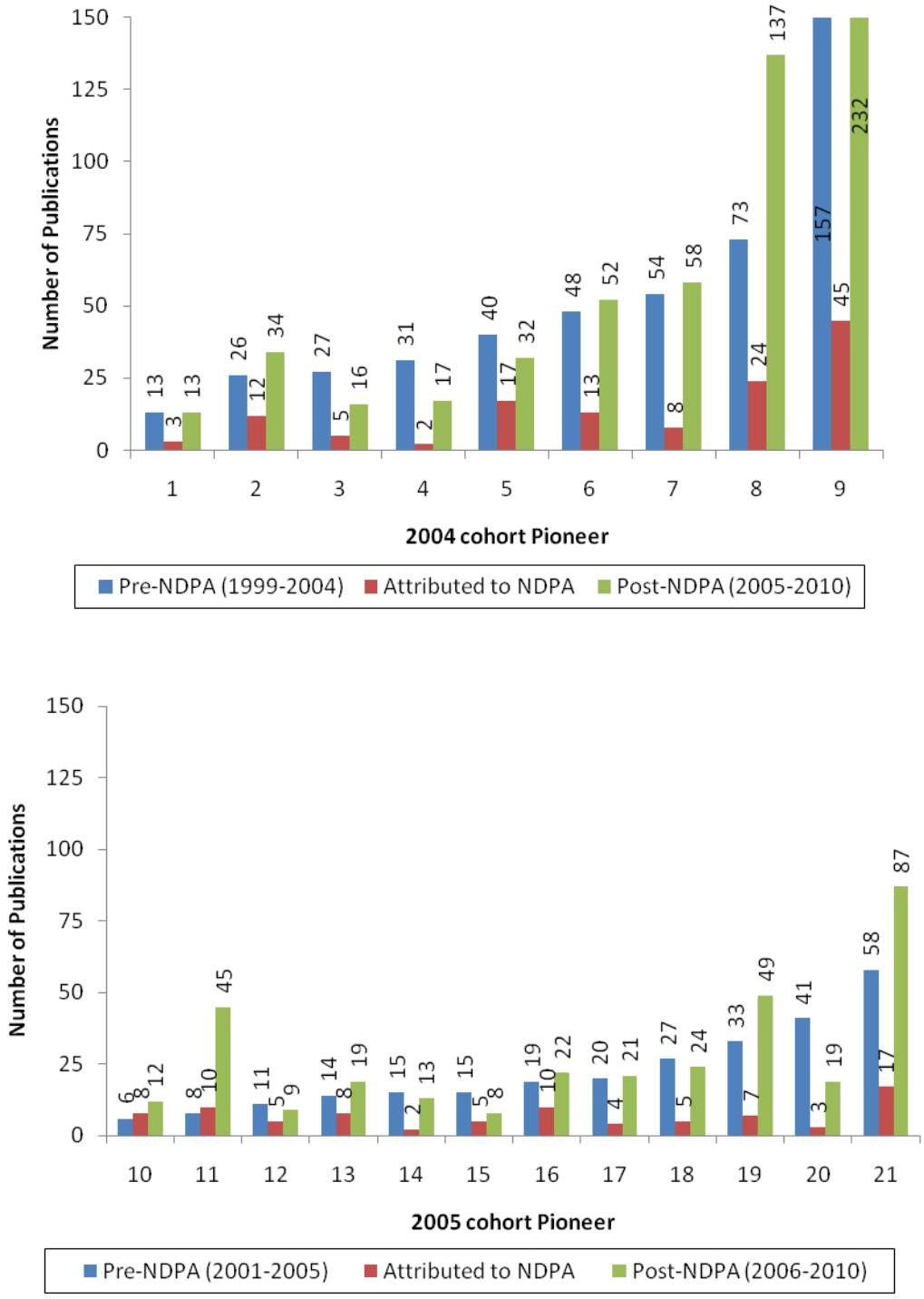
Productivity is used as a descriptive to characterize an individual awardee and the group of awardees collectively. It is measured by the number of publications before and after receiving the award (see Table 7 and Figure 4).

Table 7. Number of articles published by each pioneer pre-NDPA, attributed to NDPA, and post-NDPA for Pioneers

Pioneer	Number of Publications (Pre-NDPA)	Number of Publications (Attributed to NDPA Funding)	Number of Publications (Post-NDPA)
1	13	3	13
2	26	7	34
3	27	5	16
4	31	2	17
5	40	9	32
6	48	11	52
7	54	7	58
8	73	19	137
9	157	37	232
10	6	5	12
11	8	10	45
12	11	1	9
13	14	3	19
14	15	1	13
15	15	3	8
16	19	5	22
17	20	2	21
18	27	2	24
19	33	6	49
20	41	2	19
21	58	14	87

Source: Web of Science.

(Pre-NDPA is 5 years before receipt of the award; post-NDPA is 5 years after receipt of the award)



Source: Web of Science.

Note: Publication data are for the 21 pioneers who completed their funding for their award. Clare Waterman gave up her grant when she moved to NIH.

Figure 4. Number of publications pre-NDPA, attributed to NDPA, and post-NDPA for Pioneers

There was no clear pattern of whether the number of publications increased or decreased for the collective group of awardees after receiving the award. For the 2004 cohort, while the number of publications did not necessarily increase in the period after the award, individuals who published frequently (≥ 40 publications) in the period before the award continued to publish a high volume after the award. Similarly, awardees who were not high-volume publishers before the award did not drastically change their publication behaviors after the award.

Similar patterns were observed for the 2005 cohort, as frequent publishers in the period before the award continued to publish a high number in the period after receiving the award and infrequent publishers before the award remained as such after the NDPA. Two notable exceptions were awardees "11" and "20". Awardee 11 stated that s/he observed a significant increase in publication because the NDPA greatly enhanced his/her research capacity. Awardee 20 greatly decreased how often s/he was publishing. In his/her interview, the awardee explained that during the NDPA funding period, s/he followed the mantra "build the tools, build the foundation and what comes of that will be much greater than what you can achieve by having a very short timeframe." S/he wanted to take more time to produce impactful results, so his/her focus on publishing greatly decreased at this time.

The literature review in Chapter 2 presented two different theories of productivity. One suggested that a greater number of publications over a career means there is a greater likelihood that a peer will find the researcher creative. Another hypothesized that high-risk research takes a longer time to produce results. While this analysis does not attempt to prove or disprove either theory, the short-period of time since the receipt of the award makes the data more susceptible to the second hypothesis. We could not capture the full effect of the NDPA based on publications, so the application of this data is limited.

Of the 21 awardees, 12 of them published more after receiving the award and 8 published less. One published the same amount The awardees seem to have been productive researchers over the duration of the NDPA funding period, despite the reduced pressure to publish.

C. Impact

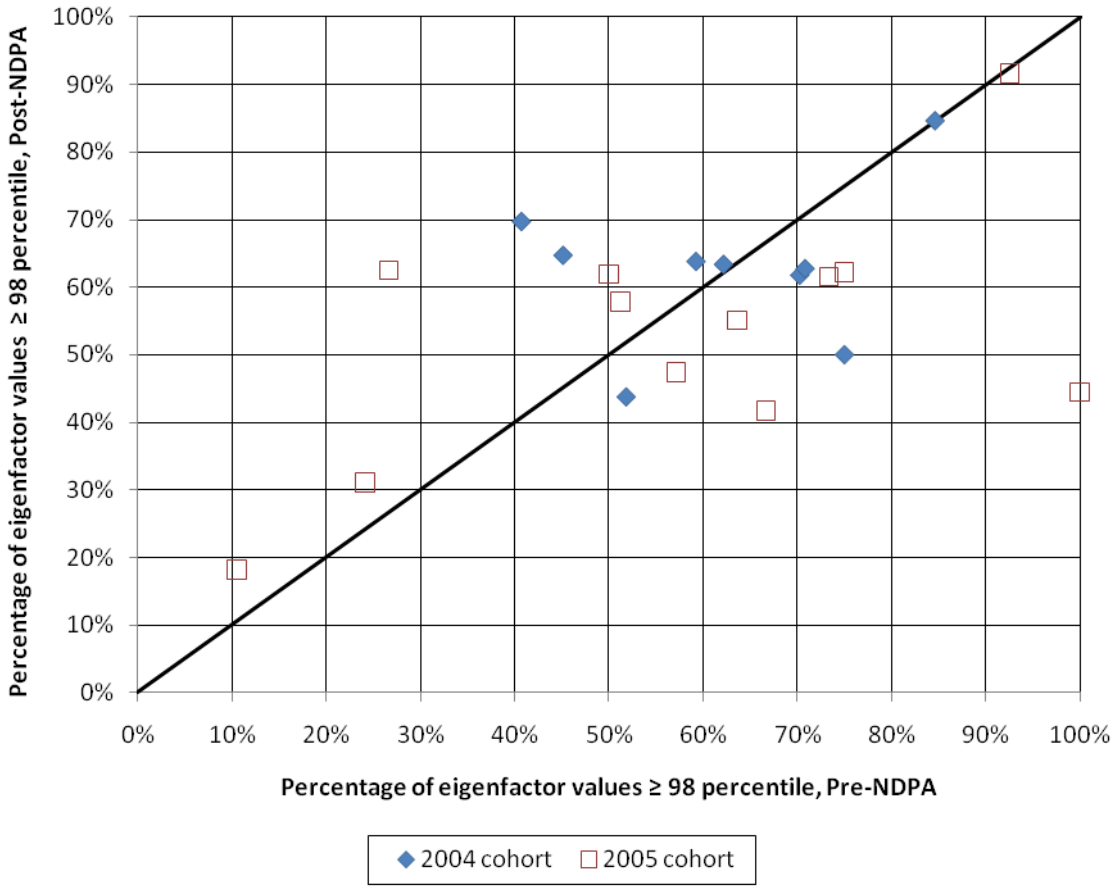
1. Journal Impact Factors

The prevalent method of assessing journal quality and influence is journal impact (Eigenfactor) values. The *Eigenfactor Score* is an open-source journal impact metric.[51] Its calculation is based on the idea that journals are considered more influential if they are

[51] *See* Eignfactor website, accessed February 24, 2011, www.eigenfactor.org.

cited often by other influential journals. There are concerns that impact factors conceal the difference in article citation rates, are unrelated to the quality of the articles, and vary depending on the research field (Seglen 1997), but other studies have demonstrated a correlation between high impact factors and journal quality (Saha, Saint, and Christakis 2003). In this evaluation, we use journal impact factors to gauge the potential exposure of the awardees' research.

The change over time in the impact factor of the journals in which NDPA awardees published is represented in Figure 5.



Source: STPI analysis based on publication data from Web of Science. Eigenfactor values percentiles are from Eigenfactor.org. Analysis is based on 5 years before (pre-NDPA) and 5 years after (post-NDPA).

Figure 5. The percentage of awardee publications with Eigenfactor values greater than or equal to 98 percentile (journal impact factor), before and after receiving the award

As figure 6 shows, awardees were already publishing in high impact journals in the period before the award and they continue to do so after receiving the award. However, those who were not publishing in such influential journals before the award began to

publish more in journals such as *Proceedings of the National Academy of Sciences of the United States of America*, *Nature*, and *Proceedings of the Royal Society B-Biological Sciences*.

That all of the awardees had multiple publications in 98 percentile journals before and after receiving the award indicates that these researchers were already influential before receiving the NDPA and continued their success throughout the funding period.

Table 8 characterizes the number of publications with high *Eigenfactor* value percentiles for the NDPA-attributed publication set.

Table 8. Number of papers per NDPA award in high-Eigenfactor (high-impact) journals

	Number of publications in a journal with an Eigenfactor value ≥ 98 percentile
Minimum	1
Maximum	31
Mean	6.43
Median	4
Mode	3

Source: STPI analysis based on publication data from Web of Science. Eigenfactor values percentiles are from Eigenfactor.org.

On average, awardees have had 6.43 NDPA-attributed publications in influential journals.

2. Citations, Age-Weighted Citation Rates, and H-indices

Bibliometric citation analysis can be used to estimate the impact of a researcher's work. The expectation is that the awardees' work would have high impact due to the size of the NDPA award and the funding opportunity announcement's call for research that had "the potential to produce an unusually high impact" on biomedical research.[52] Articles written after receiving the award, however, were only written within the past few years. The number of citations to these articles is expected to be lower than the number of citations to articles written before the award. The age-weighted citation rate (the number of citations to a given paper divided by the age of that paper) is also presented. The h-index measures the cumulative impact of a researcher's output by counting the number of citations his/her work has received. (A researcher has an index h if h of his/her Np papers

[52] *See* the NIH Director's Pioneer Award Program Notice, January 3, 2005, available at http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-05-021.html.

have at least h citations each, and the other (Np-h) papers have no more than h citations each).[53]

The number of citations, age-weighted citation rate, and h-index are used to characterize the impact of awardee research (Table 9).

Table 9. Measures of impact of research performed by NDPA awardees

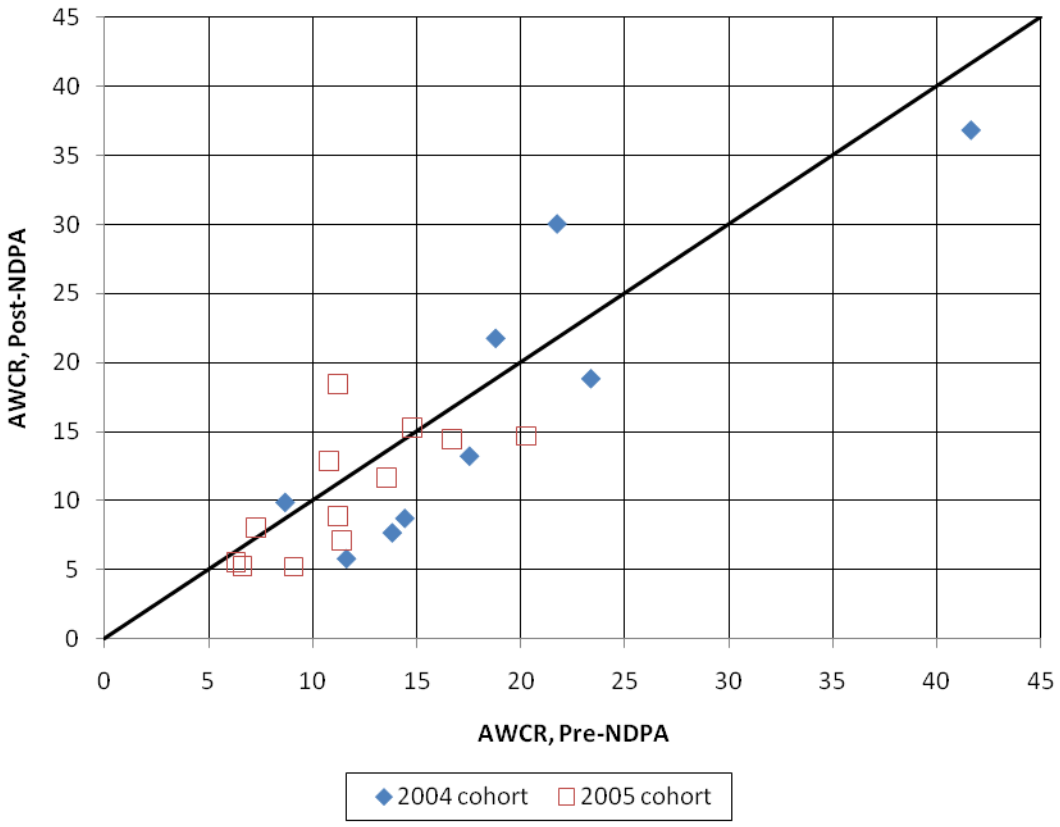
Pioneer	Number of Citations to Pre-NDPA Articles	Number of Citations to Post-NDPA Articles	Age-Weighted Citation Rate for Pre-NDPA Articles	Age-Weighted Citation Rate for Post-NDPA Articles	H-index
1	348	97	6.62	5.26	17
2	356	101	6.31	5.53	18
3	448	255	7.26	8.06	31
4	577	100	9.10	5.24	15
5	749	389	10.80	12.85	13
6	781	484	8.67	9.89	24
7	987	1,026	11.21	18.46	27
8	1,049	189	11.41	7.13	23
9	1,140	329	11.21	8.87	34
10	1,216	147	11.62	5.81	31
11	1,385	546	13.54	11.69	30
12	1,567	807	14.78	15.30	37
13	1,896	277	13.82	7.69	54
14	2,005	362	14.42	8.74	53
15	2,217	740	16.70	14.45	57
16	3,057	596	17.53	13.24	43
17	3,257	2,172	18.79	21.77	43
18	3,375	721	20.26	14.70	61
19	4,448	2,902	21.74	30.07	44
20	5,115	1,415	23.37	18.85	41
21	16,293	5,803	41.65	36.85	72

Source: Web of Science.

Age-weighted citation rates (AWCR) to original publications excluding reviews were compared for articles published before and after the award (Figure 6). Fourteen

[53] Multiple variants proposed in the literature differentiate themselves from the h-index by correcting for researcher career length (h-rate), highly-cited articles (g-index), and more. Despite the propagation of h-index variants, the original h-index remains the most prominent indicator of its kind in the literature. In this evaluation, the h-index is used to capture a researcher's productivity and the impact of his or her publications to date.

awardees had lower Age-weighted Citation Rates (AWCR). Seven awardees, however, had higher age-weighted citation rates for their publication set after the award. For awardees 3, 5, 6, 7, 12, 17, and 19 in Table 9, their research after the award seems to be having a greater impact than their research before the award. It is important to keep in mind, however, that not all of the publications considered resulted from their NDPA projects.



Source: Publication data are from Web of Science. Analysis is based on 5 years before (pre-NDPA) and 5 years after (post-NDPA).

Figure 6. Age-weighted citation rate before and after receiving the award (a proxy for awardee research impact)

Despite the AWCR's attempt to normalize for the amount of time an article has been published, the near-term nature of this evaluation renders assessments of citation rates difficult. As shown above, more twice as many awardees (14) had lower AWCRs five years after receiving the NDPA awardee than those who had higher AWCRs during the same time frame (7).

The h-index of awardees ranges from 13 to 72. H-index factors measure a researcher's productivity and impact, so the range of scores indicates diversity amongst awardee publishing behaviors. The wide range of h-index values reflects the length of time that they have published, since more citations are likely to occur over a longer timeframe.

Descriptive statistics for the number of citations to publications attributed to NDPA funding are shown in Table 10.

Table 10. Number of citations to publications attributed to NDPA funding (a proxy for impact)

	Number of Citations to NDPA-Attributed Publications
Minimum	11
Maximum	661
Mean	180.67
Median	134
Mode	32

Source: Web of Science.

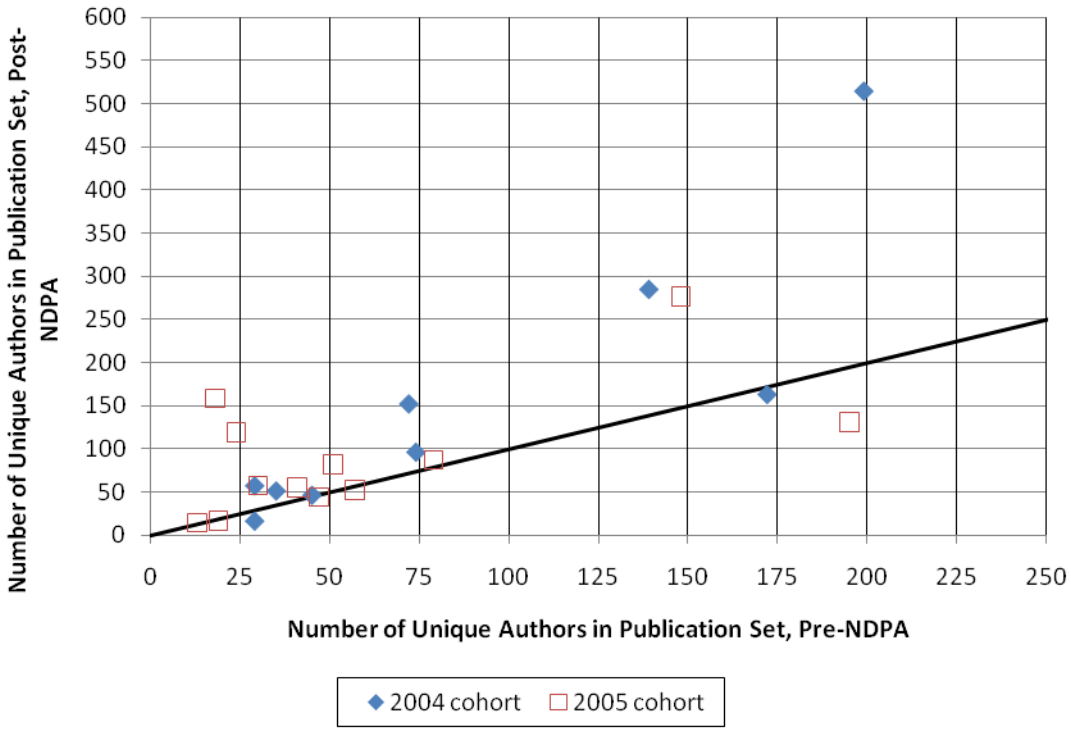
All of the NDPA-attributed publications have been cited at least 11 times. A few publications are already highly-cited. The wide discrepancy may be due to the visibility of the journal in which the articles were published, or to the fact that some disciplines tend to cite more often than others. On the other hand, a high number of citations may indicate that the research is pioneering.

D. Co-authorship

One indicator of collaboration is the number of unique authors in an investigator's publication set. According to the literature, spanning multiple groups of clustered investigators—potential collaborators—may stimulate creativity. While full social network analyses were not performed for this evaluation, assessing the awardees' network of co-authors on publications before and after receiving the NDPA was performed in order to identify collaboration patterns as a result of the award. Increased collaborations may be an indicator of creative and pioneering research (Burt 1992).

1. Co-authorship of Awardees' Full Publication Set (pre- and post-NDPA)

Comparisons of the number of unique authors in each awardee's publication set before (5 years before) and after receiving the NDPA are visualized in Figure 7.



Source: Web of Science. Analysis is based on 5 years before (pre-NDPA) and 5 years after (post-NDPA).

Figure 7. Size of co-authorship network size of awardees, before and after receiving NDPA award

The change in co-authorship size differs by awardee. Awardees generally published with the same number of people, but six awardees displayed an increase in the period after receiving the award. Only one awardee had a significant decrease in the number of co-authors in the period after the award.

The great diversity in the co-authorship of awardees re-emphasizes the fact that the Pioneer Award funded a diversity of researchers. While some awardees published with less than 25 people over a five year period, others published with more than 200 other researchers in that same time span.

2. Co-authorship of Awardees' Publications Acknowledging the NDPA award

The minimum, maximum, mean, median, and mode of the number of unique authors in awardees' publications acknowledging the NDPA award are shown below in

Table 11. There are an average of 34 unique co-authors for each awardee, ranging from 3 for one awardees to 102 for another.

Table 11. Size of co-authorship network when considering only publications attributed to NDPA funding

	Number of Unique Authors in Publication Set
Minimum	3
Maximum	102
Mean	34
Median	22
Mode	5

Source: Web of Science.

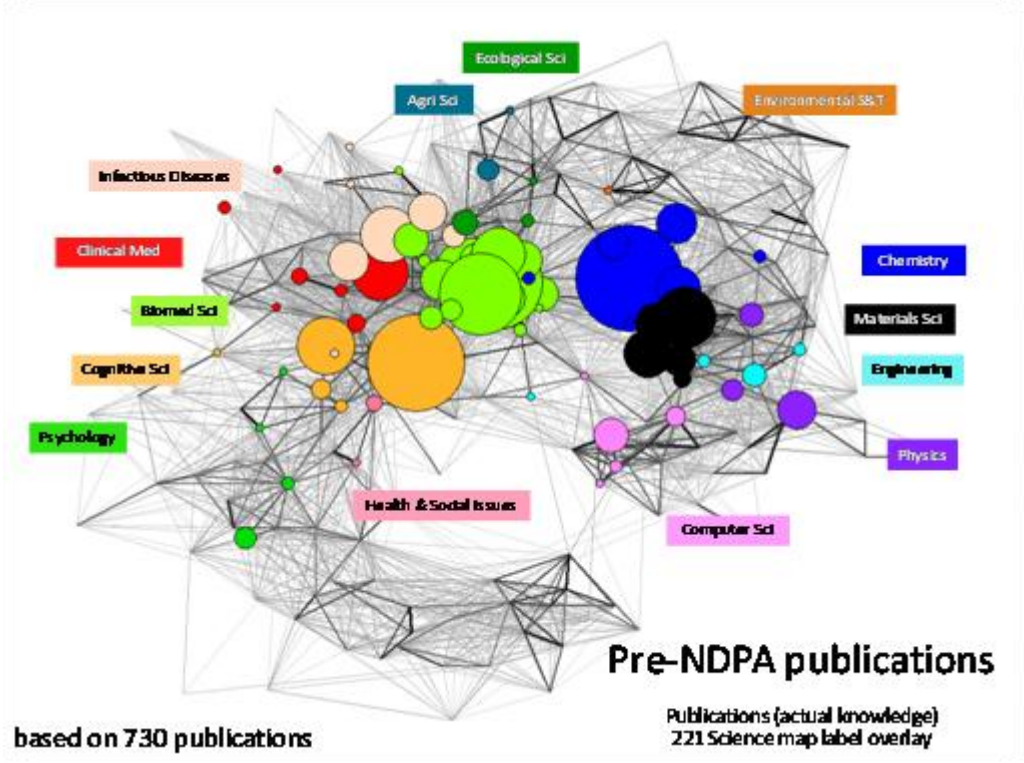
The range of co-authorship network sizes is smaller for the NDPA-attributed publication set than the full publication set of awardees.

