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

Case Studies

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1. Introduction

This supplement to "Outcome Evaluation of the National Institutes of Health (NIH) Director's Pioneer Award (NDPA), FY 2004–2005: Final Report" presents detailed case studies for 22 NDPA awardees. The NDPA was initiated in FY 2004 as part of the NIH Roadmap for Medical Research, which strived to establish programs that promoted high-impact, cutting-edge, research, which often did not fall within the purview of a single NIH institution or center. [1] Based on the premise that great individuals—not solely great research plans–result in groundbreaking ideas, the NDPA aimed to award investigators who demonstrated the skills and creativity to take productive risks and make significant contributions to biomedical research.[2]

In 2008, the IDA Science and Technology Policy Institute (STPI) was commissioned by the NIH to conduct an outcome evaluation to assess whether the outcomes of