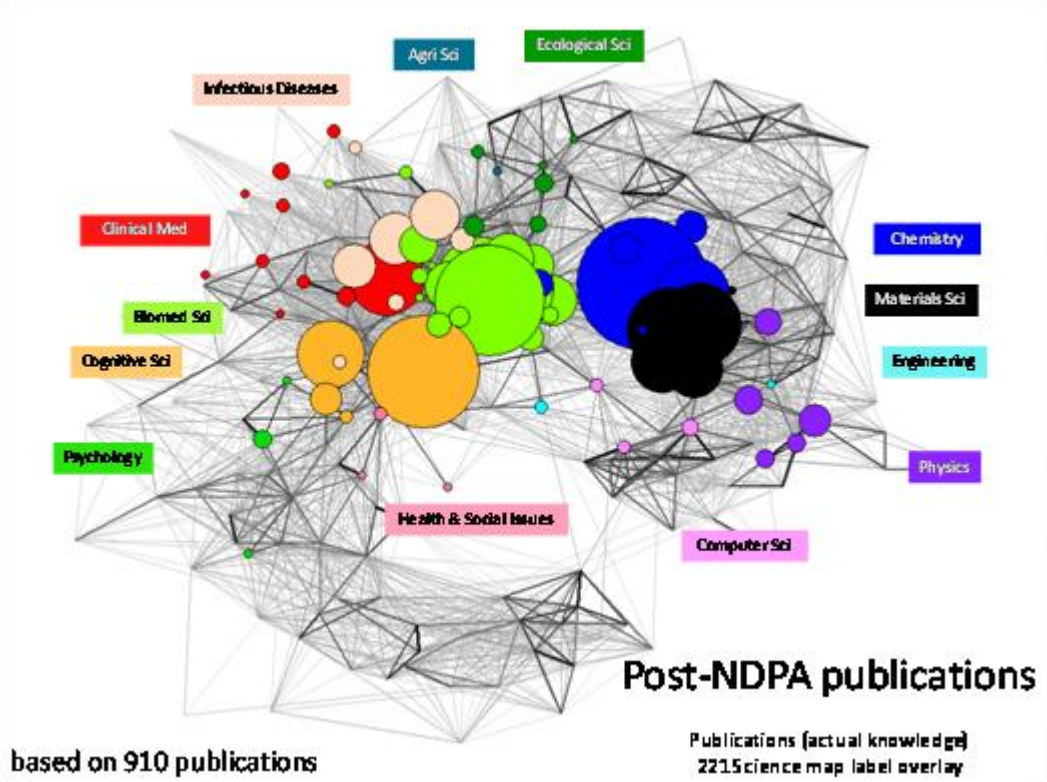
E. Measures of Interdisciplinarity

1. Placing NDPA Research on a 'Map of Science'

Another method of visualizing interdisciplinarity is to overlay a researcher's body of references on a "map of science," a visual representation of the relationships among scientific disciplines (Leydesdorff and Rafols 2009). In this evaluation, researcher publications and cited references are overlaid onto a map of science in order to characterize research focus and scope (Rafols, Porter, and Leydesdorff 2010).

The disciplines in which the collective group of NDPA awardees published before and after receiving the award are shown in Figure 8.





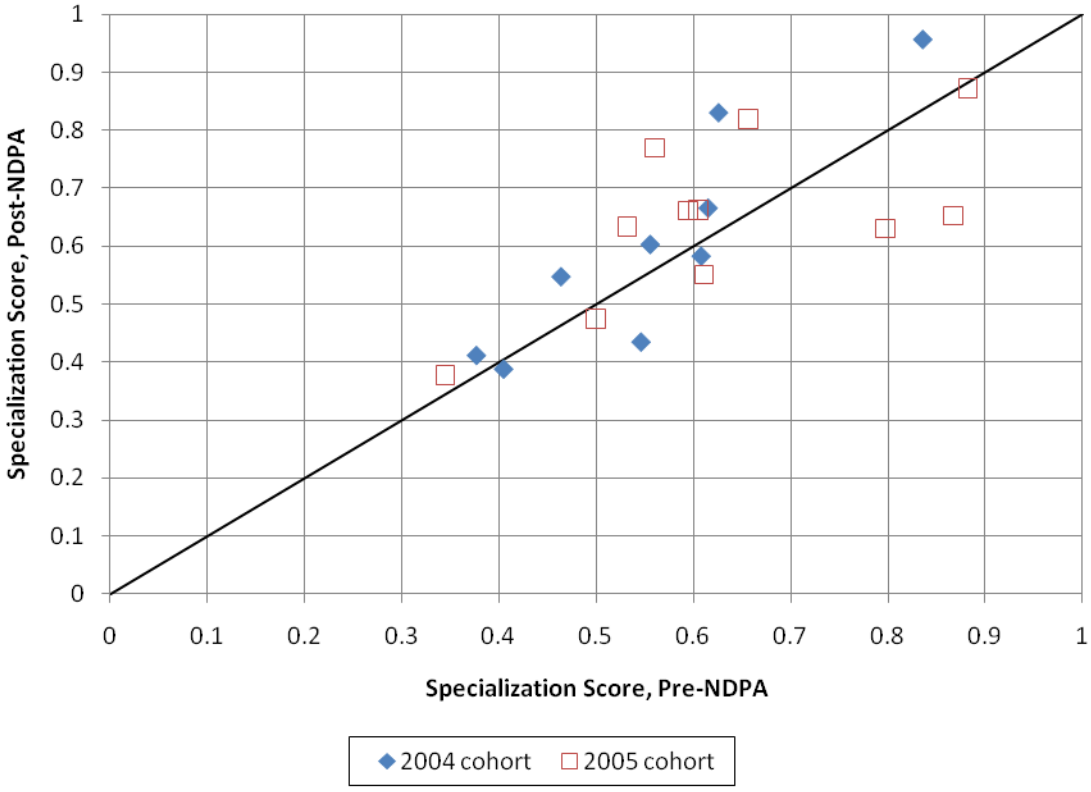
Source: Publication data are from Web of Science. Vectors were created with VantagePoint. Pajek was used to overlay the publication vectors onto maps of science.

Figure 8. Disciplines that awardees published before and after the NDPA award

In the period after the award, the number of publications in engineering, computer science, and agricultural science decreased while the number of biomedical science, cognitive science, and clinical medicine publications increased. The awardees shifted into more biomedical and health-related fields as a result of the Pioneer Award.

2. Specialization

The specialization score is another descriptive publication indicator that measures the interdisciplinary nature of the awardees' research. Specialization, which ranges from 0 (low specialization/high diversity) to 1 (high specialization/low diversity), displays the scope of the awardees' research foci based on the disciplines of the journals in which they publish (Figure 9).



Source: Publication data are from Web of Science. Specialization scores were calculated using VantagePoint software. Analysis is based on 5 years before (pre-NDPA) and 5 years after (post-NDPA).

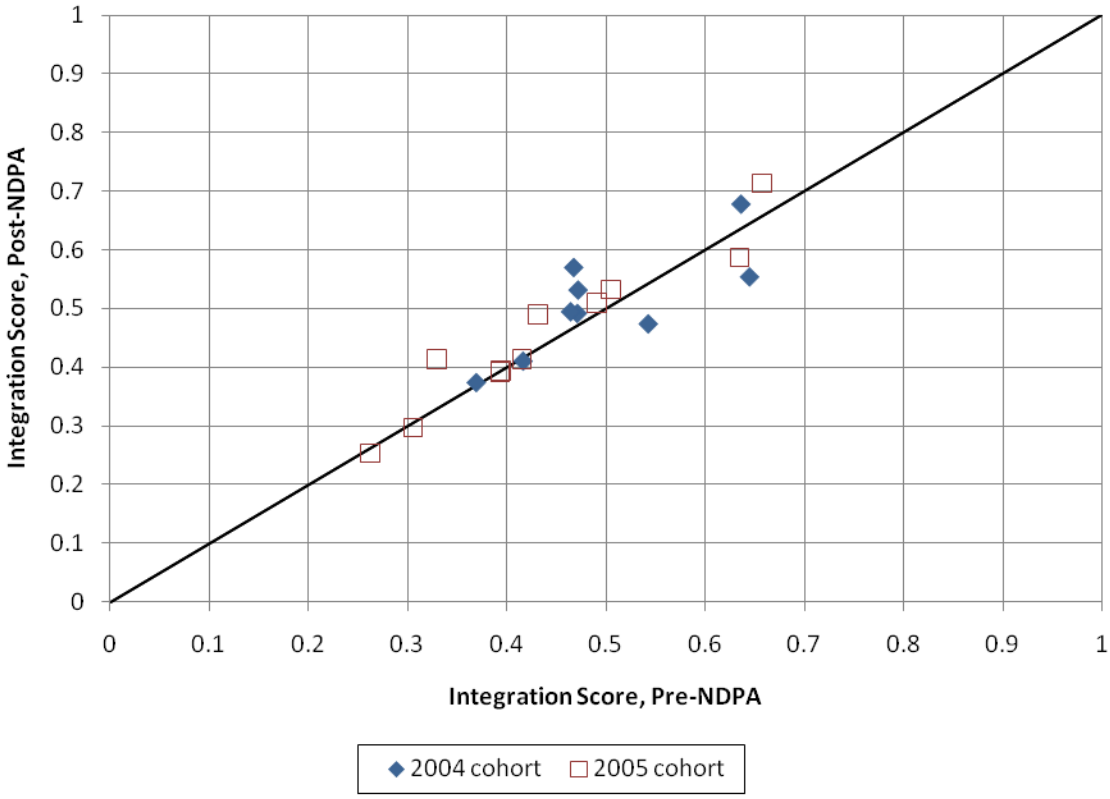
Figure 9. Specialization scores of awardees before and after receiving NDPA award

While specialization scores generally hover around the same value across both time periods, specialization scores increased for 13 of the 21 awardees after receiving the award. These 13 researchers either published in fewer disciplines or had a less even

distribution of publications in disciplines after the award. One possible explanation for the general increase in specialization scores may be an increased rate of publication in large multidisciplinary journals. Well-known journals such as *Nature*, *Science*, and *Proceedings of the National Academy of Sciences of the United States of America* are placed into one category called Multidisciplinary Sciences. Nevertheless, when examining the publications themselves, there does not appear to be a marked increase in the number of publications in multidisciplinary journals.

3. Integration

A descriptive measure of the interdisciplinary nature of cited references is the integration score. Integration, which ranges from 0 (low integration of information and diversity) to 1 (high integration of information and diversity), displays the scope of the awardees' cited references (Figure 10).



Source: Publication data are from Web of Science. Integration scores were calculated using VantagePoint software. Analysis is based on 5 years before (pre-NDPA) and 5 years after (post-NDPA).

Figure 10. Integration scores of awardees before and after receiving NDPA awards

Integration scores remained similar before and after the award. Eleven awardees integrated a greater diversity of knowledge in the period after the award, while ten

awardees had a decrease in integration score after the award. For the majority of these data points, however, the changes between scores before and after the award are less than 0.05.

4. Relationship Between Specialization and Integration

Interdisciplinarity may be measured using integration (I) and specialization (S) scores. Integration captures the integration of knowledge across a body of research, while specialization considers the scope of knowledge of a researcher's publications. Porter et al. (2007) define categories of researchers by their I and S scores (see Table 12). They find that the majority of researchers are Disciplinarians or Renaissance Integrators. Integration and specialization are sister metrics which, together, provide a estimation of the interdisciplinary nature of the awardees' research. Specialization represents publication information, while integration represents cited references. The integration and specialization scores of the awardees are displayed in a manner similar to that described by Porter et al. (2007) (Figure 11). The two scores have a negative correlation.

Porter et al. apply categories to each of the quadrants explained in Table 12, and find that the majority of researchers fall into the upper left and lower right quadrants.

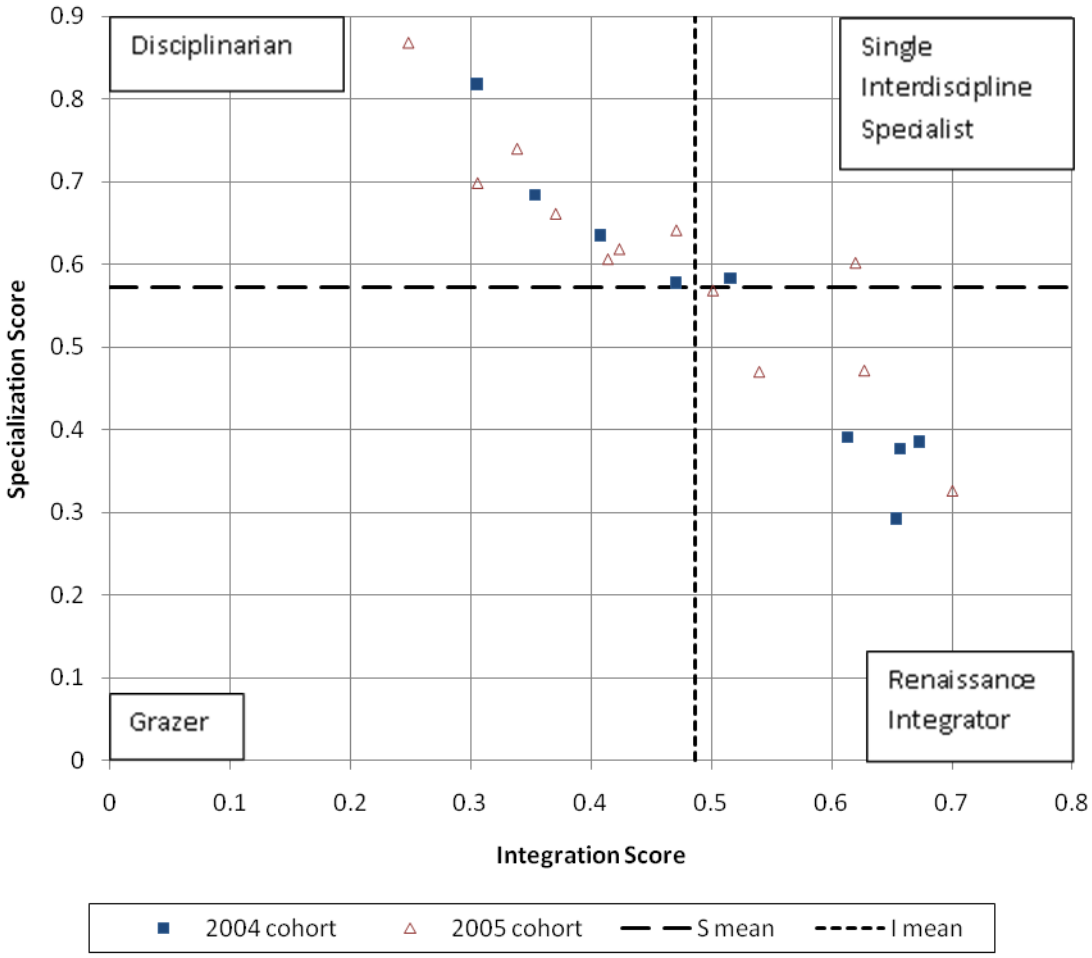
Table 12. Categories of researchers according to interdisciplinarity

	Low Integration Score	**High Integration Score**
High Specialization Score	*Disciplinarians*—researchers with sharply focused research interests	*Single Interdiscipline Specialists*—researchers who integrate many fields of knowledge into a few specialized areas
Low Specialization Score	*Grazers*—researchers who neither integrate knowledge from many different fields nor specialize into one field	*Renaissance Integrators* – interdisciplinary researchers who integrate knowledge from many fields and publish in many fields

Source: Descriptions of researcher types are adapted from information in Porter et al. (2007).

Burt's theory (2004) describes how brokers stand at the intersection of social worlds and create value by bridging them (Heinze and Bauer 2007). The theory also implies that creative researchers are more interdisciplinary because of their tendency to span multiple groups of researchers.

While we only use I and S scores to describe the interdisciplinary nature of awardees, if Burt's theory is correct, creative researchers are more likely to have high I scores and low S scores than other investigators, in other words, to be Renaissance Integrators. This is somewhat in contrast to Porter et al. who found that researchers tend to be Disciplinarian or Renaissance Integrators.



Source: Publication data are from Web of Science. Scores were calculated using VantagePoint software.
Note: Refer to literature review for further information on labels.

Figure 11. Relationship between integration and specialization scores of awardees

Based on the correlation of the specialization and interdisciplinary scores for each awardee's entire set of publications, the majority of awardees are either "Disciplinarians" or "Renaissance Integrators". Half (11/21) of NDPA awardees are Disciplinarians (high specialization and low interdisciplinary scores) and two are single interdisciplinary specialists. One-third (7/21) of the NDPA awardees are Renaissance Integrators. This is consistent with Porter et al (2007) findings and somewhat different than what Burt predicted.

F. Summary

Bibliometric analyses related to creative research were performed for publications citing NPDA work, as well as other publications by the awardees themselves. Differences between the five years preceding the receipt of the award and the subsequent five years do not show differences in publications, citations, co-authorship, and other related measures.

6. Experts' Assessment of Awardees Research

A. Introduction

A virtual panel of three experts (methodology described in detail in Chapter 3) was conducted for each of the awardees. Experts were given a research summary, three publications selected by the awardee, and information describing the NDPA program and its goals. The experts were asked to fill out a brief questionnaire on their assessment of the research and the NDPA program as a whole. Each expert reviewed and answered the questionnaire independently. This chapter describes the results of the expert panel process.

B. Assessing the NDPA-Funded Research

1. Risks

Each awardee's expert panel was asked to use the Colwell typology to characterize the risk associated with the proposed research. If at least two of the three experts agreed on a statement, the statement was reported as being chosen by the experts. The responses to this question are shown in

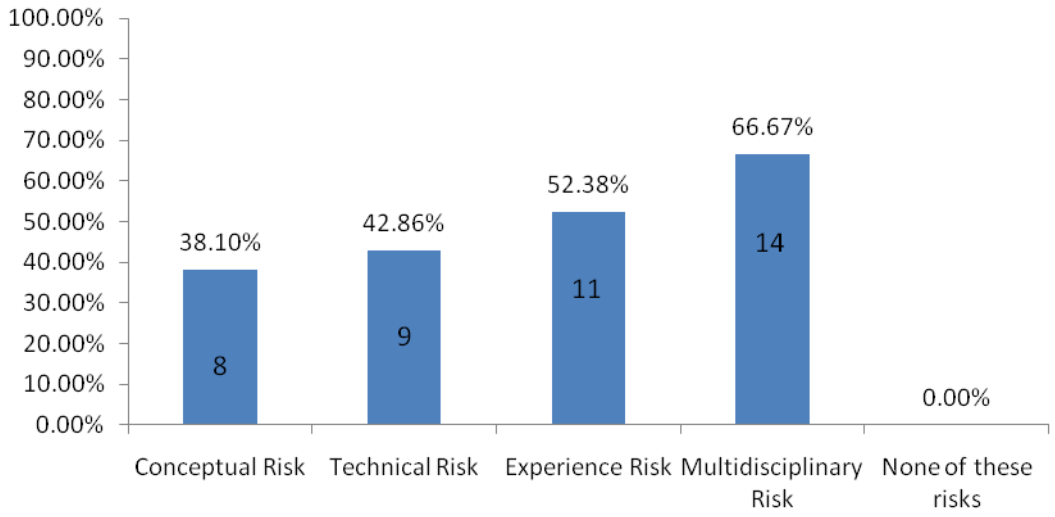
Table 13 and Figure 12. Refer to literature review for an explanation of Colwell's typology.

Table 13. Experts' assessment about the nature of the risks of the awardees' proposed research

Pioneer	Conceptual Risk	Technical Risk	Experience Risk	Multidisciplinary Risk	None of these risks
1	X				
2			X		
3			X		
4			X		
5				X	
6	X	X			
7	X			X	
8	X			X	
9	X			X	
10	X			X	
11		X	X		
12		X	X		
13		X		X	
14		X		X	
15		X		X	
16			X	X	
17			X	X	
18	X		X	X	
19		X	X	X	
20	X	X	X	X	
21	X	X	X	X	
Total	8	9	11	14	0

Source: Expert review.

Note: This table displays consensual expert assessments (at least two of three experts in agreement) of Colwell typology risks for each Pioneer in anonymous order. Experts were able to select as many of the risks that applied.



Source: Expert review.

Figure 12. Percentage of awardees attributed with each Colwell typology risk, based on experts' assessment

The most common risks the experts associated with the awardees' proposals were multidisciplinary risk (14/21) and experience risk (11/21). Experts also agreed that all of the Pioneer proposals incorporated at least one form of risk. These results suggest that all of the funded investigators and projects can be considered risky, although the nature of the risk varied. Below is a selection of comments from experts regarding the awardees they reviewed:

> *"The expertise needed to meet the evolving goals of this project required flexible access to a wide variety of potentially changing co-investigators."*
>
> *"The work is truly interdisciplinary, incorporating sophisticated theory and mathematics, but also providing serious connection to and adherence to the constraints of experimental data."*
>
> *"By the nature of the work and its outcomes, new avenues of investigation beyond the investigator's expertise ensued."*
>
> *"This NDPA application involved a unique combination of antigenic mapping, molecular phylogenetics, and fitness measures. [The awardee] is the only one doing this sort of research, and he has provided fundamental new insights into the basic biology of influenza virus."*

Experts found many of the applicant proposals to be multidisciplinary, in that they incorporated information from a number of different fields and used a combination of different approaches.

2. Rewards

In addition to characterizing risk, each awardee's panel was asked to characterize whether and in what ways the research is pioneering. As part of this process, experts were asked to identify which aspects of the Heinze et al. (2007) typology describe the research outcomes of the awardees (Table 14 and Figure 13).[54]

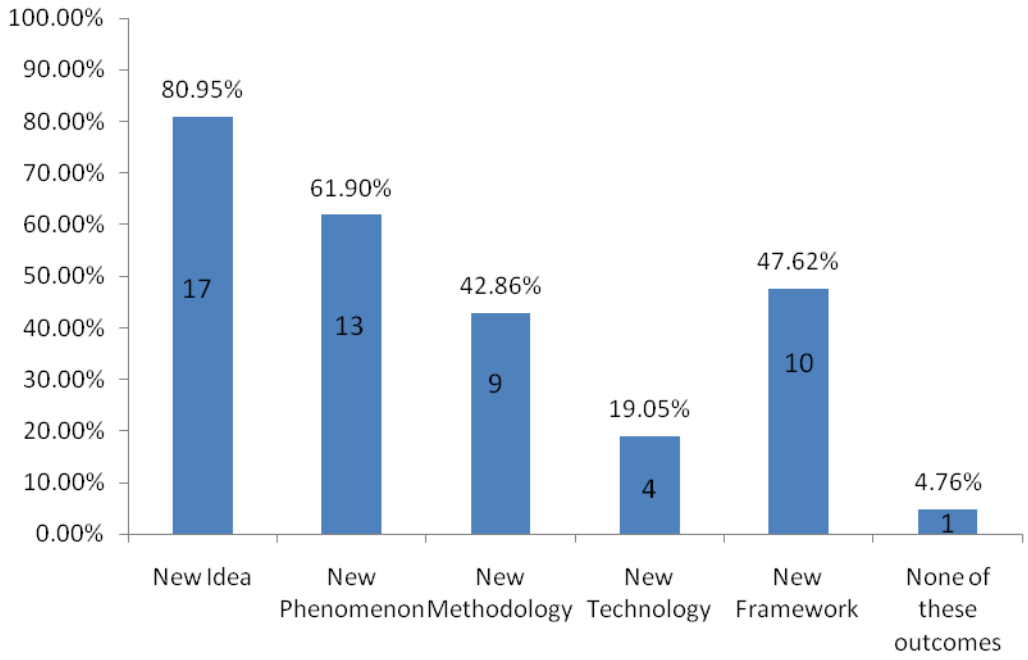
Table 14. Experts' assessment about the nature of the outcomes of the awardees' research

Pioneer	New Idea	New Phenomenon	New Methodology	New Technology	New Framework	None of These Outcomes
1						x
2	X					
3	X					
4	X					
5			X			
6	X	X				
7	X	X				
8	X	X				
9	X				X	
10	X				X	
11	X				X	
12	X	X	X			
13	X	X			X	
14	X	X			X	
15		X	X	X		
16		X	X	X		
17	X	X	X		X	
18	X	X	X		X	
19	X	X	X		X	
20	X	X	X	X	X	
21	X	X	X	X	X	
Total	17	13	9	4	10	1

Source: Expert Review.

Note: This table displays consensus expert assessments (at least two of three experts in agreement) of Heinze et al. (2007) typology risks for each Pioneer in anonymous order. Experts were able to select as many of the outcomes that applied.

[54] Refer to the literature review for an explanation of Heinze's typology.



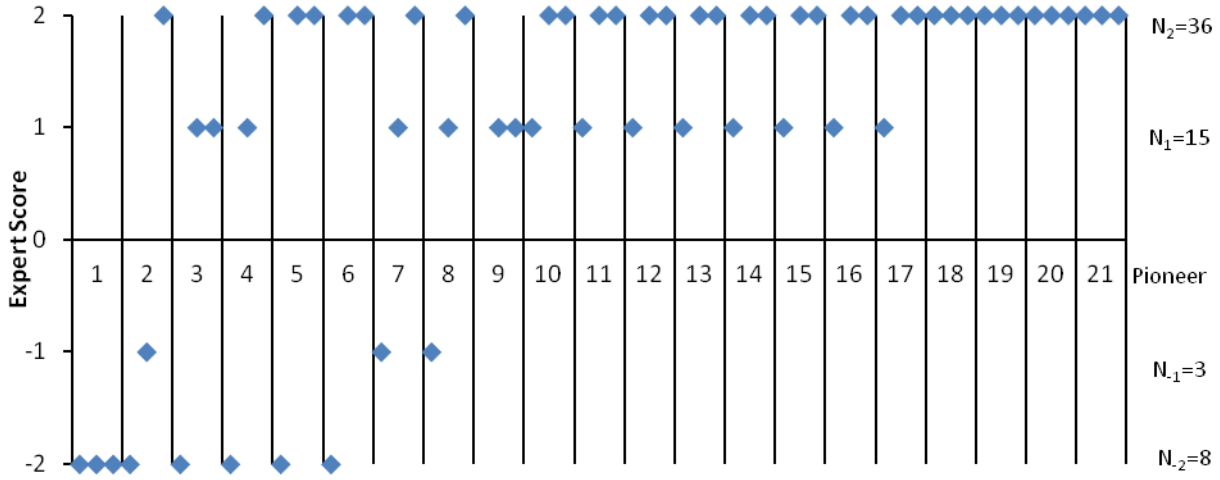
Source: Expert review.

Figure 13. Percentage of awardees attributed with each Heinze typology outcome, based on experts' assessment

The experts assessed that 17 of 21 awardees were conducting research that had the potential to formulate new ideas, while 13 of 21 were conducting research that had the potential to discover new phenomena. The experts also thought that 20 of 21 were performing research that is likely to result in at least one Heinze typology outcome.

3. Pioneering Nature of Research

The expert reviewers were additionally asked to agree or disagree with the statement "The accomplished research is pioneering." with regard to the awardee that they evaluated (Figure 14). Of the 62 expert responses to this question (three for each of the 21 awardees who completed their funding term, and one refusal to answer), 36 strongly agreed and 15 moderately agreed that the awardee conducted pioneering research. Three experts moderately disagreed and eight strongly disagreed that the awardee they reviewed was pioneering. These responses suggest that the experts found the awardees to be pioneering. For two awardees, two or more of their three experts did not find their research to be pioneering.



Source: Expert review.

Note: Each data point represents the assessment of a single expert. Experts were asked to rate this statement on a scale where 2 is strongly agree, 1 is moderately agree, -1 is moderately disagree, and -2 is strongly disagree.

Figure 14. Expert Question: Rate this statement—"The Accomplished Research is Pioneering."

4. Role of NDPA Research in Changing Field

The expert reviewers were asked about developments in the awardees' research areas during the five-year funding period of the award, and whether their NDPA work influenced scientific progress in the field. Eleven of the awardees were named as leading researchers or major contributors to their fields, and five were noted for incorporating multiple disciplines into their field to solve research question. The coded responses from the expert reviewer (panel) are shown in Table 15.

Table 15. Expert Question: How has the research field in which this research is taking place changed over the past five years? What role do you believe has the NDPA research played in those changes?

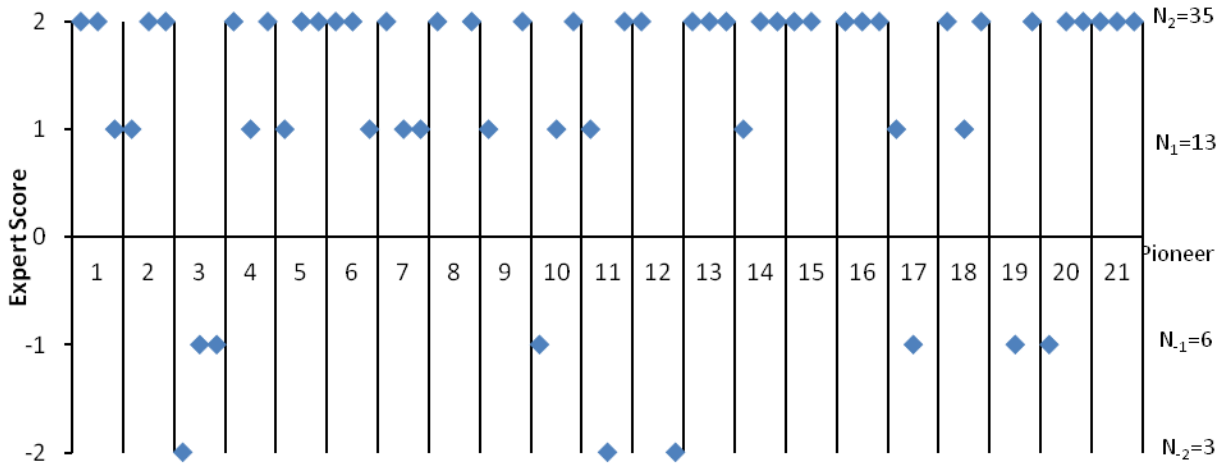
Coded Response	Number of Responses
The awardee has been a major contributor/leading researcher in their field	11
The awardee did not make any significant contributions to the research field	6
The NDPA work by the awardee has influenced other researchers	5
The awardee has connected formerly disparate disciplines or research fields	5
It is too early to tell the effects of the awardee's research	3
The awardee has changed prevailing wisdom or provided a novel perspective	2
The awardee has increased the prominence of the research field	2
The awardee has developed new techniques	2

Source: STPI coding of interviews with experts.

Note: Each of the three experts reviewing the awardee were asked the same question, and when two or more participating experts were in agreement, the response was considered to be true for the particular awardee. Expert groups were able to have more than one response. Number of expert groups = 21.

C. Assessing the Value of NDPA

As part of their participation in this evaluation, the expert reviewers were asked whether the NDPA was adding value to the NIH. More than four out of five of the experts (51/62 or 82%) agreed that the program was adding value (Figure 15). The reasons most frequently given for why the NDPA added value were that it supported highly talented scientists, and that it encouraged new approaches (Table 16).



Source: STPI coding of interviews with experts.

Note: Each data point represents the assessment of a single expert. Experts were asked to rate this statement on a scale where 2 is strongly agree, 1 is moderately agree, -1 is moderately disagree, and -2 is strongly disagree.

Figure 15. Expert Question: Rate this statement—"The Pioneer Award is adding value to the NIH portfolio."

Table 16. Expert Question: Please explain why you agree or disagree that the NDPA is adding value to the NIH.

	Coded Responses	Number of Experts
Agree	Guaranteed support to talented scientists	16
	Encourages new approaches and encourages researchers to take risks	15
	Supports potentially transformative, impactful science	12
	Promotes interdisciplinary research and areas not typically funded by NIH	5
	Demonstrates the importance of innovation to younger scientists	2
Disagree	Value is not clear; it seems same work could be accomplished through traditional mechanisms	4
	Funding should be going to R01	3

Source: STPI coding of results of interviews with experts.

Note: Experts were able to make multiple responses. This question was asked of all the participating experts, but 12 stated that they were not familiar enough with the program or with NIH as a whole, and chose not to answer. Number of Respondents = 51.

The key features that make the program unique—funding people, not just projects, and encouraging pioneering—compared with traditional mechanisms, were the reasons why the experts thought the NDPA added value to the NIH. Examples of the experts' responses are given below:

"The biggest value added by the NDPA program is that it allows researchers to take more risks, something that the typical NIH portfolio does not encourage. It is very hard to imagine many researchers taking on genuinely new experimental and theoretical challenges -something essential to our making progress on the major issues—without unwavering support for at least five years."

"I think the a program that provides flexibility to particularly promising researchers is a crucial part of funding system that aims to support forefront research—the most risky experiments are often the most groundbreaking but may sound outlandish in the context of the normal NIH R01 review process."

"The program is essential to the NIH portfolio as it adds imagination, flexibility, and the freedom to pursue novel ideas. The established grant routes fund the science of the present—following well established research trends that have already proven productive. But only highly innovative and novel research projects can shift the existing paradigms rather than enforce them. Upon discussions with colleagues I so often encounter a reaction along the lines of: 'this is a wonderful idea but I have no funding to explore it.'"

D. Summary

A virtual expert panel was held to assess the research performed under the NDPA. Each awardee's research (in the form of a research summary and three publications submitted by the awardee) was reviewed by three experts in their area of research. Experts were asked about the risks and rewards in the research, whether the research was pioneering, whether the outcomes could have been achieved using traditional mechanisms, and whether the NDPA program is adding value to the NIH portfolio. Most (about two-thirds) experts believed the research performed was pioneering and that the NDPA program is adding value to the NIH portfolio. The remaining experts (about one-third) stated that the same work could be accomplished using traditional mechanisms.

7. Unfunded Applicants

A. Introduction

To assess potential spillover effects of the NDPA, it was proposed to study not only the progress of awardees, but to also follow the trajectory of unfunded applicants and their ideas. Currently approximately 450 proposals per year are submitted to the NDPA. Since the NDPA funds only a very small fraction (~2 percent) of applicants, there potentially remain a large number of skilled researchers with unfunded ideas that may have a significant impact on biomedical science.

To understand what happened to unfunded applicants and their ideas, STPI surveyed individuals who were not awarded the NDPA through a Survey of Unfunded Applicants (SUFA). The SUFA focused on career developments of the unfunded applicants, and the progress, if any, in pursuing their NDPA-proposed idea. The following detailed study questions were addressed through the survey: (1) how were the unfunded ideas characterized in terms of risk and potential to be pioneering? (2) what progress has been made toward the NDPA-proposed ideas? and (3) how have the careers of the unfunded applicants developed since the NDPA? A total of 526 unfunded applicants (50 percent response rate) responded to the SUFA.[55] The following sections reflect the findings from the survey.

B. Risks of Unfunded Ideas and Potential to be Pioneering

Approximately three out of five (58 percent) of respondents reported that they would not have submitted their NDPA-proposed idea to the NIH if the NDPA program had not existed. Over 90 percent of respondents believed their NDPA-proposed idea to be very risky or of medium risk and 75 percent believed their idea to be a significant departure from their previous research. More than half of respondents believed their idea was very unlikely to receive other NIH funding, and a third believed their idea was also very unlikely to receive funding outside of NIH. Most of these respondents believed their NDPA-proposed ideas to be different than what is typically funded by NIH due to lack of

[55] The response rate for the survey was slightly less than 50 percent, although the demographic distribution of the respondents was statistically similar for most characteristics, (race, ethnicity, seniority, research area, and doctoral degree), except gender, where the number of females in the respondent pool was found to be slightly greater than would be expected based on the gender distribution of the entire unfunded applicant pool.

preliminary data and to the idea not falling into the research interest of a single NIH Institute or Center (IC). See

Table 17.

Table 17. SUFA Question: In what way was your NDPA idea different from what is typically funded by the NIH?

Reason	Number of Respondents	Percentage of Respondents
It had very little or no preliminary data	283	56%
It did not fall into the research interest of a single NIH Institute/Center	257	51%
It lacked an appropriate NIH study section	188	37%
As an investigator I had limited or no prior history in the proposed field	184	36%
My NDPA idea was not different from what is typically funded by the NIH	2	0.4%
I do not know	3	0.6%
Other	49	10%

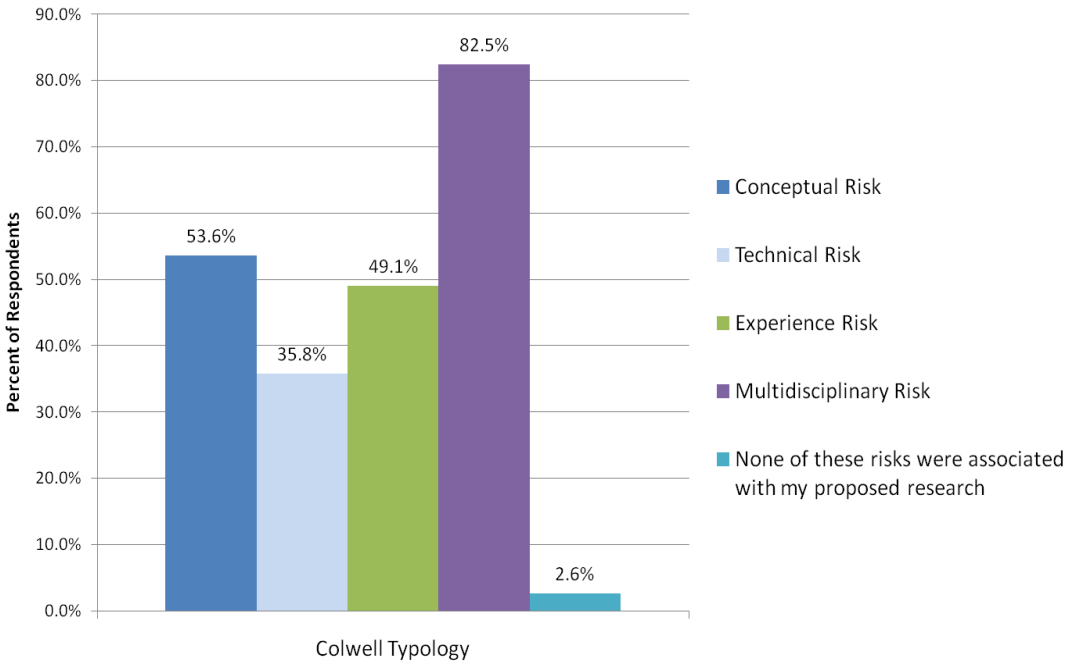
Source: NDPA Survey of Unfunded Applicants.

Note: Survey respondents were able to select multiple answers. Number of respondents = 505 out of 526 possible respondents.

Of the unfunded applicants who pursued alternative NIH funding for their NDPA-proposed idea, there appears to be a statistically significant relationship between how likely respondents thought their idea was to receive NIH funding and how whether the respondents actually were later able to receive NIH funding.[56] However, this may be a result of hindsight bias.

In response to the two typology questions regarding the high-risk and creative nature of the NDPA-proposed ideas, the large majority of SUFA respondents indicated that their ideas involved a novel combination of disciplines or an unprecedented scientific perspective (Figure 16), and that their proposed research could result in the formulation of new ideas or advancement of theories (Figure 17).

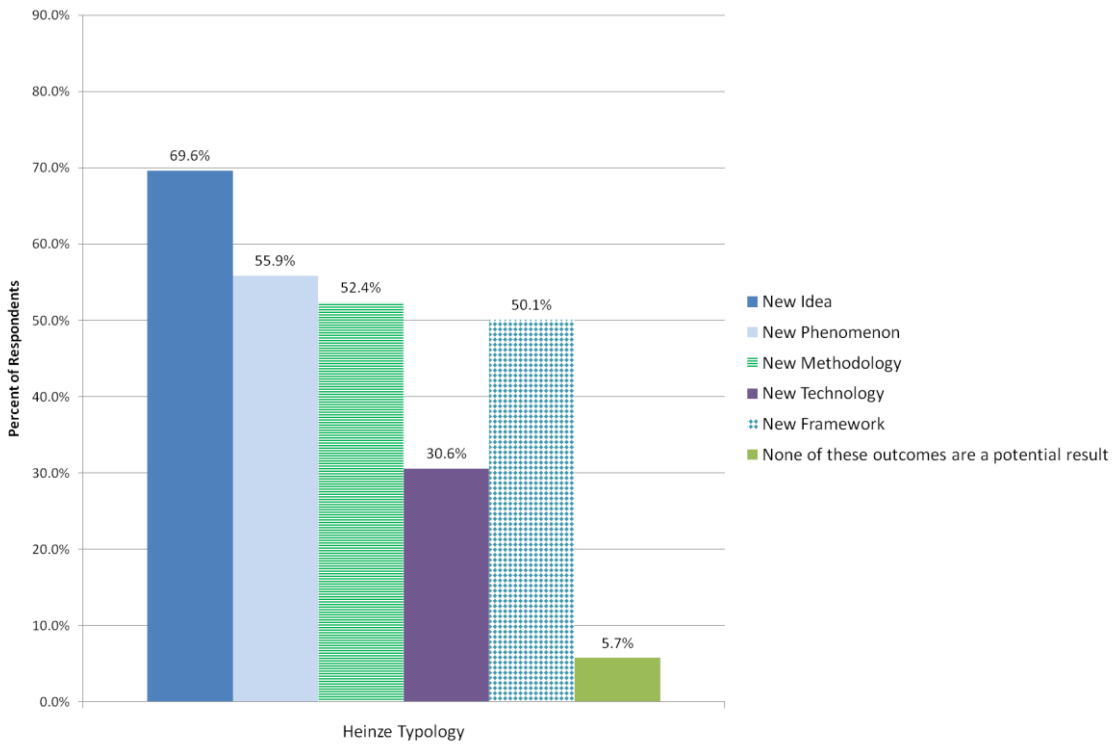
[56] χ^2=26.95, df = 3, p = 6.03E-6



Source: NDPA Survey of Unfunded Applicants.

Note: This question is based on Rita Colwell's (2003) typology of characterizing creative research, by the associated risks. The graph shows the percentage of survey respondents who associated a specific risk with their NDPA proposed research. Survey respondents were able to select multiple answers. Number of respondents = 491 out of 526 possible respondents.

Figure 16. SUFA Question: Please indicate which of the following statements (if any) are true of your proposed NDPA project.



Source: NDPA Survey of Unfunded Applicants.

Note: This question was based on the Heinze typology of identifying realized or potential outcomes of creative research. The graph shows the percentage of survey respondents who associated the potential outcome with their NDPA proposed research. Survey respondents were able to select multiple answers. Number of respondents = 487 out of 526 possible respondents.

Figure 17. SUFA Question: Please indicate which of the following statements (if any) are true of your proposed NDPA project.

C. Progress of Unfunded Ideas

Despite not receiving the NDPA, more than 80 percent of SUFA respondents indicated that they were still able to pursue their proposed ideas at least partially, and nearly a quarter of respondents (24 percent) indicated that they pursued the ideas in their entirety (data not shown). Those who were not able to pursue the idea cited lack of funding as the most common reason (data not shown). It also appeared that several respondents who applied for an NDPA in FY 2006-2007 were still gathering preliminary data to apply for other grants, while none who applied in FY 2004-2005 were still gathering preliminary data.

The majority of respondents who were able to pursue their NDPA-proposed idea indicated that they used other grants, institutional funds, or donated their time in order to work on the idea (Table 18). STPI compared the NDPA scoring data of SUFA respondents with whether or not they received other funding to work on their idea.

Respondents who received other funding had higher scores on their NDPA application than those who did not receive other funding.[57] Of the individuals who used other grants to work on their NDPA idea, 50 percent reported using grants from the NIH, and 43 percent reported using funding from private foundations (Table 19).

Table 18. SUFA Question: How were you able to work on the proposed NDPA project?

Response	Number of Respondents	Percentage of Respondents
By using other grants that I have	207	52%
I donated my time	202	51%
By using institutional funds	161	40%
I collaborated with a colleague who provides the funding	67	17%
Other	119	30%

Source: NDPA Survey of Unfunded Applicants.

Note: Survey respondents were able to select multiple answers. Number of respondents = 399.

Table 19. SUFA Question: What source of funding did you receive for your NDPA-proposed research?

Response	Number of Respondents	Percentage of Respondents
NIH	199	67%
Private Foundations	154	52%
Other Government Agencies	78	26%
Institutional Funds	74	25%
Other	44	15%

Source: NDPA Survey of Unfunded Applicants.

Note: Survey respondents were able to select multiple answers. Number of respondents = 212.

Nearly two-thirds of respondents (65 percent) who pursued their proposed idea reported modifying the proposal in some way. A higher percentage of unfunded NDPA applicants who reportedly modified their idea were able to secure other NIH funding than

[57] Those who received other funding to work on their idea had higher scores for each of the three review criteria below, as well as higher overall scores, relative to those who did not receive other funding. Mann-Whitney U tests were used to compare scores for each of the three criteria as well as overall scores. P values are based on two-tailed probabilities.

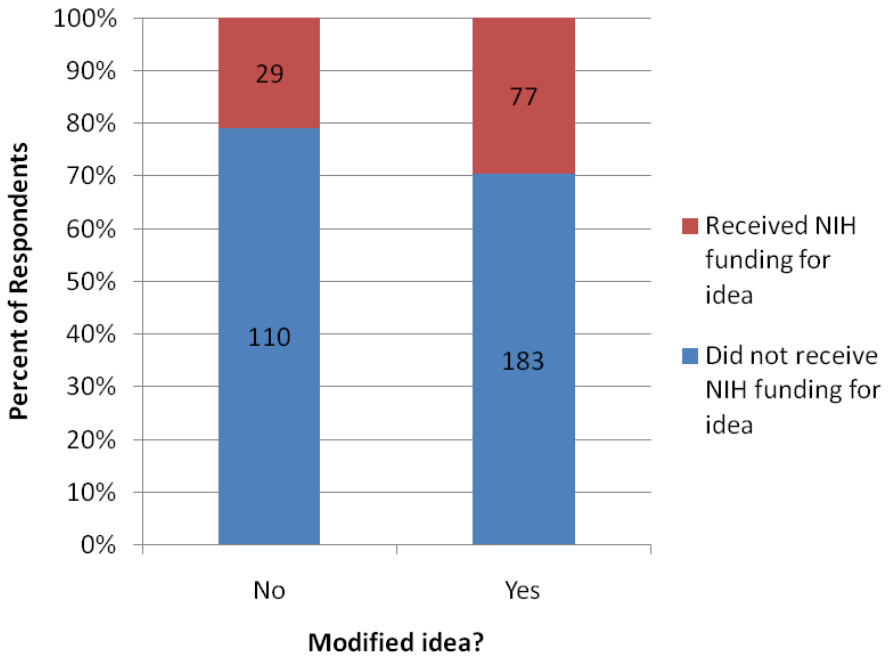
Scientific problem ($x_{funded} = 3.54$, $x_{unfunded} = 3.37$): U = 1.93E5, $n_{funded} = 645$, $n_{unfunded} = 554$, p = 0.013

Investigator qualifications ($x_{funded} = 3.58$, $x_{unfunded} = 3.34$): U = 2.00E5, $n_{funded} = 645$, $n_{unfunded} = 554$, p = 3.18E-3

Suitability for NDPA ($x_{funded} = 3.11$, $x_{unfunded} = 2.94$): U = 1.92E5, $n_{funded} = 645$, $n_{unfunded} = 554$, p = 0.027

Overall score ($x_{funded} = 3.21$, $x_{unfunded} = 2.99$): U = 1.81E5, $n_{funded} = 627$, $n_{unfunded} = 521$, p = 1.21E-3

those who did not (Figure 18).[58] The majority of respondents who were able to pursue their idea reported making significant progress on the idea. Nearly 80 percent of those who pursued their idea have published related peer-reviewed journal articles or are preparing manuscripts for publication. Approximately one-third of respondents who pursued their idea have been issued patents or patents pending related to the idea.[59]



Source: NDPA Survey of Unfunded Applicants.

Note: Respondents were asked to rate their modification of their NDPA-proposed idea on a 1 to 5 scale, with 1 being "Not at all," 3 being "Somewhat," and 5 being "Completely." For this analysis, choice 1 was counted as not modified (No), and choices 2 through 5 were grouped as modified (Yes). Number of Respondents = 399.

Figure 18. SUFA Question: Did you modify your NDPA-proposed idea in order to pursue it? Have you received NIH fuding for the idea?

D. Career Development of Unfunded Applicants

The large majority of SUFA respondents appeared to have received additional funding, published peer-reviewed journal articles, and changed or expanded their research focus since their NDPA application (Figure 19).

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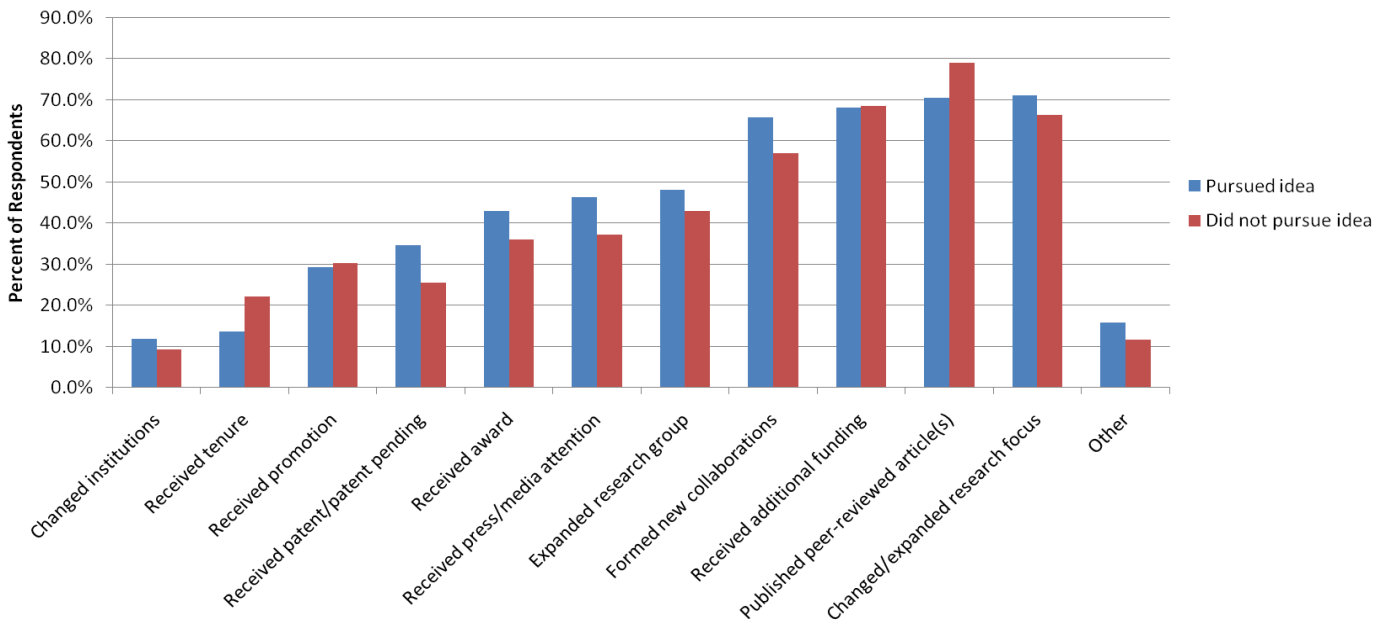
[58] χ^2=4.69, df = 1, p = 0.030

[59] The percentage of applicants who received or have filed patents is likely related to the overall number of projects that are actually suitable for patent applications.



Source: NDPA Survey of Unfunded Applicants.

Note: Survey respondents were able to select multiple answers. Number of respondents = 479 out of 526 possible respondents.

Figure 19. SUFA Question: Did you pursue your NDPA-proposed idea? What career developments have occurred since your NDPA application?

Of SUFA respondents who reported a change in their research focus, 37 percent indicated that the change was at least to some extent a result of applying to the NDPA program. There appeared to be no significant difference between the career developments of respondents who were able to pursue their NDPA-proposed idea and of respondents who were not.[60]

Among respondents who reported receiving an award(s) since their NDPA application:

- 5 were named Howard Hughes Medical Institute (HHMI) Investigators
- 1 was named a HHMI Early Career Scientist
- 2 were elected to the National Academy of Sciences
- 2 received the NIH EUREKA Award
- 1 was named a MacArthur Fellow
- 1 received the Nobel Prize in Chemistry

Five of the twelve individuals described above participated in the interview phase of the NDPA competition. Reviewer comments on the NDPA applications of these individuals were generally positive but appeared to highlight their lack of suitability for the NDPA and their lack of need for additional funding. Some of these comments included:

> *"Excellent investigator and quite good problem but not obviously suited for, or requiring, NDPA mechanism of funding."*
>
> *"Neither [s/he] nor [his/her] referees explain why this is a Pioneer project, although clearly innovative and important."*
>
> *"Has R01 on related topic. This could be funded via the R01 mechanism."*
>
> *"The candidate is outstanding and the ideas seem quite good. However, it doesn't seem to be much of a departure from what [s/he] is currently pursuing…"*
>
> *"Innovative, high impact and stellar young investigator. I question whether this should be in a new category for young investigators."*
>
> *"This is a very excellent PI and the questions that [s/he] raises have great intrinsic interest and health relevance. However, this is an area [s/he] has long worked in and in fact has an NIH R01 grant pending."*
>
> *"Incredible recommendations—what need does [s/he] have for large funding?"*

[60] χ^2=13.2, df = 11, p = 0.279

When asked what difference the NDPA would have made to their research, 58 percent of respondents indicated that the award would have greatly accelerated the progress of their proposed project (Table 20). Other common responses were that the NDPA would have provided the personnel and resources required for the proposed project, that the NDPA would have broadened the scope and impact of the project, and that the NDPA would have allowed the applicant more time and effort to focus on the project.

Table 20. SUFA Question: If you had received the NDPA award, what difference would it have made to your research, to your lab, etc.?

Coded Response	Number of Respondents	Percentage of Respondents
The NDPA would have significantly accelerated the progress of the proposed project.	208	58.3%
The NDPA would have provided the personnel and/or resources required for the proposed project.	66	18.5%
The NDPA would have broadened the scope and/or impact of the proposed project.	60	16.8%
The NDPA would have allowed me to put significantly more time and/or effort into the proposed project.	51	14.3%
The NDPA would have enabled the proposed project to change or influence prevailing views in the scientific community.	33	9.2%
The NDPA would have allowed the commercialization of the project outputs or the translation of the project to clinical trials.	25	7.0%
The NDPA would have gotten the proposed project off the ground.	18	5.0%
The NDPA would have opened a new avenue(s) of research for my lab or other labs.	17	4.8%
The NDPA would have enabled the proposed project to generate breakthroughs in medical practice.	13	3.6%
The NDPA would have maintained the stability of my career.	12	3.4%
Other	35	9.8%

Source: NDPA Survey of Unfunded Applicants.

Note: This was an open-ended question, and survey responses were coded by STPI. Number of respondents = 357 out of 526 possible respondents.

E. Summary

Based on the responses to the SUFA, it appears that many unfunded applicants were able to obtain other funding to pursue their idea and to make significant progress on the idea. It also appears that many SUFA respondents believe the NDPA would have made a significant difference in their pursuit of the proposed research. Regardless of having been able to pursue their idea or not, most respondents reported having important career developments since the time of their NDPA application.

8. Changes at NIH and Beyond

A. Introduction

The NDPA was designed to be a unique funding mechanism for the NIH, specifically created for high-risk research proposals which have the potential for high-reward. The program was an experiment that was intended to influence a change in culture to support more innovative biomedical research. The following detailed study questions are addressed in this section: (1) have other HRHR-funding programs been influenced by the NDPA? (2) have there been any changes at the NIH due to the NDPA? and (3) what value has the NDPA added to the NIH research portfolio?

Representatives from all of the programs within NIH and those programs outside that appeared to be similar to NDPA were interviewed to assess to what extent they were influenced by NDPA. To briefly summarize, interviewees of programs outside the NIH confirmed that they had been influenced by the NDPA's design. Within the NIH, interviewees felt that the NDPA was part of a larger change within NIH to fund high-risk research and that their programs were reflective of that larger change rather than a direct cause of the NDPA. Nevertheless, interviewees did say they felt the culture of the NIH towards funding innovative research was changing as a result of the NDPA and other high-risk programs.

B. NDPA's Influence on HR-HR Programs in Other Funding Agencies

One way to assess whether the NDPA has influenced a change in culture is to examine whether any new programs have been modeled after it. Since the NDPA was created, a number of seemingly similar programs have been created, both at the NIH and beyond. STPI examined two of the programs external to NIH in detail: the Department of Defense (DOD) National Security Science and Engineering Faculty Fellows (NSSEFF), and the Juvenile Diabetes Research Foundation (JDRF) Scholar Award, and our findings from the assessment are explained below.

1. DOD National Security Science and Engineering Faculty Fellowship

The NSSEFF program was founded in 2008 to "recruit and retain highly innovative, results-oriented, university researchers that support defense needs…to conduct unclassified, fundamental research on topics of interest to the DOD." The NSSEFF provides a substantial award of up to $4.25 million over five years, but also intends to foster long-term relationships between the awarded fellows and the DOD. This aspect of

the award is similar to the NDPA, which specifically recruited investigators from areas not typically funded by the NIH, with the hope of introducing new research methodology to address areas of need within biomedical research. The NSSEFF program is also similar to the NDPA in that it awards a person, rather than a project or a proposal.

The NSSEFF program grants approximately 10 fellows—a number of awards similar to the NDPA—and also employs a review process similar to that of the NDPA, with an external review of the application, letters of reference, and an interview stage. Through interviews conducted with NSSEFF leadership, STPI determined that evaluators who were familiar with the NDPA program briefed DOD staff on the NDPA program before the start of the NSSEFF program, which may point to similarities in the design of the two programs.

2. Juvenile Diabetes Research Foundation Scholar Award

The language in the Scholar Award program announcement is similar to that of the NDPA program, as the award is described "to support individual scientists of exceptional creativity who propose pioneering research to reach these goals," and like the NDPA, the Scholar Award is meant "to support investigators who intend to pursue new research directions that are not funded from other sources."[61] The JDRF Scholar Awards are for the same amount as the NDPA (up to $2.5 million over five years), but fewer investigators are awarded. The application for the JDRF Scholar Award is equivalent to the NDPA as essay length, the inclusion of a biographical sketch and letters of recommendation are the same, and the review is conducted by JDRF Lay Review Committee members but the review criteria are the same as for the NDPA. Also, like the NDPA, the JDRF awards an individual, and the scholars present their research progress at an annual symposium. Many aspects of JDRF and NDPA are similar, from which we infer that JDRF was influenced by NDPA."

C. NDPA's Influence on HR-HR Programs at the NIH

Several NIH programs have been created to fund highly impactful and innovative research since the creation of the NDPA. HR-HR programs introduced at the NIH have been operated both by the OD through the Common Fund, as well as by individual ICs. Of the eight programs within NIH examined as part of this evaluation, six of the programs' founders were affiliated with NDPA, through either co-chairing the program, or serving on the NDPA Evaluation Advisory Committee (EAC), or having been involved with the High Risk Working Group (HRWG). This section briefly examines the

[61] *See* JDRF website, "JDRF Scholar Award 2005 Program Announcement," accessed February 24, 2011, http://www.jdrf.org/files/Research/RFAs_2005/scholar-award-web.pdf.

HR-HR programs at the NIH, and provides an assessment on how each program compares with the NDPA.

1. Common Fund Programs

Since the NPDA, three other programs for HR-HR research which have been added to the Common Fund: the NIH Director's New Innovator Award, the NIH Director's Transformative R01, and the NIH Director's Early Independence Awards. A detailed comparison of each program and the NDPA is presented in this section.

a. NIH Director's New Innovator Award (NIA)

The NIA was initiated in FY 2007 and modeled largely after the NDPA, but was designed to support "exceptionally creative new investigators who propose highly innovative projects that have the potential for unusually high impact."[62] According to program officials, the NIA program design and selection process were greatly influenced by the NDPA program. Many aspects of the NIA process emulate the NDPA program, including the abbreviated application, an external review process, the lack of required preliminary data, or a detailed budget, and a short biosketch. The review criteria are similar to the NDPA, as NIA applications are evaluated by the significance of the scientific problem, the innovativeness of the proposal, and the investigator's qualifications. All NIA applications undergo an external review, and since FY 2009, proposals deemed as finalists (approximately 20 percent of all submitted applications) undergo a second phase of review, concluded by a conference call.

NIA grants more awards than the NDPA (between 30 and 50 awards), of up to $1.5 million over five years. A more detailed comparison of the programs can be found in the NIA Process Evaluation (Lal et al. 2011).

b. NIH Director's Transformative R01 (T-R01)

The T-R01 was added to the Common Fund portfolio in FY 2009, "to support exceptionally innovative, high risk, original and/or unconventional research projects that have the potential to create or overturn fundamental paradigms."[63] Unlike the NIA and the NDPA, the T-R01 was designed to fund creative ideas rather than individuals.

Like the NDPA, the T-R01 also has a shortened application length and a focus on the problem to be addressed broadly rather than on experimental details. The T-R01 applications are reviewed by the following criteria: the significance of the problem,

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[62] *See* NIH website, "NIH Director's New Innovator Award Program," accessed February 28, 2011, http://commonfund.nih.gov/newinnovator/.

[63] *See* NIH website, "NIH Director's T-R01 Award Program," accessed May 18, 2011, http://commonfund.nih.gov/T-R01/.

innovation, approach, the investigator(s)'s qualifications, and the research environment.[64] All applications undergo external review and only those deemed of interest to the program are reviewed by a study section, which is similar to the two-phased review processes of the NDPA and the NIA.

A unique aspect of the T-R01 is that the size of a T-R01 award has no budget limit, but the annual size of the program limits the number of possible projects. Awards are granted through the traditional R01 mechanism.

c. NIH Director's Early Independence Awards (EIA)

The newest high risk program to the Common Fund is the EIA, which was established based on research that indicated that a longer post-doctoral training period correlates with an increased amount of time before the investigator achieves research independence. The EIA serves to support "talented young scientists who have the intellect, scientific creativity, drive and maturity to flourish independently without the need for traditional post-doctoral training."[65] The EIA is different from the other HR-HR programs under the Common Fund in that the target grantees are still graduate students at the time of their applications, and that the program aims to help the individuals launch "innovative research programs as early in their careers as possible." Similar to the other HR-HR programs, the applicant proposes a specific idea to the EIA, but this award also provides administrative funds to establish the individual as an independent researcher.

The EIA provides an opportunity for research institutions to "actively recruit eligible junior scientists," by directing them to apply for this program. The review process will incorporate elements of multiple programs, as applications will first be reviewed by a Peer Review Center for Scientific Review Committee, and the strongest candidates will be invited to be interviewed by a panel of external reviewers, as with the NDPA. The EIA applications are reviewed by the following criteria: the significance of the problem, innovation, approach, the investigator's qualifications, and the research environment. The first cohort of awardees will be granted in FY 2011. An estimated 10 awards will be granted, of up to $250,000 in direct costs for five years like the NDPA—not including applicable facilities and administrative costs for setting up the laboratories.

Overall, many elements of the three programs described above share design elements of the NDPA. Unsurprisingly, program leadership for the NIA, T-R01, and the

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[64] As noted in Chapter 3, STPI ended data collection on the NDPA program design in 2010. Since FY 2009, the review criteria have changed to include the five criteria named for the T-R01, the EIA, the EUREKA, the BRAINS, and the ONES programs, which are: significance, investigator, innovation, approach, and environment.

[65] *See* NIH website, "NIH Director's Early Independence Awards (DP5) Request for Applications, October 6, 2010," RFA-RM-10-019, accessed May 18, 2011, http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-10-019.html.

EIA overlap with the NDPA, as all four of the programs are operated through the OD, as part of the initiative promoting potentially transformative research. All three of the new Common Fund programs appear to have been directly influenced by the NDPA since their criteria and purpose to encourage high risk research are the same.

2. Other High Risk-High Reward (HR-HR) programs at the NIH

STPI also examined three HR-HR programs at the NIH, operated by individual ICs. A brief description of how each program compares to the NDPA follows.

a. NIH National Institute on Drug Abuse (NIDA) Avant-Garde Award

Of all programs we examined, the NIDA Avant-Garde Award most closely resembles the NDPA, even sharing the grant funding mechanism of NDPA (DP1). The Avant-Garde Award was started in 2007 and is "designed to support individual scientists of exceptional creativity who propose cutting edge—and possibly transformative—approaches to major challenges in biomedical and behavioral research on drug abuse and HIV/AIDS."[66] The Frequently Asked Questions published online states that the Avant-Garde Award is "conceptually similar to the NIH Pioneer Award, but focuses on drug abuse and HIV/AIDS."

The review criteria for the Avant-Garde Award are equal to the NDPA, as the reviewers evaluate the application based on the significance of the problem addressed, the qualifications of the investigator, and on the suitability of the project for the Avant-Garde mechanism. Similar to the NDPA, the Avant-Garde Award also funds an individual rather than a project, and the awards are nearly the same size as the NDPA (up to $2 million over five years), but only a two to three individuals receive the award each year. Interviews with the program officer, who came to NIDA after having been part of NDPA implementation, indicate that Avant-Garde is in fact modeled on NDPA.-

b. Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA)

The EUREKA program was established in 2007 and intended to support "investigators who are testing novel, unconventional hypothesis or are pursuing major methodological or technical challenges."[67] At the time it was founded, the EUREKA program was funded by five different NIH institutes, but eight ICs will participate in FY

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[66] *See* NIH website, "2008 NIDA Avant-Garde Award Program for HIV/AIDS Research (DP1) Request for Applications, November 9, 2007," RFA-DA-08-003, accessed May 18, 2011. http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-08-003.html.

[67] *See* NIH website, "Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA) (R01) Request for Applications, July 23, 2007," RFA-GM-08-002, accessed May 18, 2011, http://grants1.nih.gov/grants/guide/rfa-files/RFA-GM-08-002.html.

2011. Applications need be targeted to the objectives of an individual institute, as each IC reviews applications of interest in their own process.

Several aspects of the EUREKA program mirror the NDPA program; for example, the proposal must introduce a new project, and the proposal is also shortened compared to traditional R01 applications. The EUREKA applications are reviewed by the following criteria: the significance of the problem, innovation, approach, the investigator(s)'s qualifications, and the research environment. Applications undergo an external review, and only those that are deemed of high significance and innovation are discussed in a study section conducted online.

EUREKA differs from the NDPA in that it does not require letters of reference, but does require a timeline. Also, teams may receive EUREKA grants, and the effort of commitment need not be as high as for NDPA. EUREKA was specifically designed to award a project, rather than an individual, and funded projects are expected to be completed during the grant period. EUREKA grants are funded through the R01 mechanism, and because the nature and scope of differs across each proposal, the funding amount and duration of each award differs. The review of EUREKA applications, while different than and separate from a conventional R01 study section, still involves a teleconference between reviewers to discuss the applications.

c. Biobehavioral Research Awards for Innovative New Scientists (BRAINS)

The BRAINS program was launched in 2008 and seeks to "assist those individuals in launching an innovative clinical, translational, or basic research program that holds the potential to profoundly transform the understanding, diagnosis, treatment, or prevention of mental disorders."[68] BRAINS was designed for investigators early in their careers, as the program requires that applicants be no more than eight years out from their last terminal degree, and no more than five years out from their last fellowship/residency. The BRAINS applications are reviewed by the following criteria: the significance of the problem, innovation, approach, the investigator's qualifications, and the research environment. The application length is an abbreviated ten pages, and specifically focuses on the research design and methodology. Nonetheless, the BRAINS program focuses on the development

Design features unique to the BRAINS program include that the awardees' institutions are asked to release time so that the awardees can devote 75 percent of their effort to research, and awardees are asked to develop an advisory committee that will meet annually to assess the progress of the research and to provide research career

[68] *See* NIH website, "Biobehavioral Research Awards for Innovative New Scientists (BRAINS) (R01) Request for Applications, October 30, 2008," RFA-MH-09-100, accessed May 18, 2011, http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-09-100.html.

guidance during the course of the award. The BRAINS program funds approximately six investigators each year, each with a budget up to $1.625 million over five years.

d. Outstanding New Environmental Scientist Award (ONES)

The ONES program was started in 2005 with the intention to "identify outstanding scientists who are in the early, formative stages of their careers and who intend to make a long-term career commitment to research in the mission areas of the NIEHS and assist them in launching an innovative research program."[69] Similar to the BRAINS, and the NIA, the ONES program funds individuals rather than projects, and also targets new investigators early in their research careers. The ONES applications are reviewed by the following criteria: the significance of the problem, innovation, approach, the investigator's qualifications, and the research environment. Through the R01 mechanism, the ONES program funds approximately six individuals each year, each with a budget up to $1.625 million over five years.

3. NIH HR-HR Programs Summary

In recent years, many programs within NIH and in other federal agencies and private foundations have been implemented to fund innovative and potentially transformative research. Here, we examined only as subset of programs that contain design aspects similar to the NDPA. Based on interviews with NIH staff, these new programs were influenced by the NDPA. The following design elements were based on the NDPA program:

- All of the programs provide funds specifically supporting highly innovative research ideas and approaches to solving important biomedical questions.
- The proposed research addresses top priorities within the funding organization, and thus has the potential to be highly impactful.
- Many of the grants are named "awards," as they are specifically designed to provide long-term funding for an individual who has demonstrated the potential to be creative or outstanding talent as a researcher.
- The program applications are shortened compared to the traditional R01 applications[70] designed to highlight the investigator or the proposed project.
- All of the programs have the goal to fund individual investigators and projects which have the potential to make a long-standing impact in biomedical science.

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[69] *See* NIH website, "Outstanding New Environmental Scientist Award (ONES) (R01) Request for Applications, July 19, 2006," RFA-ES-06-007, accessed May 18, 2011, http://grants.nih.gov/grants/guide/rfa-files/RFA-ES-06-007.html.

[70] A discussion on the shortened R01 applications, implemented in January 2010, follows in 8.D.

D. Broader Changes at the NIH Due to the NDPA

STPI interviewed members of the High-Risk Research Working Group (HRWG) who were responsible for the initial development of the NDPA, and the majority of the members believed the NDPA has led to substantial changes across NIH. As described by the HRWG, at the time of its inception, the NDPA was envisioned as a way to introduce the initiative of promoting innovation at the NIH. In the years leading up to the NDPA, the NIH received substantial criticism for becoming too conservative, and the Roadmap Initiative and the NDPA were supposed to help usher in a change in culture to promote research with high-risk, but also the potential for high reward.

Awardees were also asked during their interviews whether they believed the NIH had experienced a change in culture as a result of the NDPA. Awardees were split, as 8 out of the 21 interviewed agreed that there have been some changes, but that the changes happened concurrently with the implementation of the NDPA and were not a result of the NDPA. Seven of awardees did not believe that there had been a change in culture at the NIH, and some were doubtful that the biomedical community could ever shift away from being conservative. The other six were could not tell or were not familiar enough with the NIH culture.

A substantial change that has occurred at the NIH since the NDPA was created is the "Enhancing Peer Review" initiative, including the shortened R01 application. The initiative was deemed necessary to account for the "increasing breadth, complexity, and interdisciplinary nature of modern research."[71] The application for the traditional funding mechanism, R01, was shortened beginning in January 2010, from 25 pages to 12 to lessen the administrative burden on applicants and reviewers, and to shift the focus from methodological details to the "essentials of the science." (Wadman 2011).

These changes to the traditional peer review system at NIH bear similarity to the NDPA process, as the applications for the NDPA were designed to be short in order to focus on the investigator as a person, and on the potential impact of the proposed project. Also, by design, the NDPA aimed to bring in researchers from a variety of disciplines, particularly from those not typically funded by the NIH. The purpose of the Enhancing Peer Review Initiative is similar to unique aspects of the original NDPA design, which suggests that the NDPA may have influenced a major change across the NIH.

E. Summary

The question of the effect of NDPA on the NIH is a hard one to answer. A review of selected programs that are designed to support innovative research at the NIH and in

[71] *See* NIH website, "Enhancing Peer Review at NIH," accessed May 18, 2011, http://enhancing-peer-review.nih.gov/index.html.

other federal agencies and foundations was also performed as a part of this evaluation. The review was based on program documents and interviews with program staff. The interviewees stated that their programs were influenced by the NDPA program design. NIH interviewees also stated that they felt the culture of the NIH towards funding innovative research was changing as a result of the NDPA and other high-risk programs.

9. Findings and Recommendations

A. Summary of Findings

This study of the short-term outcomes of the NDPA focused on two high-level study questions: (1) Did the NDPA awardees conduct pioneering research with the NDPA funds? and (2) What are the spillover effects of the program?

Several high-level findings emerge from the data.

1. *The NDPA funded a broad range of research projects, many of which could be considered "high risk" in several different ways.* The projects funded in the first two years were assessed by experts to be high risk in a number of ways. The most common type of risk present in the projects was a risk of bringing together multiple fields of study, and the second most common was that the project required expertise that was not present in the investigator's previous experience.

2. *Awardees stated they were able to undertake a variety of research activities under the NDPA funding that they wouldn't have been able to perform with traditional grants.* The NDPA was designed to give researchers flexibility in how the funds were used to support their projects, and the awardees stated this flexibility, along with the size and duration of the award, allowed them to undertake many activities that wouldn't be possible under traditional granting mechanisms. Awardees gave a number of examples of how the research activities differed; the most common response was that the NDPA allowed the researchers to follow a more natural research trajectory. Some explained their view that traditional single investigator grants have become overly burdensome in terms of requiring detailed information on the experiment before it is to be done and don't allow for flexibility as the research moves along. The NDPA grant allowed them to switch paths when it appeared opportune to do so.

3. *Although the majority of the awardees pursued their originally proposed ideas, a few abandoned those projects and pursued other avenues.* The reasons for abandoning the ideas varied. In some cases, it was because the original proposal was found to be unfeasible. In another case, the research goal was accomplished by another laboratory, and so the awardee had to change the focus of the research. Most awardees also modified their original research plans, either by broadening the scope because they were able to accomplish their original goals, or pursuing off-avenues that were opened up by the original plan.

4. *Most expert panels agreed that the research accomplished under the NDPA was pioneering.* The majority (four-fifths) of the expert panels either strongly or moderately agreed that the research they reviewed was pioneering. Some of the terms used in the reviews were 'paradigm-shifting' and 'transformational.' Experts gave a plethora of reasons why they felt the research was pioneering, and characterized the NDPA research as having several different potential research outcomes.

5. *Some expert panels agreed that the accomplished research could have been achieved using traditional mechanisms.* The experts who said it could have been done under other mechanisms made the argument that the awardee was so scientifically strong that the work would have been funded somehow.

6. *The awardees produced a range of bibliometric outputs, but the time since award is too short to fully assess the impact of these outputs. The literature proposes that impact, collaboration, productivity and creativity can be measured using bibliometric tools. However,* publications and citations to publications about NDPA-funded work varied significantly across the 22 awardees studied. Awardees stated that publishing rates are a matter of personal preference, and that in most cases having the NDPA had not changed their view on when to publish, although some mentioned the award, with no renewal, gave them more freedom to push the work forward and not publish in increments.

7. This evaluation demonstrates that multiple methods are required when assessing the pioneeringness of research. *There are no push-button or mechanical ways to assess whether research is pioneering.*

8. *Most unfunded applicants who responded to the study's survey were able to pursue their NDPA-proposed ideas.* A survey of unfunded applicants showed that most of the respondents were able to pursue their NDPA-proposed ideas, either partially or in full. Some had been able to secure funding to pursue the ideas, while others used other funding or donated their own time.

9. *A number of programs to support innovative research have been established since the launching of the NDPA. Although program representatives did not say the programs' designs were directly influenced by NDPA, NIH interviewees did state that NDPA led the way for other innovative programs within NIH.* The NDPA was the flagship program of the Roadmap for Medical Research. Since its establishment, there have been several different programs developed at the NIH that are designed to support innovative research. Speaking with program officers affiliated with those programs revealed that although most are not directly tied to the NDPA, they are part of a larger change within NIH to fund high-risk research and that their programs were reflective of that larger change

rather than a direct cause of the NDPA. In other cases, the programs were explicitly designed to mirror the NDPA.

This evaluation was itself an experiment in whether methods that are used for evaluating traditional research programs can be translated for use in evaluations of innovative research programs. Thus it may be instructive to future evaluation efforts to understand which methodologies worked well and which did not. Here we briefly summarize our lessons learned:

- The analysis of applications and progress reports was useful for understanding what research was proposed and how the projects evolved over the duration of the award. The progress reports are unstructured, however, and awardees varied significantly in the level of detail they provided.
- The interviews were critical for understanding awardees' perspective on what NDPA allowed them to do. Based on the coding of responses heard in this phase of the evaluation, a survey with several open-ended questions could be used in the future.
- The bibliometrics did not provide useful insights. Standard bibliometric measures are inappropriate to evaluate a program like the NDPA that encourages non-traditional research and expects some level of failure in the projects funded.

The expert reviews were crucial for the assessment of whether the research should be considered pioneering. Their reviews were necessary for understanding the role of the awardee's work in moving scientific fields forward. If expert reviews were to be used in future evaluations improvements could be made to the questionnaire. In particular, providing a Likert scale for the categorizations of risk and rewards would likely yield a more nuanced profile of the research than was possible given the binary choices available to the experts.

B. Key Recommendations

Based on our findings, we make the following recommendations:

1. *NIH should be more explicit with the concept of failure, distinguishing between failure of a project and failure in eyes of the NDPA program.* The connotation of failure makes it such that programs, even those designed to fund high-risk research, are wary to discuss it. The NDPA should be explicit about the concept of failure and separate it from the idea of failure of the program. For example, the program may fund an individual to pursue an idea that, after many years of research, is found to be infeasible. This may be a failure in the project, but it should not be seen as a failure from the perspective of the program if the

research is high risk. On the other hand, if a researcher uses the NDPA funds to not pursue the NDPA-proposed idea but instead to undertake more traditional research, even if it is high-quality, then the program should view that as a failure. Several awardees stated they would like to see the concept of project failure highlighted more at the annual symposia.

2. *NIH should continue to monitor the outcomes of the awardees.* This evaluation focused on the short-term outcomes of the NDPA, specifically tracking the outcomes of the awards from the first few years. In order to further understand the impact of the program, the outcomes of the research and researchers funded should be tracked over a longer time frame.

3. *If future evaluations are performed, a quasi-experimental design should be considered.* There were a number of reasons why a non-experimental design was used for this evaluation. One of those reasons, found through the literature and confirmed through this study, is that there are no mechanical ways in which pioneering research can be measured. That said, this evaluation used a number of methods that could be tailored to incorporate a comparison group. Finding a suitable comparison group is no easy feat. If one can be found, the use of a comparison group would greatly strengthen the understanding of the impact of the NDPA as compared to other granting mechanisms that exist within the NIH.

C. Conclusion

The NIH Director's Pioneer Award represented a novel approach within the NIH for supporting biomedical and behavioral research. The short-term outcomes of the program have been positive. The evaluation showed the diversity of the types of risks and rewards in the research funded through the NDPA, and the variety of outputs emerging from the NDPA. While there were a few cases where the project was found to be infeasible, and the research was abandoned, the majority of the awardees pursued their originally proposed ideas, and the majority of experts agreed that the accomplished research was pioneering. Most experts stated the NDPA is adding value to the portfolio of NIH programs.

Appendix A. Indicators of Pioneering Research (A-1) and Researcher's Career (A-2)

Table A-1. Example Indicators of Innovative Research (not all were referenced in the literature review)

Outcome	Metric	Data Needed	Description	Selected Reference
Creativity	Consensual assessment	Expert Review	This method uses a panel of judges to rate the creativity of an artistic product by using their own subjective definition rather than any given objective criteria. (Amabile 1982)	Amabile (1982); Heinze et al. (2007);Grant and Allen (1999), National Academies (1999)
Productivity	Overall productivity	Number of author publications	This measure provides a coarse measure of the potential impact of a researcher's work, according to the theory that when a researcher has published more, there is a greater likelihood that his or her work will be considered high-impact by peers.	Heinze and Bauer (2007); Simonton (2003)
Impact	Citation rates	Citation count for each publication, Year of publication	This is a measure of research impact. Creative and impactful publications should be cited more frequently, which can be normalized for the age of the publication.	Heinze and Bauer (2007); Azoulay, Zivin, and Manso (2009)
	Fractional counting of citations	Citation count for each publication, Number of cited references of each citing publication	This method normalizes for differential citation patterns between research fields.	Leydesdorff and Shin (2010)
	H-index	Number of publications, Citation count for each publication	The H-index is a combined measure of the productivity and impact of a scientist. It is insensitive to never or seldom cited papers as well as to one or several highly cited papers.	Hirsch (2005); Cronin and Meho (2006); Azoulay, Zivin, and Manso (2009)
	H-rate	Number of publications, Citation count for each publication, year of publications	This measure builds on the H-index and addresses variations in publication frequency and citation rates over the length of a researcher's career. It is based on the average annual increase in an	Burrell 2007

Outcome	Metric	Data Needed	Description	Selected Reference
			author's H-index .	
	G-index	Number of publications, Citation count for each publication	This measure builds on the H-index by giving more weight to highly-cited articles in an attempt to capture the difference in citation patterns of the most highly cited papers	Egghe (2011)
	AR-index (AWCR)	Number of publications, Citation count for each publication, year of publication	This measure normalizes the citation rate of each article in an author's publication set for the age of the article.	Jin (2007)
	Journal impact factor	Journal Impact Factor (calculated by other parties)	This is a proxy for journal quality and characterizes the potential exposure and impact of an article published in a specific journal. A journal is considered "high-impact" if it is cited often by other highly cited journals.	Saha, Saint, and Christakis (2003); Seglen (1997); Bergstrom (2010)
Network Brokerage	Network brokerage	Authors of each publication in data set	This is a measure of an individual's connections. People with more connections to distinct social networks are considered brokers and hypothesized to have more creative outputs since they are exposed to more diverse ideas.	Burt (2004); Heinze and Bauer (2007)
Interdisciplinarity	Degree centrality	Number of authors for each publication in data set	This measures the size of a researcher's network. While degree centrality does not predict a creative event, but it does correlate with impact (via the number of author-level citations).	Heinze and Bauer (2007)
	Integration score	List of References in Publications, Subject Categories of each publication	This measures the diversity and distribution of knowledge used to create the research by using cited references. Multiple applied works have used integration scores as a sign of creativity. It ranges from zero (low diversity of cited references) to one (high diversity of cited references)	Porter et al. (2007); Heinze and Bauer (2007)
	Specialization score	List of publications, Subject Categories for each publication	This is an indicator of the multidisciplinarity of a publication set. This score is based on the span and distribution of subject categories of a researcher's publications.	Porter et al. (2007)

Table A-2. Example Indicators of Career Status (not all were referenced in the literature review)

Outcome	Metric	Data Needed	Description	Selected Reference
Researcher Recognition	Awards/honors	List of awards and honors received by PI	Honors and awards listed on researchers' curricula vitae as a proxy of the impact of creative research, as well as of career independence.	Simonton (2003), Westat (2007)
	Awards/honors to lab trainees	List of awards and honors received by students from a given lab	Students and fellows trained at the lab who go on to win honors/awards recognizing creative researchers such as Pew, Searle, Beckman, Packard, and Rita Allen scholarships.	Azoulay, Zivin, and Manso (2009)
	Patents	Patents	Patents are filed in the case when an invention has been made that may be of use to protect.	Stephan et al. (2007); Azoulay, Ding, and Stuart (2006), Westat (2007)
	Professional Development	Service on Review Committees	Service on Review Committees can be a measure of the involvement in the research community	Westat (2007)
Researcher Career Path	Employment Status	Tenure	The status of the researcher as to whether they have been awarded tenure or not, and the time to tenure is a measure of researcher independence	NRC (2006); Westat (2007)
		Prestige of Faculty Position	If the researcher is employed at a top-tier university	NRC (2006);
	Funding Status	Time to Obtain first R01 grant	The obtaining of an NIH R01 grant is seen as a stage in researcher independence.	NRC (2006); Westat (2007)

Appendix B: Awardee Interview Protocol

This appendix displays the full NDPA awardee interview protocol. Awardee interviews were conducted between February 2009 and February 2010. A total of 21 of the 22 awardees were able to be reached for comment, and 12 of them were interviewed in person and 9 were interviewed over the phone.[72]

[72] Stephen Quake was not interviewed. Clare Waterman was interviewed in 2007. Although she relinquished her award when she took a position at the National Heart, Lung, and Blood Institute at NIH, she has continued her work on developing the cytomechanical system proposed in her NDPA application.

Supporting Statement for the Paperwork Reduction Act Submission Survey Instruments (Attachment 2)

National Institutes of Health An Outcome Evaluation of the NIH Director's Pioneer Award (NDPA) Program

Interview Protocol

Last Name, First Name:

Title:
Date:
STPI staff:

STATEMENT OF INFORMED CONSENT

The Science and Technology Policy Institute (STPI), a federally funded research and development center based in Washington, DC, has been requested by the National Institutes of Health (NIH) to evaluate the outcomes of the NIH Director's Pioneer Award (NDPA) program. The primary objectives of the evaluation are to: (1) assess whether the awardees are doing pioneering research and (2) determine the spillover effects of the NDPA program.

We are employing various data collection techniques to answer these questions; however, we believe that information from those who have received the award is essential. These interviews are one mechanism that will provide important information concerning the overall outcomes of the NDPA program, and will hopefully highlight common markers of pioneers that can contribute to our understanding of high-risk, high-impact research. We anticipate conducting approximately 22 such interviews.

Please note that:

- **Your participation is entirely voluntary:** You are under no obligation to interview with us, but we strongly encourage you to do so. A successful evaluation of the NDPA awards outcomes depends on a high response rate to gather as much information and as many perspectives as possible. There are no consequences or risks for participating. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled, and you may discontinue the interview at any time without penalty or loss of benefits to which you are otherwise entitled.
- **Whom to contact for additional information:** For additional information about the study you may contact Bhavya Lal, STPI project director XX. If you have any questions that you would like to address to the NIH Office of the Director (OD), please contact G. Stephane Philogene, Ph.D., the OD Program Officer responsible for this evaluation (e-mail: PhilogeS@OD.NIH.GOV).

Interview Protocol for Pioneers

A. Research Description and Progress

1. **Please briefly describe your NDPA project.**
    a. What factors, influences, previous work, etc. gave rise to this idea?
    b. How does it differ from what you were doing before receiving the NDPA?
    c. Was your research field before receiving the NDPA the same as it is now?
    d. In what ways was your proposed research ***pioneering***?
        i. Describe the landscape of the field (publications, theories, trends, etc.) before you began this project.
        ii. Was the proposed work substantially different from research being pursued elsewhere?
        iii. Were others doing similar work?

2. Please indicate which of the following statements (if any) are true of your NDPA-funded project[1]:
{Choose all that apply}
( ) One or more of the fundamental ideas underlying my project are at odds with prevailing wisdom
( ) My project requires use of equipment or techniques that have not been proven or are extraordinarily difficult
( ) My project requires knowledge of fields beyond my previously demonstrated area of expertise
( ) My project involves a unique combination of disciplines or an unprecedented scientific perspective
( ) None of these statements is true of my project

3. **What is the progress of your NDPA-funded research?**
    a. To what extent have you been able to achieve your proposed objectives for the project?
    b. To what extent, if at all, did you need to modify your research concept or approach since the initial proposal?
    c. Were you able to document these variants from the original plan?

4. **How did your goals/expectations for your research change over the time of the NDPA award?**
    a. Why did they change?
    b. Was this change captured in your annual progress reports to NIH?
    c. Describe any obstacles you experienced in implementing your proposed work.

5. **What, if anything, has the NDPA grant allowed you to do that you could not do without it?**
    a. What aspects of the award (e.g. funding period, funding amount, no 'specific aims') allowed this?
    b. If you had not received the NDPA, do you believe you would have pursued this work? If so, how?

[1] Dr. Rita R. Colwell, Keynote Address to the International Life Sciences Summit of Georgetown University, Washington, D.C., October 20, 2003. Accessed from http://www.nsf.gov/news/speeches/colwell/rc031020lifesci_summit.htm

c. Is there a difference in the way that you approach your NDPA-funded project versus your non-NDPA work?

B. Research Outputs

1. Please indicate which of the following potential and/or realized outcomes apply to your NDPA-funded project[2]:
   {Choose all that apply}
   ( ) My project could result in the formulation of new ideas or the advancement of theoretical concepts
   ( ) My project could result in the discovery of new empirical phenomena
   ( ) My project could result in the development of a new methodology, enabling empirical testing of theories
   ( ) My project could result in the invention of novel instruments that would open up new research possibilities
   ( ) My project could result in the new synthesis of existing ideas
   ( ) None of these statements is a potential result of my project

2. **Have you published or are you in the process of publishing any work supported by the NDPA?**
   a. If not, when do you expect to publish?
   b. How do these publications compare (e.g. expected impact factor, type of journal) to your previous or current non-NDPA research publications?
   c. How would you compare your NDPA-funded work to your other research in terms of rate of publication? In terms of approach to publishing?
   d. Has your general approach to publishing changed as a result of receiving the NDPA?

3. **Have you filed or do you expect to file any patents resulting from your NDPA-funded work?**
   a. Have you had any interactions with the commercial sector due to your NDPA work?

4. **Has your NDPA-funded work resulted in any presentations at professional meetings or other public events?**

5. **Has your NDPA work resulted in any exposure in the popular press or media? If yes, please elaborate.**
   a. Does the NDPA work have more public exposure than your other work?

6. **Has the NDPA-funded work produced any other tangible outputs (e.g. textbooks, software, technology, etc.)?**

7. **Can you describe your future plans for this project?**
   a. What is your ultimate vision for this work?

8. **How are your research results applicable to the diagnosis and treatment of disease?**
   a. What is the predicted timeline to see them becoming applicable?

[2] T. Heinze et al., "Identifying creative research accomplishments: Methodology and results for nanotechnology and human genetics." Scientometrics, Vol. 70, No. 1 (2007) 125–152

C. Funding

1. **Had your NDPA project previously been supported by other funds?**
    a. If so, what was the source(s) and approximately how much funding did it provide?
        i. Was the supported project the same as the NDPA-funded project?
    b. If not, had you previously applied for funding to support the NDPA-funded work?

2. **Is the amount of the NDPA funding sufficient to carry out the project? Is it too much?**
    a. Was the required 51% effort commitment reasonable?

3. **Besides the NDPA, do you currently have funding from other sources?**
    a. If yes, are the projects supported by these other grants related to your NDPA-funded work?
    b. How do these other grants received post-NDPA differ from those received prior to the NDPA?
    c. What other grants have you applied for (but not received) since receiving the NDPA?
    d. Have you been able to secure funding to continue your NDPA project after the funding period ends? If so, from which programs?

4. **How did the NDPA funding affect other projects in your lab?**
    a. Is the NDPA-funded work a standalone project?
        i. How is it related to other projects in your lab?

5. **Have you been involved in any other high-risk research programs?**
    a. Was NDPA your first non-traditional grant?
    b. Do you think there are similar programs that can be compared to the NDPA?

D. Spillover Effects

On Awardee Career Trajectories

1. **How has your career changed since receiving the NDPA?**
    a. Are you still at the same institution?
    b. Have you received a promotion or tenure?
    c. To what degree are these changes due to the NDPA?

2. **Has the way you approach research has changed as a result of receiving the NDPA?**
    a. Do you engage in more high-risk research?

3. **Have you won any awards (monetary or non-monetary, research specific or non-research specific, grants versus personal award for accomplishments) since receiving the NDPA?**
    a. Are these awards different than ones you received before the NDPA?

On Labs and Institutions

4. **Have there been any significant changes in lab size or personnel as a result of the NDPA?**

5. **What impacts has the NDPA had on lab management/administration**?
    a. On lab capacity/capabilities?

Appendix C: Awardees and Their Research

Overview

This appendix provides an overview of the research conducted by each of the 22 awardees from the first two years of the NDPA program. The research summaries in this section were written by STPI, based on the application and progress reports. These reports were used to provide the expert panel with an overview of what was proposed by the awardee, and some assessment of what had been accomplished during the funding period. The research summaries were edited and approved by each of the awardees.

The following pages provide biographies for the awardees listed below:

- Abbott, Larry
- Chandler, Vicki
- Cline, Hollis
- Cosmides, Leda
- Daley, George
- De Lange, Titia
- Deisseroth, Karl
- Harbury, Pehr
- Hellinga, Homme
- Jarvis, Erich
- McCune, Joseph (Mike)
- McKnight, Steven
- Mirkin, Chad
- Phillips, Rob
- Quake, Stephen
- Rando, Thomas
- Smith, Derek
- Tononi, Giulio
- Waterman, Clare
- Wolfe, Nathan
- Xie, Xiaoliang (Sunney)
- Yuan, Junying

The year each received his or her award is also provided. Photographs are from NIH's Common Fund Website, NIH Director's Pioneer Award Program, Award Recipients, https://commonfund.nih.gov/pioneer/AwardRecipients.aspx.

Larry Abbott (2004)

Larry Abbott was awarded the NDPA in 2004, as he prepared to move his laboratory from Brandeis University to join the Center for Theoretical Neuroscience at Columbia University. Abbott, having received his PhD training in theoretical particle physics in 1977, began studying neuroscience in the early 1990s. Abbott, with collaborator Eve Marder, developed in 1994 a technique known as dynamic clamp that is widely used in neuroscience, and authored the standard textbook "Theoretical Neuroscience" in 2000.

In his application, Abbott proposed to extend his studies on addressing the complex mechanisms of cognitive processing by understanding neural circuit dynamics. Specifically, he hoped to address two major principles of neural circuit dynamics that exhibit paradoxical features—(1) how neural systems can generate internal complex patterns of activity, yet remain sensitive to the external world; and (2) how neural systems are able to exhibit dynamics on multiple and wide-ranging timescales (from milliseconds to months and years). Abbott proposed to link his theoretical models with experimental data, by proposing general principles that can be tested and verified experimentally.

At the time of his application, Abbott had already begun exploring neural circuit dynamics in a wide range of areas such as maintenance and regulation of intrinsic conductance in neurons, short- and long-term synaptic plasticity, and simple and complex cell responses in the primary visual cortex. His NDPA proposal was to take on the broader issues of overarching relevance to these and similar research projects.

With the NDPA, Abbott and his colleagues took the approach of using random matrices to be able to understand why background levels of neural activity are so high. Using this approach, they were able to construct circuits that act as general purpose pattern generators, and also to develop models that combine complex internally-generated activity with extreme sensitivity to external inputs. Their results showed that mechanisms of plasticity or modulation that affect the variance (rather than the mean) of the synaptic strengths are the most effective at modifying network dynamics.

Working with collaborators at the Hebrew University, Abbott showed that information regarding visual stimuli may be better conveyed by a network displaying chaotic background activity than by a network without spontaneous activity as might be expected. In another counter-intuitive finding, Abbott and colleagues discovered that the antennal lobe of the fly olfactory system compresses the neural representation of odors, allowing for the higher-level processing systems (the protocerebrum and mushroom bodies) to be highly selective.

Abbott also undertook a variety of projects related to the properties of neural circuits including studying the limits on the memory-storage capacity of bounded synapses, deriving the mathematics that can distinguish between mechanisms of gain modulation at the single neuron and network levels, illustrating signal gating and detailed balance in neuronal networks, and discovering a phase transition between spontaneous and stimulus-driven neuronal activity.

The models developed by Abbott through his NDPA work have brought together how external stimuli drive perception and how internal processing influences behavior. Defects in the relationship between these two forms of activity are likely to result in mental illness such as schizophrenia, and Abbott's models enable predictions of such behaviors and other aspects of human perception and behavior.

Vicki Chandler (2005)

Vicki Chandler was awarded the NDPA in 2005, as a full professor at the University of Arizona with joint appointments in the Departments of Plant Sciences and Molecular & Cellular Biology. Chandler received her PhD in Biochemistry in 1983, completing her doctoral research in gene regulation in the lab of Keith Yamamoto at the University of California, San Francisco. She also pursued post-doctoral work in plant genetics in the lab of Virginia Walbot at Stanford University. Prior to receiving the NDPA, Chandler was already a recipient of numerous prestigious awards, including election to the National Academy of Sciences in 2002. Since 2002, she has also held the position of Director of the BIO5 Institute, an interdisciplinary group of researchers working to addresses complex, biology-based problems in areas ranging from agriculture to medicine.

In her NDPA application, Chandler proposed to pursue a new research direction by bringing her expertise in plant epigenetics—specifically of homology-dependent gene silencing (paramutation)—in animals and humans. Insight into the phenomenon of paramutation has implications for understanding a wide range of genetic diseases. Chandler's goals as stated in her NDPA application were to pursue three approaches: (1) search for characteristics that mediate paramutation in the genomes of animal models and humans and form collaborations with appropriate experts to determine if those characteristics mediate altered gene expression, (2) investigate whether the homologs of genes involved in maize paramutation also impact epigenetic regulation in animal models, and (3) explore the human genetics literature and work with appropriate collaborators to identify candidate diseases that might directly involve paramutation-like phenomena. As paramutation is difficult to investigate with classical genetics techniques, Chandler proposed that the systems she developed for studying this phenomenon in

plants—for which she already held two pending patents—would be highly applicable to animal models as well.

A major finding in the first year of Chandler's NDPA funding period was that paramutation in plants is mediated by a RNA-directed mechanism. This resulted in a *Nature* publication and motivated the search for a similar silencing mechanism in animals. Within the next three years, Chandler made progress in cataloging the characteristics of tandem repeats (which mediate paramutation in maize) within the human genome, discovering that many of these are in association with genes previously linked with genetic cancer predisposition. Chandler had also formed several collaborations with clinical researchers to study the epigenetic mechanisms involved in numerous forms of cancer as well as longevity. These studies resulted in publications in high-impact journals as well as publicly available web-based tools for identifying genomic characteristics of epigenetic regulation. In future years, Chandler aims to continue evaluating genomic characteristics involved in paramutation and epigenetic regulation. She and her collaborators also plan to expand their clinical studies of breast and prostate cancer to further establish the link between characteristics mediating paramutation and genetic predisposition to aggressive forms of cancer.

Hollis Cline (2005)

Hollis Cline received the NDPA in 2005, as a full professor in the Watson School of Biological Sciences at Cold Spring Harbor Laboratory. Cline received her PhD in Neurobiology from the University of California, Berkeley, in 1985. She also pursued postdoctoral research in neurobiology in the lab of Martha Constantine-Paton at Yale University and in the lab of Richard Tsien at Stanford University. Prior to her NDPA, Cline had already received numerous awards, served on several national scientific advisory committees, and served as Director of Research at Cold Spring Harbor.

In her NDPA application, Cline proposed to study the connectivity of neuronal circuits using a live imaging approach. Aberrant circuit connectivity in the brain is associated with neurological diseases ranging from autism to schizophrenia, yet previous methods of studying neuronal circuit connections primarily utilized fixed tissue or were limited by the difficulty of visualizing tracer reagents in live tissue. To circumvent these problems, Cline proposed to take advantage of the yeast Gal4/UAS transactivator/promoter system in visualizing neuronal circuits in Xenopus tadpoles. Specifically, Cline aimed to use "Trojan peptides" to carry the Gal4 transactivator across synapses and into downstream target neurons, where it will drive expression of green fluorescent protein (GFP) flanking the UAS promoter, thus amplifying the visual signal from downstream neurons in a particular circuit. While the proposed project would draw

on Cline's previous experience with in vivo imaging and molecular biological manipulations of the Xenopus system, it was a departure from Cline's previous research in that it involved multiple components of entire functional neuronal circuits whereas Cline's previous work focused on plasticity within single neurons.

Within the first two years of her NDPA funding period, Cline and her colleagues worked to develop the requisite transgenic animal models in which to perform the proposed visualization. Although the Gal4/UAS system works well in Xenopus, preliminary experiments revealed that the Trojan peptide delivery system had a limited success rate. Consequently, Cline moved to the Scripps Research Institute in La Jolla, CA in 2008, and redirected the methodological basis of the project to search for other means of visually identifying functionally connected neurons. Before the move to Scripps, Cline had established collaborations with two researchers in La Jolla.

Cline and her colleagues found that it was possible to use rabies virus to infect and thus identify neurons connected within the developing Xenopus brain. They also identified another possible method of tracing neuronal connections using endogenous proteins that are transported across synapses. In conjunction with establishing a trans-synaptic system of labeling functionally connected neural circuits for live imaging, Cline and her colleagues developed methods to combine in vivo 2-photon imaging and serial section transmission electron microscopy to create a full, three-dimensional reconstruction of neurons in intact animals.

Leda Cosmides (2005)

Leda Cosmides received the NDPA in 2005, after being named a finalist in the first year of the program. At the time of receiving the award, Cosmides was a professor in Psychology at the University of California, Santa Barbara (UCSB), and was known for establishing the field of "evolutionary psychology" along with her collaborator, John Tooby. Evolutionary psychology integrates the cognitive sciences with evolutionary biology, neuroscience, genetics, and anthropology into a new framework for thinking about psychology; one in which the mind is comprised of many information-processing networks, each of which evolved to solve a different adaptive problem faced by our hunter-gather ancestors.

For the NDPA, Cosmides proposed to develop a new approach to motivation that is both computational and grounded in evolutionary theories of function. She proposed that motivational systems require computational elements that are not concepts, beliefs, desires, preferences, or drives, but something else: *internal regulatory variables* (IRVs) and evolved specializations that compute them and deliver them to evolved decision-making systems. IRVs evolved to track those narrow, targeted properties of the body, the

social environment, and the physical environment whose computation provided the necessary inputs to evolved decision rules.

By hypothesis, IRVs have magnitudes and they either express value or provide input to mechanisms that compute value. While motivational systems regulating hunger and breathing use IRVs such as blood glucose levels and CO2/O2 ratios, motivational systems regulating social behavior require IRVs such as the kinship index (whose magnitude reflects genetic relatedness between self and another) and the welfare-tradeoff ratio (whose magnitude reflects how much weight one puts on the welfare of another individual relative to one's own). With the NDPA, Cosmides proposed to explore this framework in three specific test systems: (1) the existence of a kinship index and its role in regulating family-directed altruism and inhibiting within-family sexual attraction, (2) the computational design of anger and (3) guilt, with anger and guilt conceptualized as systems that evolved to recalibrate the magnitude of welfare tradeoff ratios (WTRs) in another person's brain and/or one's own (these investigations later expanded to include gratitude and shame (as distinct from guilt)). Over the course of the NDPA, Cosmides and her colleagues have conducted studies with several thousand subjects, including college students, Argentinean pastoralists, and hunter-horticulturalists in Ecuador (Shuar) and Bolivia (Tsimane).

Cosmides' group has found converging evidence for the existence of WTRs, and has evidence of its role in regulating the human motivational systems for anger, gratitude, guilt, and shame, and their relationship to cooperation (some of these papers are out, some in preparation). For example, they found that, holding *benefits received from the partner* constant, an individual's anger is triggered by actions indicating that the partner places too little weight on one's welfare (low WTR), gratitude is triggered when the partner's actions indicate a willingness to sacrifice his or her own welfare to enhance one's own (high WTR), and cooperation is down- or up-regulated accordingly.

Their studies on kin detection provide evidence that the kinship index is real, and computed from two ancestrally reliable cues correlated with genetic relatedness of siblings. These cues, through the kinship index, jointly regulate in precisely the same pattern two very different motivational systems (sibling altruism and sexual aversion).

Mapping the neurocomputational architecture of the brain, understood as composed of systems that evolved to accomplish specific adaptive functions during an ancestral past, could provide significant insight for the field of mental health, and has the potential to assist the clinical diagnosis and treatment of mental disorders. In the future, Cosmides hopes to continue her NDPA investigations, and is interested in exploring the possibility that psychopathy, narcissistic personality disorder, and borderline personality disorder may be disorders of the systems that compute and recalibrate WTRs and other regulatory variables.

George Daley (2004)

George Daley was in the inaugural class of NDPA, in 2004. At the time of receiving the award, Daley was an Associate Professor of Biological Chemistry and Pediatrics, at Harvard Medical School. Daley earned a PhD in 1989 from the Massachusetts Institute of Technology, where he worked in the laboratory of Nobel Laureate David Baltimore, and an M.D. in 1991 from Harvard Medical School where he graduated summa cum laude. In 1990, Daley notably identified the role of BCR/ABL as the cancer-causing gene responsible for Chronic Myeloid Leukemia (CML), and throughout his career has been known for his contributions the study of CML and to stem cell research.

For his NDPA project, Daley proposed to discover the pathway for reprogramming a differentiated tissue cell towards a regenerative state, by first determining how the mechanism of germ cell pluripotency is preserved following differentiation from the embryonic stem cell (ESC) state. Daley hypothesized that if the specific genes which facilitate germ cell pluripotency were identified, they could potentially be applied to cellular reprogramming methods to restore plasticity in somatic cells.

By the time he was awarded the NDPA, Daley had established himself as a pioneer in the field of stem cell research. His lab had been the first to transform mouse embryonic stem cells (ESCs) into hematopoietic stem cells and to produce sperm, capable of fertilizing eggs of ESC-derived germ cells, and was cited by *Science* as a "Top Ten" breakthrough for 2003. Daley had also collaborated with Rudolph Jaenisch (MIT) to be the first to combine ESCs with gene therapy, by introducing corrective genes into mouse ESCs to treat immune deficiency.

With his NDPA, Daley initially pursued the mechanisms for maintaining germ cell pluripotency, but his research focus shifted in 2006 after investigator Shinya Yamanaka successfully produced Induced Pluripotent Stem Cells (iPS) from mouse somatic cells, partially achieving Daley's proposed objective for the Pioneer project. Propelled by the discovery, Daley and his colleagues became one of the first labs to successfully create iPS cells from human somatic cells. Daley went on to be the first researcher to generate patient-specific stem cells derived from individuals suffering from a variety of genetic diseases, getting him one step closer to his goal proposed in the NDPA application of utilizing cellular reprogramming to transform medical therapies through cellular and tissue regeneration for specific diseases.

While pursuing his initial hypothesis of finding genes regulating embryonic development, germ cell formation, and pluripotency, Daley found through micro-RNA profiling analysis of ESC differentiation that the protein Lin28 blocked let7 micro-RNAs, which he then showed regulated germ cell production. Surprisingly, Lin28 also has a role

in regulating cell proliferation in tumor lines, and in reprogramming to pluripotency. Lin28 has become a significant focus of Daley's lab, and he hypothesizes that Lin28 plays a role in balancing the relationship between stem cells and transit amplifying progenitors in multiple tissues. Daley intends to explore the role of Lin28 in reprogramming and in cellular proliferation in tumor cell lines.

Titia de Lange (2005)

Titia de Lange received the NDPA in 2005, in the eighth year of her full professorship at The Rockefeller University in New York. De Lange received her PhD in Biochemistry in 1985 from the University of Amsterdam and went on to complete a postdoctoral fellowship at the University of California, San Francisco in the laboratory of Harold Varmus, a Nobel Laureate who formerly served as the Director of the National Institutes of Health and currently serves as the Director of the National Cancer Institute. Although de Lange originally planned to research genome instability in cancer in the Varmus lab, her experimental interests eventually led her to the study of telomeres—a field she continued to pursue as a principal investigator and in which she had long been lauded and recognized as a leading expert. Prior to receiving the NDPA, de Lange had already been the principal investigator on numerous R01s related to her telomere research.

In her NDPA application, de Lange proposed to bring her expertise in telomere biology to the broader study of genomic DNA damage and repair, a process that is extremely difficult to study but relevant to important health problems such as cancer, hereditary disorders, and infertility. Specifically, de Lange aimed to develop a new system for probing the initiation of the DNA damage response pathway in mammalian cells. For the development of this system, she specified several collaborations she planned to undertake with other researchers from fields such as chemistry and chemical biology. De Lange's system would be based on simulating physiological DNA damage by removing the protective caps at the ends of chromosomes, and then monitoring DNA and protein changes comprising the immediate response to the damage. De Lange noted that this new system of studying DNA damage has advantages over previous methods in that it creates physiological DNA breaks instantaneously, at specific locations marked by telomeric elements, and on a scale large enough to allow proteomic study. She also emphasized in her application that, due to the broad approach required for this work and its significant divergence from her previous research focus, she did not plan to apply for other funding mechanisms for the project and would only initiate the work if she received the NDPA.

In the first two years of her NDPA funding period, with the help of several collaborators, de Lange focused on developing various methods of simulating

physiological DNA damage by removing the protective cap protein TRF2 from telomeres. These methods ranged from small molecule inhibition of TRF2 to temperature-sensitive mutants of TRF2 in mouse cells. A major finding during these two years was that nucleosomal organization remained intact at telomeres even after they had been converted to DNA damage sites. De Lange and her colleagues also found that removal of another protective capping protein, POT1, induces a different DNA damage response pathway than that resulting from TRF2 removal. These two pathways were further pursued in the subsequent years of de Lange's funding period, resulting in novel mechanistic hypotheses that were described in three publications in high-impact journals such as *Nature*. In future years, de Lange plans to continue pursuing these new hypotheses regarding DNA damage responses.

Karl Deisseroth (2005)

Karl Deisseroth was awarded the NDPA in 2005, eight months after he officially began his assistant professorship in Psychiatry and Bioengineering at the Stanford University School of Medicine. With an MD and a PhD in Neuroscience from Stanford, Deisseroth conducted his graduate research in the lab of cell biologist Richard Tsien and pursued post-doctoral work in synaptic physiology in the lab of Robert Malenka.

In his NDPA application, Deisseroth proposed to develop new bioengineering technology for studying psychiatric disease. His goal was to employ a circuit engineering approach to describe the abnormal patterns of neuronal circuit activity underlying complex diseases such as depression, autism, and schizophrenia. Specifically, Deisseroth aimed to combine real-time, optical control of neuronal circuit activity with simultaneous visualization of this activity.

At the time of his application, Deisseroth and his colleagues had already demonstrated optical control of neuronal activity, using a light-activated cation channel known as channelrhodopsin-2 (ChR2). ChR2, when introduced via viral vectors into specific neuron types (by way of cell-specific promoters), was shown to drive light-triggered neuronal activity with single-spike temporal resolution. To visually track the light-triggered neuronal activity, Deisseroth was also developing low-noise, CCD-based imaging techniques. The preliminary data presented in his application illustrated that Deisseroth's proposed approach allowed millisecond-scale temporal resolution in the control and visualization of neuronal excitation. These data were published in *Nature Neuroscience* around the same time that Deisseroth officially received his NDPA funding.

Within the first three years of his NDPA funding period, Deisseroth and his colleagues further developed their optical neuronal control methods, termed

"optogenetics," in order to study more complex circuit dynamics. They tested light-driven, inhibitory chloride channels called halorhodopsins as well as other excitatory channelrhodopsins with action spectra independent of that of ChR2. These experiments fundamentally expanded the optical control technology by (1) allowing inhibition, as well as stimulation, of neuronal action potentials and (2) allowing independent stimulation of multiple neuron types. The work within these three years resulted in eight peer-reviewed publications, including Science and Nature articles describing the first applications of optogenetics to the study of narcolepsy and depression. It was also during this time period that Deisseroth's lab produced the first evidence that optical control of motor cortex circuits could be used to modulate mammalian behavior. Demonstrations of using optogenetics to control rodent movement appeared in the popular media when Deisseroth was interviewed by ABC News and the *New York Times* in 2007 and invited to give a Google Tech Talk (broadcast on YouTube) in 2008.[73]

In the last two years of his NDPA funding period, Deisseroth and his lab continued to apply optogenetics to the circuit-level study of psychiatric diseases such as Parkinson's, producing several more publications in *Nature* and *Science*. In one of these publications, Deisseroth and his colleagues described their modification of optogenetic techniques to directly couple optical stimulation with biochemical signaling (rather than with action potential initiation). This modification expanded the possible applications of Deisseroth's technology, allowing the study of animal behavior from a biochemical, rather than purely electrophysiological, approach.

In his NDPA funding period, Deisseroth and his colleagues have filed seven patent applications related to their NDPA-funded research. By early 2009, they have also distributed their optogenetics technology to more than 600 labs, in the United States and abroad, enabling multiple collaborations with other researchers in fields such as parasitology and cardiology. In future years, Deisseroth plans to (1) find additional biochemical pathways that can be coupled with his approach to optical stimulation, (2) develop optogenetics techniques for long-term, *in vivo* function, (3) expand the technology to allow more sophisticated study of complex neuronal circuitry, and (4) continue applying the technology to the study of important psychiatric diseases.

[73] Since the completion of our data collection for this study, optogenetics has been named Method of the Year for 2010 by Nature magazine.

Pehr Harbury (2005)

Pehr Harbury received the NDPA in 2005, as an Associate Professor in the Department of Biochemistry at Stanford University. Harbury received his PhD in Biological Chemistry from Harvard University in 1994 and pursued postdoctoral work in the lab of chemist Peter Schultz at the University of California at Berkeley. Prior to being awarded the NDPA, Harbury had already received numerous prestigious distinctions, including being named as a Burroughs Wellcome Young Investigator and one of MIT Technology Review's 100 Young Innovators of 1999. In 2005, Harbury was also named a MacArthur Fellow.

In his NDPA application, Harbury proposed a novel method of drug discovery based on "chemical evolution." Using the recently developed technologies of DNA display and DNA-templated synthesis, Harbury's proposed method of *in vitro* evolution would screen diverse libraries of gene products, each physically attached to its corresponding DNA blueprint, for pharmacological properties, such as binding to an immobilized target molecule. The products with the desired properties would be isolated, amplified and translated to produce a second-generation library. Over multiple iterations of this process, a population of molecules with high affinity and high specificity for the desired target would emerge. This approach would overcome the difficulties of the prevailing paradigm of drug synthesis and screening, which is costly and requires vast amounts of manpower and lengthy periods of time. Harbury's proposed method of evolving drugs *in vitro* would be straightforward, relatively inexpensive, and would be able to screen 10^{14} compounds per day—over 300 million times more than what is possible with traditional drug screening methods. At the time of his NDPA application, Harbury had already begun preliminary efforts along with collaborators to evolve drugs against Dengue Virus infection, asthma, leukemia and other cancers.

In the first two years of Harbury's NDPA funding period, he and his research group focused on developing the requisite technology to perform the proposed chemical evolution of small molecules. After identifying the optimal materials for constructing the necessary fluidic supports and fluidic transfer devices, Harbury and his colleagues built a ceramic reaction vessel with an internal gasketing system called the "ChemBot." Pilot studies of the ChemBot, reported in *Journal of the American Chemical Society* in 2007, revealed that it was capable of automating the combinatorial chemical reactions required for in vitro evolution. Having amassed a sizeable collection of versatile chemical building blocks in developing his chemical evolution system, Harbury is also undertaking efforts to make this system easily available to other research groups and thus expand its range of possible applications.

With his technological platform largely complete, Harbury began turning his attentions to applying the ChemBot to drug development. In collaboration with several

colleagues (one of whom was Karla Kierkegaard, a 2006 NDPA recipient), Harbury has begun preliminary work on synthesizing drugs against important molecular targets involved in Dengue Virus infection and carcinogenesis. In future years, Harbury plans to further characterize the activity of these drugs in mouse models of the human diseases in question. In addition to his work on *in vitro* drug evolution, Harbury has also used his NDPA funds to support development of a molecular "ruler" to more accurately measure the physical properties of DNA and to pursue work on protein "footprinting" to better understand the native structure of proteins in physiological conditions.

Homme Hellinga (2004)

Homme Hellinga was among the first cohort of NDPA recipients in 2004. Hellinga received his PhD in Molecular Biology from the University of Cambridge in 1986 and pursued postdoctoral work in the labs of Robert Baldwin at Stanford University and Fred Richards at Yale University. At the time of receiving his NDPA, Hellinga was an Associate Professor of Biochemistry at Duke University Medical Center and was well known for his work in the area of protein design.

In his NDPA application, Hellinga proposed to develop a technological platform for custom-designing proteins with a wide range of desired practical functions including, but not limited to, drug synthesis and biosensor detection of explosives and nerve agents. Using existing information about structure-function relationships in proteins, Hellinga aimed to use computational design techniques to predict protein sequences that would achieve the requisite functions. In addition to developing these design algorithms, Hellinga proposed to build a collection of "robust engineerable parts" that would constitute a versatile toolbox for constructing biological systems with a diverse range of novel functions. At the time of his NDPA application, Hellinga had already demonstrated the ability of his computational design techniques to construct proteins with novel ligand-binding functions in a 2003 *Nature* publication.

Within the first few years of his NDPA funding period, Hellinga and his research group focused on building and refining an automated protein fabrication platform—integrating control software, a PCR-based gene assembly system, liquid-handling robotics, and *in vitro* transcription and translation with bacterial extracts. This platform allowed the building of a novel protein in a matter of days. Among the first proteins constructed by this fabrication platform was an enzyme, termed novoTIM, resulting from the computational conversion of a ribose-binding protein native to E. coli. In a 2007 paper in the *Journal of Molecular Biology*, Hellinga described the design and function of novoTIM. He planned to further characterize the enzyme's structure by X-ray crystallography and to evaluate the accuracy of the design predictions involved in its construction. However, when it was later discovered that the previously reported

properties of novoTIM were not experimentally replicable, Hellinga retracted the *JMB* paper, along with a *Science* paper he previously published in 2004. Hellinga noted that while the design of the novoTIM enzyme was ultimately found to be incorrect, the technology he had developed for novel protein fabrication was still robust.

In the final years of his NDPA, Hellinga and his group expanded their protein fabrication technology by developing a new, colorimetric assay for testing the stability of proteins synthesized by their automated platform. They also created a novel algorithm for designing specific protein-protein interactions of pre-specified geometry. In future years Hellinga plans to continue using his technology to generate and experimentally test proteins with novel enzymatic functions, interactions, and ligand-binding properties.

Erich Jarvis (2005)

Erich Jarvis received the NDPA in 2005 as an Associate professor of Neurobiology at Duke University, shortly after receiving tenure. In 1995, Jarvis completed his PhD in Molecular Neurobiology and Animal Behavior at the Rockefeller University. He studied under the notable Fernando Nottebohm, with whom he pioneered techniques for behavioral molecular brain mapping to study brain pathways for vocal learning in birds.

For his NDPA project, Jarvis aimed to determine the molecular basis of vocal learning by evaluating the genetic differences between species with and without the trait. Jarvis hypothesized that vocal-learning species (e.g. zebra finch, human, elephant, dolphin, etc.) differ from vocal non-learning species (e.g. chicken, chimp, etc.) by connections from the forebrain for motor learning onto the brainstem vocal motor neurons, and that these differences are controlled by genetic changes in genes involved in neural connectivity. Jarvis proposed to test his hypothesis with the following goals: 1) identify the molecular differences between vocal learners and non-learners, 2) develop tools to genetically manipulate vocalization network connectivity, and 3) use the tools to introduce vocal learning into a vocal non-learning species. Jarvis' ultimate goal is to recreate the vocal learning system with potential applications to remedy damaged vocal systems.

With his NDPA, Jarvis and his students pursued this hypothesis and discovered that the convergent vocal learning systems of all avian vocal learners is embedded within and shares many properties with the forebrain motor system that controls limb and body movements. This led to Jarvis' "Motor theory of vocal learning origin", where he argued, that similar to gene evolution, brain pathways that control vocal learning emerged independently in different lineages first by pathway duplication from a motor learning pathway and then by divergence of the duplicated copy to control vocalizations. This work provided the first reasonable explanation of why distantly related vocal learners

have similar vocal learning pathways, not found in vocal non-learners with closer phylogenetic relationships. This work was featured in various media outlets including Scientific American and in documentary on NOVA.

Jarvis and his group then developed high-throughput genomic, proteomic, and computational approaches to identify candidate genes with convergent changes in the brains of vocal-learning species. His findings suggest that multiple genes within the same pathways were altered throughout evolution of vocal learning. Jarvis intends to further investigate how these genes may help generate and function in vocal learning pathways.

Jarvis and his students also investigated vocalization in mice, a species they initially intended to use as a control vocal non-learner in which to genetically induce vocal learning. These findings suggest that mice have limited vocal learning capabilities with an associated neural system that to date has only been found in humans amongst mammals.

With the NDPA, Jarvis and colleagues also tried to induce vocal learning in a non-learning species by transplanting the telencephalic neural tube of a learner (zebra finch) into a non-learner host (quail) during embryonic development. In future experiments, they intend to determine whether the transplanted forebrain can synapse directly onto the vocal motor neurons, which normally only occurs in vocal learners, attempting to reconstruct the pathway in non-learning species.

To develop a method for generating targeted gene manipulation in transgenic avian vocal learning species, Jarvis and colleagues adopted the induced pluripotent stem cells (iPSC) approach to generate iPSCs of zebra finch cells and other vertebrate (bird and fish) and in insect (drosophila) cells, indicating a conserved, universal mechanism of stem cell induction across the metazoa animal kingdom. Future experiments include using the iPSCs to generate transgenic birds to investigate the role of specific genes in vocal learning and to differentiate the iPSCs into neurons across species to study brain evolution.

Since receiving the NDPA, among other media outlets, Jarvis' work has been featured as a top 100 science discovery of 2005 in *Discover*, in the *New York Times—Science Times* twice, and in the World Science Festival in 2009. He has been named one of *Popular Science's* Brilliant 10 under 45, *Diverse Magazine's* top 10 emerging scholars, and *Mental Floss Magazine's* 10 trail blazing scientist. Jarvis has also been awarded a Howard Hughes Medical Institute Investigator's position in 2008.

Joseph (Mike) McCune (2004)

Joseph (Mike) McCune was awarded the NDPA in 2004, after spending a year long mid-career sabbatical at the Pasteur Institute in Paris in which he asked the question: why has it been so difficult to make an AIDS vaccine? McCune was led to this question after two decades of studying HIV and AIDS, most recently holding multiple appointments as a Senior Investigator at the Gladstone Institute of Virology and Immunology, as a Professor of Medicine at the University of California, San Francisco, and as an Attending Physician at the San Francisco General Hospital's AIDS Clinic.

Based on reflections during his sabbatical and results from prior research, McCune proposed a hypothesis different from the mainstream: that for HIV infection, it may be as important to find ways to inhibit the inflammatory response against the virus as it is to find ways to proactively induce an antiviral immune response. On the one hand, this hypothesis was supported by the observation that many nonhuman primates harbor circulating lentiviruses in the absence of disease and also in the absence of inflammation; in pathogenic infections of nonhuman primates and in humans, on the other hand, the presence of high levels of inflammation predicts rapid disease progression. To test this hypothesis, McCune laid out five specific sub-hypotheses that were tied together with the common need to better understand the immune response to infectious agents in humans. This research question represented an entirely new research direction for McCune, who previously had focused on HIV pathogenesis and treatment in the SCID-hu Thy/Liv mouse, and on T cell production and immune reconstitution in HIV-infected humans.

To test his underlying hypotheses, McCune evaluated three cases that might serve to illustrate the role of immune response during lentiviral infection: (1) HIV-infected humans who are able to suppress the progression of the virus without treatment; (2) non-human primates that have the simian version of HIV (SIV) but do not get sick (such as the African green monkey) compared to those that do (such as the rhesus macaque); and (3) non-infected human and non-human primate infants born to mothers who are HIV or SIV infected. To date, analysis of the latter two cases has yielded interesting clues that largely form the basis for McCune's ongoing work.

Thus, the characterization of human fetal immune systems showed quantitative and qualitative differences from adult immune systems. As shown in studies published in the *Journal of Immunology* in 2006, the human fetus generates many regulatory T cells (Tregs) that suppress immune responses. Trying to understand why such cells might be present, McCune and his colleagues found (and published in *Science* in 2008) that cells from the mother commonly move across the placenta into the fetus during the course of pregnancy and that the fetus carries Tregs to suppress its own immune response against these genetically foreign maternal cells. Possibly, this ability of the fetus to "tolerate" the

mother may facilitate the process of in utero gestation. These observations, however, raise the questions: if the mother is infected with HIV, isn't it likely that HIV also moves across the placenta into the fetus? If so, are fetal Tregs raised to prevent an active immune response to HIV? Could this and other fetal immune responses underlie the observation that so few fetuses (less than 5-10 percent) are infected with HIV in utero? These questions are now being addressed in human and in nonhuman primate models of lentiviral infection.

In parallel, McCune and his colleagues showed that, after acute infection of "natural hosts" such as the African green monkey with SIV, an inflammatory response is initiated but rapidly shut down. The ability to curtail inflammation was associated with the preservation of key T cell subsets, including Tregs and "Th17" cells producing the cytokine, IL-17. By contrast, SIV infection of the macaque leads to loss of Th17 cells, persistent inflammation, and a disease resembling AIDS. After publishing these results in 2009, the McCune lab has now gone on to show that similar events occur in humans.

McCune plans on following these research leads, pushing most of his efforts towards developing an effective HIV vaccine for newborns, and expanding his work to include other chronic viral infections such as hepatitis C.

Steven McKnight (2004)

Steven McKnight was among the first cohort of NDPA awardees in 2004. At the time of receiving the award, McKnight was Chairman of the Biochemistry Department at the University of Texas Southwestern (UTSW) Medical Center. After receiving his PhD in Biology from the University of Virginia in 1977, McKnight was a researcher for many years at the Carnegie Institution of Washington and the Howard Hughes Medical Institute before joining UTSW.

McKnight's prior achievements in molecular and cellular biology included being among the first to describe the leucine zipper protein structure and inventing the "linker scanning" method of probing cellular regulatory mechanisms that control gene expression. In his NDPA application, McKnight proposed to leverage his technical expertise to tackle a broad biological question—how the eukaryotic metabolic cycle is regulated. Specifically, McKnight aimed to use yeast as the model organism in which to study this question, citing the well-established genetics and biochemical methods for probing yeast regulatory mechanisms. Moreover, McKnight argued that because the mechanisms involved in the yeast metabolic cycle might be evolutionarily conserved, a better understanding of these mechanisms might be relevant to human health as well.

Within the first two years of his NDPA funding period, McKnight and his colleagues identified the appropriate yeast strain in which to study the regulation of the

metabolic cycle. By performing DNA microarray experiments, they were able to identify distinct phases within the yeast metabolic cycle, each associated with the expression of a unique set of genes. This resulted in a *Science* publication in 2005, the same year in which McKnight was elected to the Institute of Medicine of the National Academy of Sciences. Over the next two years, McKnight and his group used mass spectrometry methods to describe the precise fluctuations of hundreds of small metabolites in the yeast metabolic cycle. These data were consistent with the regulatory logic of yeast metabolism as predicted by the periodic gene expression described in McKnight's 2005 *Science* paper. This work resulted in three papers in the *Proceedings of the National Academy of Sciences.*

In the final years of his NDPA funding period, McKnight continued his yeast metabolism studies but expanded his work to describe metabolic cycling in mammals. Preliminary experiments with mouse models have already revealed important implications for understanding the regulatory mechanisms driven by circadian rhythms. McKnight has also utilized his NDPA funding for work on the NPAS3 gene in mouse models of psychiatric and neurodegenerative diseases. In researching the role of NPAS3, McKnight found that mice missing this gene are unable to produce newborn neurons in the adult brain. Finally, McKnight has undertaken studies of the metabolic state of mouse embryonic stem cells, finding that their rapid growth hinges on the breakdown of the amino acid threonine by the enzyme threonine dehydrogenase (TDH). These findings, reported in his 2009 *Science* paper, may have important implications for research on human embryonic stem cells, which lack TDH and are difficult to grow in laboratory conditions.

Chad Mirkin (2004)

Chad Mirkin received the NDPA in 2004, while at the time serving a named professorship of Chemistry and director of the Institute of Nanotechnology and Center for Nanofabrication and Molecular Self-Assembly at Northwestern University. Mirkin previously had been the recipient of numerous awards, including the Beckman Young Investigator Award, the NSF Young Investigator Award, an Alfred P. Sloan Fellowship, and the Feynman Prize in Nanotechnology, among others. Much of Mirkin's early career was devoted to the development on nanotechnology tools, including the invention of Dip Pen Nanolithography (DPN) for patterning surfaces at the nanoscale, and the development of a nanoparticle-based barcode assay to detect molecules at extremely low concentrations.

In his NDPA application, Mirkin proposed turning the tools he had previously developed to directly tackle problems of biological relevance. He provided several examples of the power of these tools to address standing problems in biology. One

example was the ability to place receptor molecules with nanoscale precision on a surface—an ability enabled by DPN and related technologies. This ability then allows one to directly mimic the extracellular matrix so that chemical signals, electrostatic forces, and growth factors can be evaluated contextually and accurately, in normal and abnormal cell processes. Another potential example supplied by Mirkin was to study viral infectivity and recognition—given that the nanoscale tools could be used to design complex three-dimensional structures that resemble native viruses. These synthetic nanoviruses could also be coupled with imaging and diagnostic capabilities to additionally study and track infection, deliver therapy, and act as imaging devices.

The research undertaken by Mirkin through his NDPA funding was arranged by attempting to answer three core questions: (1) How do viruses recognize and infect cells, and how can this be studied using nanotechnology? (2) How can two- or three-dimensional patterned surfaces serve as recognition elements for biological entities and stimulate a desired cellular response like adhesion, motility, growth, apoptosis, or differentiation? And (3) Can functionalized gold nanoparticles be used as a tool for gene regulation, and for small molecule screening applications?

In working on the first question, Mirkin used DPN to create templates of immobilized antibodies on a Zn(II)-carboxylate-rich surface to assemble a nanoarray of biologically active virus particles. Mirkin showed that single cells can bind to these nanoarrays and subsequently be infected by the immobilized virus particles. Using virus particles that are fluorophore labeled allows for the infection process to be monitored. A detailed understanding of the interaction between a virus and an infected cell is not only of fundamental importance, but could potentially also lead to new approaches for the development of antiviral drugs.

The second question led Mirkin to generate DPN-created nanoscale architectures for protein arrays, in order to examine the formation of focal adhesion complexes in human fibrosarcoma (HT1080) cells. In these experiments, cells are adhered to a cobalt/goal surface through the use of fibronectin, an extracellular matrix protein. During the cell adhesion process, focal adhesion complexes form within the cell. The complex formation was studied as a function of surface feature characteristics such as size and spacing. The results of these studies could help scientists understand how external cell signaling affects cancer cell behavior, especially with regard to apoptosis or metastasis. Mirkin also demonstrated an approach to inking pen arrays that solves the multiplexing and ink uniformity challenges in the context of DPN and related nanolithographies.

Mirkin’s exploration of functionalizing gold nanoparticles with short DNA strands opened the door to several applications, including the study of a new type of DNA hybridization that occurs only when DNA is linked with a nanoparticle, a new Polymerase Chain Reaction-free approach to amplified telomerase detection, and the use

of these particles as therapeutic agents, and the study of the immune response to introduction of these particles.

Mirkin plans to continue the work on DNA-functionalized nanoparticles as therapeutics, expanding to target specific cells using antibodies and also testing RNA-interference nanoparticle payloads for gene expression.

Rob Phillips (2004)

Rob Phillips was awarded the NDPA in 2004, a few years after moving from Brown University to the California Institute of Technology (Caltech) as a full professor to switch research directions. Phillips had previously focused on computational materials science (and authored a 2000 textbook on the topic), but chose to turn his efforts towards quantitative modeling of biological phenomena. To school himself in biology, Phillips spent a year-long sabbatical studying classical biology at the Institut National Polytechnique de Grenoble in France. This was not a new approach for Phillips; earlier in his career, Phillips left high school to undertake an independent study course, and went on to receive a B.S. in Physics without ever having attended college.

At the time of his NDPA application, Phillips was undertaking the writing of a textbook on the *Physical Biology of the Cell*, with the intent that this book would serve as a quantitative companion to the canonical cell biology textbook, Alberts's *Molecular Biology of the Cell*. Phillips' approach was to build his work around several key case studies of biological phenomena, including how viruses assemble, how ion channels are gated by mechanical forces, and the dynamics of transcriptional regulation. The goal of these case studies was to make precise predictions of biological events using coarse-grained mathematical models. Phillips proposed to continue these case studies—and their verification/falsification in the laboratory—as his NDPA project. Phillips also declared that training students, especially teaching them how to bridge fundamental biology with engineering applications, would be a large component of his effort. His application to the NDPA was the first time Phillips had applied for funding from the NIH.

Shortly after receiving the NDPA, Phillips and his lab moved to the Broad Center at Caltech, an interdisciplinary space for biologists, chemists, applied mathematicians, and physicists. Through his NDPA work, Phillips made a series of predictions about the mechanical forces associated with genome packing and how they depend upon genome length, predictions as to how the probability of gene expression depends upon factors such as the concentrations of repressors, activators, inducers and the distance between operators for repressor binding. Many of these predictions were tested in experimental settings and resulted in publications in journals such as *Nature Nanotechnology* and *Physical Review Letters*. Phillips also launched the Physical Biology Laboratory course

around a set of experiments on how DNA looping affects gene expression, in order to engage Caltech students in experiments at the interface of physics and biology.

In the fifth year of his award, Phillips published his 800-page textbook *Physical Biology of the Cel*l (with co-authors J. Kondev and Julie Theriot), and the textbook is currently used at Caltech and other programs. The book features many of the case studies undertaken with the NDPA.

Phillips plans to continue his work on theoretical and experimental analyses of complexes made of DNA and transcription factors, and has been able to develop an impressive array of quantitative measurements which now make it possible to query the transcription process in exquisite detail and raise the bar on how transcription is understood. He is also continuing the work on lipid-protein interactions and ion channel function using both and an experimental and theoretical approach to understand the interactions of membrane proteins and the surrounding lipid bilayer. Phillips is also furthering the work on the packaging and ejection of viral genomes, which has led to the use of digital PCR methods to co-localize phages and their hosts in the termite gut; Phillips envisions this work will apply to the understanding of how viruses and their hosts interact in generic environmental samples. Also, his popular "Physical Biology Bootcamp" courses are expected to expand based on an increased investment from Caltech.

Stephen Quake (2004)

Stephen Quake was awarded the NDPA in 2004, shortly after becoming a full professor at the California Institute of Technology, where he was specializing in single-molecule biophysics. As an undergraduate, Quake worked in the lab of Dr. Steven Chu, a 1997 winner of the Nobel Prize in Physics. Quake returned to the Chu lab to do postdoctoral work following the receipt of his PhD in Physics from Oxford University. Quake was the recipient of many early career awards, including being named one of the "100 Young Innovators that will Create the Future" by the popular science magazine *Technology Review*, and participating in the National Academies of Engineering's Frontiers of Engineering Symposium. He also co-founded two biotechnology companies, Fluidigm and Helicos Biosciences. At the time of applying to NDPA, Quake was in the process of moving his lab to Stanford in order to more directly address biological questions.

In his NDPA application, Quake proposed to explore whether it is possible to automate biology in a similar way that engineers had automated many aspects of the world with integrated circuit technologies, and whether such automation would have a similar transformative effect. Through prior work, Quake and his colleagues had

developed microfluidics tools and were testing their capabilities through several pilot projects that he proposed to continue and expand if funded.

In the first few years of his NDPA, Quake explored three main avenues of research. The first was to understand the interaction of mammalian cells with microfluidic environments to create stable, reliable, small-volume cell cultures. Quake examined the effect of small-volume culture conditions on the proliferation, differentiation, and motility of mesenchymal stem cells. Beyond developing the technology of the stable micro cell cultures, Quake also showed the applicability of these systems to questions of biological relevance by reporting in a 2009 *Nature* article the finding that stem cells produce lower levels of reactive oxygen species than do mature cells—a difference that is critical for the maintenance of the stem cell function. Quake's second avenue of research was to develop high-throughput systems for the isolation and culture of large numbers of mammalian cells.

The third project was to perform digital Polymerase Chain Reaction (PCR) using a chip designed to divide a microliter volume into thousands of independent chambers—allowing for rapid single cell genome sequencing. This technology has already shown several important applications, including its use as a noninvasive test for fetal Down's syndrome (published in *Proceedings of the National Academy of Sciences* in 2008), as a molecular screening tool for drugs effective against Hepatitis C (published in *Nature Biotechnology* in 2008), and to sequence Quake's own genome within only a week (*Nature Biotechnology*, 2009).

In the last years of his award, Quake increasingly focused on the sequencing of bacterial genomes and the mapping of the protein interaction networks within the bacteria, developing an in vitro microfluidic platform for high-throughput screening of protein interactions called the Protein Interaction Network Generator (PING). Initial results obtained with PING show a network of interactions that is surprisingly denser than would be predicted with conventional methods and suggest a number of new hypotheses about the role of proteins in multiple functions.

Thomas Rando (2005)

Tom Rando received the NDPA in 2005, as an Associate Professor in the Department of Neurology and Neurological Sciences at Stanford University. Rando received an MD and PhD in Cell Biology from Harvard University in 1987. After completing his Neurology residency in 1991 at the University of California, San Francisco, he pursued postdoctoral research in molecular pharmacology at Stanford.

In his NDPA application, Rando proposed to study the mechanisms of age-related decline in stem cell functionality and how they relate to decreased regenerative potential

in aged humans. The broad, long-term objectives described in Rando's NDPA application were to (1) search for the molecular basis of impaired stem cell function due to aging, (2) understand how age-related changes in stem cell niches affect stem cell functionality, and (3) determine if each bodily tissue has a unique mechanism of age-related decline in stem cell functionality or if this decline has a universal mechanism. In parallel with these studies, Rando proposed to find ways of translating his discoveries to clinical practice and improve tissue repair and regeneration in aged individuals by enhancing the functionality of resident, tissue-specific stem cells.

In the first few years of his NDPA funding period, Rando and his colleagues launched a large-scale screen to determine the age-related, biochemical and molecular changes in various serums and tissues collected from mouse models of different ages. Specifically, Rando aimed to use antibody arrays and commercially available screening libraries to identify the growth factors, cytokines, secreted proteins, and other elements present in serums and tissues of different ages. In parallel with these screens, Rando was also pursuing several related projects, including studying the role of the Notch signaling pathway in tissue response to injury, investigating the stability and turnover of the Pax genes in regulating muscle self-renewal, and examining the effects of the asymmetric properties of muscle stem cell division on the regenerative potential of muscle tissue. These studies resulted in several publications in *Cell*.

Serendipitously, one of Rando's non-NDPA projects yielded the result that aged muscle stem cells display enhanced basal Wnt signaling, which is detrimental to their regenerative potential. This finding has major implications for regenerative medicine and was described in a 2007 *Science* paper, and Rando has expanded his study of Wnt signaling in tissue-specific stem cells, publishing another related paper in *Cell: Stem Cell*. In future years, Rando plans to continue screening and characterizing the biochemical and molecular elements of serums and tissues of varying ages. In keeping with his broader goal of understanding stem cell aging as a whole, Rando also aims to continue pursuing his studies of the asymmetric division of muscle stem cells and of the signaling pathways involved in regulating tissue regeneration.

Derek Smith (2005)

Derek Smith received an NDPA in 2005, as a research associate in Zoology at Cambridge University in the UK, and a research scientist in Virology at Erasmus Medical Centre in Rotterdam, NL. Smith completed his PhD in Computer Science from the University of New Mexico in 1997, while working as a graduate fellow at the Santa Fe Institute. Prior to receiving his PhD, Smith worked for 10 years at Texas Instruments. With collaborative support and his mathematical

background, Smith shifted his research to the development of bioinformatics tools for characterizing antigenic data.

In his NDPA application, Smith described a unique bioinformatics tool called "antigenic cartography," which he and collaborators previously developed to quantify and characterize properties of pathogens that cause infectious disease. Smith was responding to insufficiencies in previous biochemical assays, which were unable to detect the sophisticated diversity across the various species of viral pathogens. Smith and his colleagues demonstrated how antigenic cartography can be used to phenotypically characterize and define various strains of the influenza virus, and showed it's the potential for predicting viral evolution. Smith described the tool in a 2004 *Science* article, and soon thereafter was invited to apply his method to a World Health Organization (WHO) global influenza surveillance program. Smith, having accepted a permanent position as a member the WHO influenza strain selection committee, now annually assists with the selection of the influenza strain that will be used to design the seasonal vaccine.

With his NDPA, Smith is further testing the capability of his bioinformatics tool by coupling data generated using antigenic cartography with genetic data of influenza, to understand the genetic basis for the phenotypic changes that occur as the virus evolves. Smith and his colleagues are also conducting experiments to investigate viral fitness due to immunity to vaccines in the population, and are collaborating with phylogeneticists to investigate the evolution and adaptation of influenza strains in various non-human species including horses, pigs, ferrets and birds. Integrating these analyses may give insight into the evolution of influenza in humans, and may enable vaccine design to outmaneuver the adaptive behavior of the virus.

Since receiving his NDPA, Smith has continued to work with WHO to assist in global influenza surveillance, as well as expanded his efforts. Smith has provided antigenic maps for bird flu (H5N1), evaluated viral immunity in birds, and has assisted with the efforts to prepare a human vaccine to the strain. Through his work for the WHO Smith has shown that since 2002, the seasonal flu virus H3N2 has originated in Asia. This work featured in a 2008 Science article, has since been reported in over 400 media outlets, and has influenced the WHO to focus their investigative efforts on the region which may be driving viral evolution of influenza.

Most recently Smith has been involved with the response to the H1N1 pandemic, working with the US Centers for Disease Control and Prevention to genetically and phenotypically analyze the viral strain, as well as helping with vaccine selection. Smith also worked with the WHO, The Food and Agriculture Organization of the United Nations and the World Organization for Animal Health on a collaborative effort to investigate the origin of the H1N1 pandemic.

Smith has extended his antigenic cartography to pilot investigations of additional pathogens including the Malaria, Rabies, and Dengue viruses, and also hopes to apply the phenotypic and genetic data to vaccine design. Smith has recently made his antigenic cartography software a free and open source for the greater scientific community, and offers training sessions to make his technology available to many researchers. This tool has the potential to have even greater impact on public health as it may be used to control the adaptation of influenza and other viruses through a unique approach to vaccine design.

Giulio Tononi (2005)

Giulio Tononi received his NDPA in 2005 as a professor of Psychiatry at the University of Wisconsin at Madison. At age 16, Tononi decided to study consciousness, and subsequently pursued an education in medicine and graduated from Scuola Normale Superiore in Italy with an MD in 1985, and a PhD in Neurobiology in 1988.

Tononi specialized in Psychiatry, and proceeded to study the mechanism and function of sleep and has pursued the study of consciousness—though colleagues strongly discouraged him from investigating consciousness. Through his research, Tononi has broken ground in the field with his "information integration theory on consciousness," suggesting that consciousness does not come from a unique property of brain cells, but from the integration of a large amount of information in a short period of time. This theory is supported by findings generated from computer models and human studies. Tononi has also notably contributed the original approach to studying sleep through gene expression to his field, which led to his proposed NDPA project.

Given that the function of sleep remains undefined, for his NDPA project, Tononi proposed to address his hypothesis on the biological function and mechanism of sleep. Tononi theorized the "synaptic homeostasis hypothesis," which states that sleep is the restorative cost for the plasticity of the brain during the wake state, and that in order to optimize performance, sleep returns the brain to a sustainable energy level by reducing the synaptic burden on neurons generated during wakefulness. Tononi proposed to pursue his hypothesis by testing four predictions: 1) wakefulness is associated with synaptic potentiation in several cortical circuits; 2) synaptic potentiation is tied to the homeostatic regulation of slow wave activity; 3) slow wave activity is associated with synaptic downscaling; 4) synaptic down scaling is tied to the beneficial effects of sleep on neural function.

Since receiving the NDPA, Tononi has shown in both rat and human models that strengthening synapses during wakefulness increases the sleep pressure by synchronizing slow waves that occur during subsequent sleep. These findings supported predictions Tononi and his colleagues generated from a detailed computer model that represented

over 5 million synapses. Tononi has also shown how exploratory activity, such as a learned task, induces cortical expression of genes related to the brain's plasticity, and has demonstrated how sleep may help reset metabolic rates in the brain after wakefulness.

Tononi and his colleagues have also demonstrated how local electrical stimulation can generate synaptic potentiation in the same region, and can increase slow wave activity during sleep. This finding could be a potential application for noninvasive therapy to enhance the sleep value. Through computer simulation and human studies, Tononi's work has also provided evidence demonstrating how sleep can help reduce performance errors, and can enhance task accomplishments.

Tononi intends to continue his research to find more evidence to support his theory on the mechanism and function of sleep. For example, he plans to utilize computer models to investigate time-dependence of synaptic downscaling during sleep, and further explore the brain's metabolic function during wakefulness and sleep. Another area of exploration is to use in vivo microscopy in a rat model to investigate how the quantity and size of synapses are affected by being asleep or being awake. Tononi's work has generated substantial evidence to support his synaptic homeostasis hypothesis, and has the potential for new insight on the value of sleep as a restorative process.

Clare Waterman (2005)

Clare Waterman was awarded the NDPA in 2005, as an associate professor in the Department of Cell Biology at the Scripps Research Institute. Waterman received her PhD in Cell Biology from the University of Pennsylvania in 1995, and completed her post-doctoral work in Ted Salmon's lab at the University of North Carolina, Chapel Hill, transitioning from a self-described "reductionist cell biologist" to a systems biologist interested in developing new technologies to understand how multiple sub-cellular processes contribute to overall cell outputs.

In her application, Waterman described her vision for better understanding complex single cell behavior. Her approach is based on utilizing several optical, mechanical, and environmental perturbation techniques simultaneously to develop an integrated view of the cytomechanical system. This approach relied strongly on the technique known as Fluorescent Speckle Microscopy (FSM), developed by Waterman as a post-doc. FSM uses small amounts of fluorescently labeled protein subunits that co-assemble with the natural, unlabeled subunits which form the overall macromolecular structure of interest. By measuring the time and space variation of those labeled subunits in a fluorescence microscope, one can track the movement, assembly and disassembly of the structure.

Waterman proposed using directed tissue cell migration as a platform to test her integrated cytomechanical system, given her experience in using FSM on that platform.

She proposed correlating the various cell forces and biophysical properties with the movement of the cell using FSM simultaneously with force spectroscopic and microrheological (flow) methods. Waterman projected that once these correlations are understood that she would study the interdependencies between them by perturbing the system, blocking one specific system at a time using RNA interference, genetically modified cells, and well-targeted drugs. Finally, Waterman proposed studying how cells adapt to their environmental surroundings by using this platform and perturbing the extracellular matrix. In order to pursue the ideas proposed in the application, Waterman also proposed to develop the requisite multimodal technologies and correlative analysis methods.

In her first two years of the NDPA award, Waterman focused on developing the technology needed for her cytomechanical system, coming up with a way to measure up to 10 fluorescent probes with FSM and exploring different options for instrument design. An optical trapping force spectrometer and a traction force microscope were also beginning to be integrated with the FSM design. With colleagues, Waterman designed software to perform correlative analyses. She also made progress on the systems integration of distinct actin-based machines and the protrusion of the cell leading edge during cell migration, systems integration between actin cytoskeleton dynamics and the membrane recycling pathway during cell migration, and combining traction force microscopy with multispectral FSM. All of these areas resulted in publications submitted starting in 2006.

In 2007, Waterman accepted a position to head the Laboratory of Cell and Tissue Morphodynamics at the National Heart, Lung, and Blood Institute at the National Institutes of Health. While she had to relinquish her NDPA funds, she has continued her work on developing the cytomechanical system proposed in her NDPA application.

Nathan Wolfe (2005)

Nathan Wolfe was awarded the NDPA in 2005, two years after becoming an assistant professor in Epidemiology at Johns Hopkins University's Bloomberg School of Public Health. In the same year, Wolfe was named one of the "Brilliant 10" by *Popular Science* magazine, and was a Burroughs Wellcome Fund finalist for the Investigators in Pathogenesis of Infectious Disease Award. For his NDPA project, Wolfe proposed to establish the first system to monitor and predict the emergence of infectious diseases globally.

Wolfe's interest in the topic stemmed from his graduate research in which he studied the genetic diversity of retroviruses among adults in Central Africa. During this investigation, he observed the habitual exposure of adults to animal blood and bodily fluids, primarily amongst hunters, and considered the viral potential in cross-species

transmission of vector-borne diseases. Wolfe hypothesized that if diseases endemic to these particular animal species could crossover and emerge as new, potent diseases in humans, the effects could quickly spread and become a devastating pandemic. The most notable example of this phenomenon is the Human Immunodeficiency Virus (HIV) virus, which is known to have crossed over to humans from a monkey disease lineage, Simian Immunodeficiency Virus (SIV), in Central Africa during the early 20th century.

For his NDPA work, Wolfe proposed to ally with hunters in the African region, and use their blood samples along with samples from their hunted bush meat, to monitor cross-species transmission and emerging infectious diseases. Although the potentially devastating effects of diseases such as HIV and Severe Acute Respiratory Syndrome (SARS, also of animal origin) are well known, at the time of Wolfe's proposal, little or no research was being conducted to monitor or to predict such cross-species disease emergence. Due to the limited tools for surveying pathogens of animal origin in humans, Wolfe also aimed to design generic assays that could be used to screen a variety of such pathogens.

At the time of receiving the NDPA, Wolfe had already begun to identify disease emergence among hunters in Cameroon who were highly exposed to the blood and bodily fluids of non-human primate species with a high prevalence of Simian T-Lymphotropic Virus (STLV). STLV is a retrovirus with similar disease pathology as SIV and HIV in primates. Among these hunters, Wolfe and his colleagues had identified two unique Human T-Lymphotropic Viruses (HTLVs) which they called HTLV-3, and HTLV-4. With his NDPA, Wolfe and his team have continued the hunter cohort study and HTLV and STLV analyses, as well as expanded their pathogenic analyses to include other infectious diseases in the Central African region such as Arboviruses, Ebola and Marburg viruses, and Herpes Simplex Virus Type 2 (HSV-2).

With the NDPA, Wolfe and his colleagues have discovered a novel STLV strain, a Simian Foamy Virus, and a new poxvirus. The team has also completed the full-genomic sequencing of the new STLV, HTLV-3 and HTLV-4 strains, and is now focused on creating a predictive model for understanding the diversity and distribution of HTLVs. Through his NDPA work, Wolfe has also revealed that malaria is of chimpanzee origin, and plans to utilize this discovery for designing future prophylaxis and therapy for the disease.

Since receiving his NDPA, Wolfe has also founded the Global Viral Forecasting Initiative (GVFI), to research and predict emerging infectious diseases, in international disease "hot spots" within Cameroon, Madagascar, China, Malaysia, Congo, and Laos. Wolfe and his work have been featured in the popular press and media outlets including the *New York Times*, *Wall Street Journal*, *Wired*, *The Economist*, *Seed*, *Scientific American*, and on broadcast such as NPR, CNN, BBC News, and National Geographic. In the future, to supplement the research infrastructure he is currently establishing, Wolfe

aims to build additional sustainable disease surveillance systems by creating hand-held devices that can be used in remote parts of the globe to monitor emerging diseases and help prevent pandemics.

Xiaoliang (Sunney) Xie (2004)

Xiaoliang (Sunney) Xie was awarded the NDPA in 2004, as a professor in the Department of Chemistry at Harvard University. After finishing his post-doctoral work in ultrafast spectroscopy at the University of Chicago, Xie spent several years as a senior scientist at the Pacific Northwest National Laboratory where he accomplished several "firsts" in the nascent field of single molecule imaging. In 1994, his group achieved the first fluorescence studies of single molecules at room temperature, and in 1998 he was able to resolve the dynamics of enzyme catalysis by studying enzyme binding at the single molecule level. He also developed a novel tool known as Coherent Anti-Stokes Raman Scattering (CARS), in which molecules can be imaged based on their vibrational properties—allowing the visualization of molecules without the need for tagging them with fluorophores, antibodies, or other imaging probes like nanoparticles.

In his NDPA application, Xie proposed to extend his studies of single molecule activities to live cells. In particular, his goal was to observe gene expression in real time—to image at the single-molecule level both transcription and translation—the events that make up the central dogma of molecular biology. To achieve this goal, Xie took a new approach to imaging that differed from the traditional approach of tagging a molecule with a fluorophore, which is neither sensitive enough for single molecule studies (as approximately 20 green fluorescent proteins (GFPs) are needed for detection), nor suitable for the time-scales appropriate to studying gene expression. Thus, Xie developed a method in which the cell of interest is placed on an underlying substrate that, while not fluorescent on its own, can be hydrolyzed by the enzyme β-gal to become fluorescent at amplified levels due to just the activity of one protein. Xie had begun a project two years prior to his NDPA application proving this concept by showing that a modified β-gal protein could be used to monitor some components of gene expression in E. coli. For his NDPA work, Xie proposed to extend these studies to other cell lines and other fluorescent protein/substrate combinations.

Through his NDPA work, Xie was able to use his system to probe how enzymes work at the single molecule level and showed that the chemical dynamics at the single molecule level are different from those commonly expected based on classical equations in enzymology. He also observed the binding and unbinding of a single transcription factor on DNA, and then went on to show that this detachment from DNA is critical in

controlling a cell's phenotype. All of these projects resulted in publications in high-profile journals such as *Science* and *Nature*.

Xie also used his NDPA funds to build upon his initial work in CARS microscopy, increasing the sensitivity of it by an order of magnitude using frequency modulation, replacing the traditional laser with a cheaper and more stable laser source, and showing proof of principle of a CARS endoscopy. Xie used CARS to image brain structure and pathology for tissue identification purposes *ex-vivo*, and to study lipid structures in mouse skin in-vivo, which has appeared in *Science*. The many applications of CARS, including the above mentioned projects as well as others such as drug imaging, were summarized by Xie in an *Annual Review of Analytical Chemistry* article in 2008.

Junying Yuan (2005)

Junying Yuan was awarded the NDPA in 2005, five years after becoming a tenured professor of Cell Biology at Harvard Medical School. As a PhD candidate at Harvard University, Yuan worked in Bob Horvitz' lab at MIT, and together they pursued the controversial theory of programmed cell death. Later, Horvitz went on to win the Nobel Prize for characterizing programmed cell death, termed "apoptosis," in *C. Elegans*, and Yuan started her own lab at Massachusetts General Hospital where she made pioneering discoveries in the mammalian apoptotic pathway, identifying caspases, proteins which play an essential role in apoptosis.

In her NDPA application, Yuan proposed to expose DFNA9, a form of deafness caused by a mutation in the inner ear protein cochlin, as a new protein conformational disease, similar to Prion protein-related diseases such as Mad Cow Disease. Yuan intended to demonstrate the transmissibility of mutant cochlin through an inner ear injection in a mouse model, experimentally indicating that mutant cochlin can interfere with wild-type (WT) cochlin and cause protein aggregation in the inner ear, which could lead to cellular degeneration and mimic the DFNA9 disease phenotype of hearing loss. Yuan postulated that the mutant cochlin model could provide a novel system for studying the mechanisms by which aggregated, cytotoxic protein species were selectively degraded, and inform the treatment of such protein-related diseases.

Since receiving NDPA, Yuan and her colleagues have induced hearing loss in a mouse model after injecting mutant cochlin into the inner ear of a mouse, and have shown in vitro that the mutant protein induces cell death of cochlear fibrocytes, two phenotypic effects consistent with DFNA9 disease pathology. Yuan also conducted a chemical screen of over 500,000 compounds, in search of small molecules that can increase degradation of cochlin, and obtained 241 positive hits.

With the NDPA, Yuan has discovered the unanticipated involvement of cochlin in the immune system, by demonstrating cochlin controls the LPS/TLR4 inflammatory response pathway, an immune system pathway expressed in many human and mouse cell types. Specifically, Yuan has found that cochlin dimerization is modified by proteins in the TLR4 signaling pathway. Yuan has shown that when the cochlin gene is genetically turned off in mice (COCH -/-), pro-apoptotic caspase-11 could not be induced, and two immune protein genes, MHC I and II, were upregulated in the spleen. These results suggest cochlin may control an inhibitory mechanism in immune response.

Yuan has hypothesized that cochlin may be a major component of extracellular matrix of the spleen, and that secreted cochlin is cleaved and activated upon immune signaling. With NDPA, Yuan has found that mutant cochlin constitutively forms dimers, whereas WT cochlin dimerizes in response to immune signaling via the LPS/TLR4 pathway. In the future, Yuan intends to identify the proteins that cleave and activate cochlin, and to discover cochlin's target receptor. Yuan also plans to further investigate the compounds from the chemical screen that received positive hits for enhancing cochlin degradation.

Yuan hopes these findings will inform the mechanism by which mutant cochlin controls neurodegeneration in DFNA9, and will provide a new model for studying protein-related diseases. Finding the mechanism by which cochlin is cleared and degraded may help inform potential treatment for other diseases associated with protein aggregation or misfolding, such as Huntington's and Alzheimer's.

In order to control neuronal cell death induced by misfolded proteins, Yuan started to investigate a type of cell death mediated by a novel mechanism unrelated to caspases—which are essential for apoptosis. This led to the discovery of necroptosis, a programmed necrotic cell death pathway, and small molecule inhibitors of necroptosis, termed necrostatins. Necroptosis differs from apoptosis in that it is a cellular death pathway, initiated by factors extrinsic to the cell. These discoveries have led to the acceptance of necroptosis as an alternative programmed cell death mechanism activated by death receptors. Necrostatins have been licensed by a pharmaceutical company and at the time this was written, were currently under preclinical development. This discovery could potentially translate into new therapies for human diseases that currently have no treatments.

Appendix D: Survey of Unfunded Applicants Questionnaire

This appendix displays the full text of the online Survey of Unfunded Applicants (SUFA). The SUFA was launched on December 18, 2009, and unfunded researchers who submitted full applications to the NDPA program in fiscal years 2004 through 2007 were invited via email to participate. Repeat applicants were asked to respond based on their most recent application. The survey was open for twelve weeks and email reminders were sent to the pool of unfunded applicants every two weeks during that time period.

Page 1

Welcome to the Pioneer Award (NDPA) Impact Survey. Please provide responses to the following questions to the best of your ability. You may choose not to answer specific questions and it will not affect your ability to submit the survey.

Please use the navigation bar at the bottom of each survey page to navigate the survey. Please do not use your browser's navigation buttons. If you wish to review your responses at any point, click the "Review" button in the survey navigation bar.

If you would like to save and come back to the survey, please enable cookies in your browser, click the "Save" button at the bottom of any page, and use the original link you received to return to the survey. The survey should take approximately 15 minutes to complete.

To review the NDPA Request for Applications, criteria, or processes, please visit:

http://nihroadmap.nih.gov/pioneer/

Please note that participation in this survey is entirely voluntary. Your decision to participate will have no effect on your current or future NIH funding status. Respondent confidentiality will be protected to the extent provided by law, and only aggregate information concerning overall impressions will be reported to the NIH.

If you have questions or concerns regarding completing this survey, please contact us at NIHsurvey@ida.org

OMB# 0925-0606 Exp: 11/2012

Public reporting burden for this collection of information is estimated to average 15 minutes per respondent, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to: NIH, Project Clearance Branch, 6705 Rockledge Drive, MSC 7974, Bethesda, MD 20892-7974, ATTN: PRA (0925-0534). Do not return the completed form to this address.

To begin the survey, click the "Next" button below.

How would you rate your proposed NDPA idea on risk?
{Choose one}

( ) Not risky
( ) Of medium risk
( ) Very risky
( ) I do not know
( ) I cannot recall

Would you have chosen to seek NIH funding for your NDPA idea if the NDPA program did not exist?
{Choose one}

( ) Yes
( ) No
( ) I do not know
( ) I cannot recall

Prior to your NDPA application, had you received NIH funding?
{Choose one}

( ) Yes
( ) No

Which NIH grant(s) had you received prior to your NDPA application?
{Choose all that apply}

( ) R01
( ) R03
( ) R15
( ) R21
( ) R24
( ) R25
( ) R34
( ) R56
( ) A "K" Award (e.g. K08, K99, etc.)
( ) U01
( ) A Program Project/Center Grant (e.g. P01, P20, P30, P50)
( ) Other [ ]

From which NIH Institute(s)/Center(s) did you receive the above grant(s)? {Check all that apply}
{Choose all that apply}

( ) National Cancer Institute
( ) National Eye Institute
( ) National Heart, Lung, and Blood Institute
( ) National Human Genome Research Institute
( ) National Institute on Aging
( ) National Institute on Alcohol Abuse and Alcoholism
( ) National Institute of Allergy and Infectious Diseases
( ) National Institute of Arthritis and Musculoskeletal and Skin Diseases
( ) National Institute of Biomedical Imaging and Bioengineering
( ) National Institute of Child Health and Human Development
( ) National Institute on Deafness and Other Communication Disorders
( ) National Institute of Dental and Craniofacial Research
( ) National Institute of Diabetes and Digestive and Kidney Diseases
( ) National Institute on Drug Abuse
( ) National Institute of Environmental Health Sciences
( ) National Institute of General Medical Sciences
( ) National Institute of Mental Health
( ) National Institute of Neurological Disorders and Stroke
( ) National Institute of Nursing Research
( ) National Library of Medicine
( ) Center for Information Technology
( ) Center for Scientific Review
( ) Fogarty International Center for Advanced Study in the Health Sciences
( ) National Center for Complementary and Alternative Medicine
( ) National Center on Minority Health and Health Disparities
( ) National Center for Research Resources
( ) NIH Clinical Center

Was the research proposed in your NDPA application a significant departure from your previous research focus?
{Choose one}
( ) Yes
( ) No

In what way(s) did your proposed NDPA project differ from your previous research focus?
{Enter answer in paragraph form}
{Enter answer in paragraph form}
[ ]

In what way was your NDPA idea different from what is typically funded by the NIH?
{Choose all that apply}
{Choose all that apply}
( ) It had very little or no preliminary data
( ) It did not fall into the research interest of a single NIH Institute/Center
( ) It lacked an appropriate NIH study section
( ) As an investigator I had limited or no prior history in the proposed field
( ) I do not know
( ) My NDPA idea was not different from what is typically funded by the NIH.
( ) Other [ ]

In your opinion, what is the likelihood that your proposed NDPA research would have been supported by any other funding sources (including from NIH awards and beyond)?

From the NIH
{Choose one}
( ) Very unlikely
( ) Somewhat unlikely
( ) Somewhat likely
( ) Very likely

From Other Sources
{Choose one}
( ) Very unlikely
( ) Somewhat unlikely
( ) Somewhat likely
( ) Very likely

Why do you think your proposed NDPA research could or could not have been supported by other NIH funding sources?
{Enter answer in paragraph form}
{Enter answer in paragraph form}
[ ]

Why do you think your proposed NDPA research could or could not have been supported by other non-NIH funding sources?
{Enter answer in paragraph form}
{Enter answer in paragraph form}
[ ]

Please indicate which of the following statements (if any) are true of your proposed NDPA project:
{Choose all that apply}
{Choose all that apply}

( ) One or more of the fundamental ideas underlying my proposed research were at odds with prevailing wisdom
( ) My proposed research required use of equipment or techniques that have not been proven or are extraordinarily difficult
( ) My proposed research required knowledge of fields beyond my previously demonstrated area of expertise
( ) My research involved a novel combination of disciplines or an unprecedented scientific perspective
( ) None of these statements is true of my proposed research

Please elaborate on why the above statements are applicable or not applicable to your proposed NDPA project.
{Enter answer in paragraph form}
{Enter answer in paragraph form}
[ ]

Please indicate which of the following statements (if any) are true for the potential outcomes of your proposed NDPA project:
{Choose all that apply}
{Choose all that apply}

( ) My proposed research could result in the formulation of a novel idea (or set of ideas) that could instigate a new cognitive frame or advance theories to a new level of sophistication.
( ) My proposed research could result in the discovery of new empirical phenomena that could stimulate the generation of new theories.
( ) My proposed research could result in the development of a new methodology, enabling empirical testing of theoretical problems.
( ) My proposed research could result in the invention of novel instruments that could instigate new search perspectives and research domains.
( ) My proposed research could result in new integration of formerly disparate ideas into general theoretical laws enabling analyses of diverse phenomena within a common cognitive frame.
( ) None of these statements is a potential result of my proposed research.

Please elaborate on why the above statements are applicable or not applicable to your proposed NDPA project.
{Enter answer in paragraph form}
{Enter answer in paragraph form}
[ ]

Did you choose to pursue the idea(s) proposed in your NDPA application?
{Choose one}

( ) Yes, but only partially
( ) Yes, in its entirety
( ) No

{If "No"} **Why did you not pursue the idea proposed in your NDPA application?**
{Choose all that apply}
{Choose all that apply}

( ) I applied for grants to fund the project, but was unable to get the funding
( ) I am still gathering preliminary data to apply for other grants
( ) I did not apply for grants to fund the project
( ) I am no longer interested in the idea
( ) I do not have time to pursue the idea

( ) The work proposed has been done or is being done by someone else
( ) I made a decision that the idea was not practical/feasible
( ) Other [ ]

{Skip to Page 8}

{If "Yes"} **How were you able to work on the proposed NDPA project?**
{Choose all that apply}
{Choose all that apply}
( ) By using institutional funds
( ) By using other grants that I have
( ) I collaborated with a colleague who provides the funding
( ) I donated my time
( ) Other [ ]

Approximately how much funding from the above source(s) was used to work on the proposed NDPA project?
{Enter answer in dollars}
{Enter answer in paragraph form}
[ ]

Since your NDPA application, have you sought other funding for the proposed NDPA project?
{Choose one}
( ) Yes
( ) No

What was the funding source(s)?
{Choose all that apply}
{Choose all that apply}
( ) NIH
( ) Other Government Agencies
( ) Private Foundation
( ) Institutional Resources
( ) Other [ ]

Since your NDPA application, have you received other funding for the proposed NDPA project?
{Choose one}
( ) Yes
( ) No

What was the funding source(s)?
{Choose all that apply}
{Choose all that apply}
( ) NIH
( ) Other Government Agencies
( ) Private Foundation
( ) Institutional Resources
( ) Other [ ]

Approximately how much funding from the above source(s) was used to work on the proposed NDPA project?
{Enter answer in dollars}
{Enter answer in paragraph form}
[ ]

In order to pursue your proposed NDPA idea, to what extent did you modify the idea?
{Choose one}
( ) 1 Not At All
( ) 2
( ) 3 Somewhat
( ) 4
( ) 5 Completely

Please elaborate on the nature of these modifications.
{Enter answer in paragraph form}
{Enter answer in paragraph form}
[ ]

How complete is the work on the proposed NDPA idea?
{Choose one}
( ) 1 No Progress
( ) 2
( ) 3 Significant Progress
( ) 4
( ) 5 Complete

Has the work proposed in your NDPA application resulted in a presentation at a professional meeting(s) or public event(s)?
{Choose one}
( ) Yes
( ) No

If yes, how did you get selected to present at the meeting(s) or event(s)?
{Choose all that apply}
{Choose all that apply}
( ) I was invited by the organizers to give a presentation
( ) My presentation was selected through competitive submission
( ) The meeting or event was open submission, non-competitive

Has the work proposed in your NDPA application resulted in a publication(s)?
{Choose one}
( ) No
( ) Manuscript(s) in preparation
( ) Yes

If you selected yes or manuscript(s) in preparation, please specify the type of publication(s) that resulted from the proposed NDPA work.
{Choose all that apply}
{Choose all that apply}
( ) Original, peer-reviewed article
( ) Review article
( ) Opinion piece
( ) Other [ ]

Has the work proposed in your NDPA application resulted in a patent application or issued patent?
{Choose one}
( ) Yes
( ) No

Which of these best describes your research area?
{Choose one}
( ) Behavioral and Social Science
( ) Clinical and Translational Research
( ) Instrumentation and Engineering
( ) Molecular and Cellular Biology
( ) Chemical Biology
( ) Epidemiology
( ) Physiology and Integrative Systems
( ) Quantitative and Computational Biology
( ) Neuroscience
( ) Immunology
( ) Other [ ]

To date, how would you evaluate the realized impact of your proposed NDPA project?
{Choose all that apply}
{Choose all that apply}
( ) The idea has already made some contribution to the research area I selected above
( ) The idea has already made significant contribution to the research area I selected above
( ) The idea has already made some contribution to another research area
( ) The idea has already made significant contribution to another research area
( ) The idea is being considered for licensing or commercialization
( ) The idea has already been licensed or marketed commercially
( ) No impact so far
( ) I do not know

To date, how would you evaluate the potential impact of your proposed NDPA project?
{Choose all that apply}
{Choose all that apply}
( ) The idea has the potential to make some contribution to my research area
( ) The idea has the potential to make significant contribution to my research area
( ) The idea has the potential to make some contribution to another research area
( ) The idea has the potential to make significant contribution to another research area
( ) The idea has the potential to be considered for licensing or commercialization
( ) The idea has the potential to be licensed or marketed commercially
( ) I do not know

If you had received the NDPA award, what difference would it have made to your research, to your lab, etc.? Please estimate, if possible, the extent to which the NDPA would have accelerated the progress of your proposed project.
{Answer in paragraph form}
{Enter answer in paragraph form}
[ ]

Have other scientists given you any feedback on the realized impact of your project?
{Choose all that apply}
{Choose all that apply}

( ) Other scientists think that the idea has made some contribution to my research area
( ) Other scientists think that the idea has made a significant contribution to my research area
( ) Other scientists think that the idea has made some contribution to another research area
( ) Other scientists think that the idea has made a significant contribution to another research area
( ) I did not get any feedback
( ) I cannot recall

Have other scientists given you any feedback on the potential impact of your project?
{Choose all that apply}
{Choose all that apply}

( ) Other scientists think that the idea has the potential to make some contribution to my research area
( ) Other scientists think that the idea has the potential to make a significant contribution to my research area
( ) Other scientists think that the idea has the potential to make some contribution to another research area
( ) Other scientists think that the idea has the potential to make a significant contribution to another research area
( ) I did not get any feedback
( ) I cannot recall

Please indicate which of the following important developments have taken place since your NDPA application.
{Choose all that apply}
{Choose all that apply}

( ) I received an award(s)
( ) I was promoted
( ) I have received tenure
( ) I am applying for tenure
( ) I filed a patent application or have been granted a patent
( ) I received additional funding
( ) I expanded my research group
( ) I formed new partnerships/collaborations
( ) I changed my research focus
( ) I have expanded my research focus
( ) I changed institutions
( ) My work has been featured in the popular press and/or media
( ) I published an original, peer-reviewed article(s)
( ) Other [ ]

Which award(s) have you received since your NDPA application?
{Enter answer in paragraph form}
[ ]

In what way(s) has your research focus changed or expanded?
{Enter answer in paragraph form}
{Enter answer in paragraph form}
[ ]

To what extent was the change in your research area a result of applying to the NDPA program?
{Choose one}

( ) Completely
( ) To a large extent
( ) To some extent
( ) Not at all

In which journal(s) did you publish your peer-reviewed article?
{Enter text answer}
[ ]

Please describe any other impacts of the NDPA program not captured elsewhere in this survey.
{Enter answer in paragraph form}
{Enter answer in paragraph form}
[ ]

Please feel free to share any other thoughts related to the NDPA program or to this survey.
{Enter answer in paragraph form}
{Enter answer in paragraph form}
[ ]

In our effort to continue following the paths of creative researchers, we would like to administer this survey again in 2-3 years. It would be a tremendous help to have your input again. Would you be willing to complete this survey at that time?
{Choose one}
( ) Yes
( ) No
( ) Maybe

You have reached the end of the survey. To view a summary of your responses before submitting, click the "Review" button below. Click "Finish" to submit your responses.

Exit Page

Thank you for completing the Pioneer Award Impact Survey. We appreciate your help in the assessment of this important NIH program.

Please note that your responses will be kept strictly confidential. Only aggregate data from this assessment will be reported to NIH, and your participation will have no effect on your current or future NIH funding status.

Questions regarding this survey or the NDPA program evaluation can be directed to:

NIHsurvey@ida.org

Please close this browser window to exit the survey and to ensure accurate recording of your responses.

For more information on the NDPA program, please visit:

http://nihroadmap.nih.gov/pioneer/

Glossary

Age-weighted citation rate (AWCR). A metric that calculates the citation rate of a publication set while normalizing for the age in years of each publication considered. It allows for more equal comparisons of publication sets that have publications of different ages.

bibliometrics. A category of quantitative analysis that considers publication and citation data.

cited reference. From the reference point of an article published by an awardee, a publication that is cited by the awardee's article.

cited reference publication set. The collective body of references cited by a selected body of awardee publications. As an entity, it is the body of publications from which another publication set draws its knowledge. See cited reference.

citing reference. From the reference point of an article published by an awardee, a publication that cites the awardee's article.

Eigenfactor percentile. A percentile applied to each journal with an Eigenfactor Score. Of all journals with Eigenfactor Scores in their database, journals with the highest scores will be in the 90th percentiles. Journals with the lowest Eigenfactor Scores will be at or below the 10th percentile. See Eigenfactor Score.

Eigenfactor Score. A journal impact metric that is available free on Eigenfactor.org. Its calculation is based on the iterative concept that journals are more influential if they are cited often by other influential journals. A journal with a high score has a large citation impact.

expert. An individual who contributed their knowledge and opinions to the outcome evaluation expert review. See expert review.

expert review. One phase of the outcome evaluation conducted by STPI whereby three experts per Pioneer were asked to respond to questions about the awardees' research outcomes and the changes at NIH due to the Pioneer Award. The experts chosen were in the same field as the Pioneer whom they reviewed. There were 62 experts who participated; only 21 Pioneers were reviewed by experts and one expert reviewed two awardees.

HRWG. NIH High Risk Working Group

h-index. A publication-based metric that incorporates information on the number of publications by and the corresponding number of citations to a researcher. Researchers with high h-index values are roughly estimated to have had more impact on the scientific community than researchers with lower values.

impact factor. See journal impact factor.

integration score. An interdisciplinarity metric that captures the integration of knowledge across a cited reference publication set. A score of 0 means the publication set integrates a low diversity of information. A score of 1 means the publication set has high diversity in its cited references.

journal impact factor. A generic term for a metric that represents the impact of journal on the scientific community. See Eigenfactor Score.

macro-discipline. A high-level categorization of disciplines into broader fields. The 18 macro-disciplines were derived from a factor analysis grouping of journals in Web of Science subject categories (Leydesdorff and Rafols 2009).

map of science. A physical map created by academic researchers to represent relationships among different fields of science. Each node on the map represents one Thomson Reuters (ISI) Web of Science subject category, while lines on the map indicate relationships between subject categories. The identification of relationships and the assessments of relationship strength were made based on citing reference and cited reference subject categories. The underlying map is static, in that the relationships it captures refer to a specific point in time.

map of science overlay. A visual representation of the subject categories of a publication set of an individual or group.

NDPA. An abbreviation for *NIH Director's Pioneer Award*.

NDPA-attributed publication. A publication that acknowledges NDPA funding in its funding acknowledgments section.

NIH. An abbreviation for *National Institutes of Health*.

original publications. A publication set that comprises articles with original research material. Document types categorized under this designation include journal articles, reviews, meeting abstracts, and proceedings papers.

original publications excluding reviews. A publication set that comprises journal articles, meeting abstracts, and proceedings papers. In this report, this publication set is used only for bibliometric citation analysis.

panel of reviewers. A group of non-NIH reviewers that conducted interviews with Pioneer Award finalists as part of the selection process. There were eight reviewers on the FY 2004 panel and thirteen reviewers on the FY 2005 panel.

post-NDPA. Refers to the period of years after the researcher received the Pioneer Award. For the 2004 cohort, this period is from 2005 to 2010. For the 2005 cohort, this period is from 2006 to 2010. It is important to note that awardees were receiving Pioneer Award funding throughout the post-NDPA period.

pre-NDPA. Refers to the period of years before the researcher received the Pioneer Award. For the 2004 cohort, this period is from 1999 to 2004. For the 2005 cohort, this period is from 2001 to 2005.

publication set. A collection of publications defined by parameters such as authorship, time range, or body of knowledge referred to. It may also apply to the collection of articles published by an individual or group.

R01. An activity code that represents the traditional funding mechanism at NIH.

reviewer panel. See panel of reviewers.

Science and Technology Policy Institute (STPI). A federally funded research and development center managed by the Institute for Defense Analyses (IDA). NIH commissioned STPI to perform an outcome evaluation of the NDPA.

specialization score. An interdisciplinarity metric that captures the scope of knowledge of a researcher's or group's publication set. A score of 0 means the publication set is unspecialized, while a score of 1 means the publication set is very specialized into one discipline.

subject category. A field tag in Web of Science that describes the subject focus of the journal to which it is applied. Subject categories are self-reported by journals to Web of Science, and more than one subject category may be applied to one journal.

VantagePoint. A computer software with data cleaning, text mining, data analysis and visualization, and data management capabilities.

Web of Science. An online publications database with coverage of the sciences, social sciences, arts, and humanities. It provides information on publications, citations, disciplines, authors, and more.

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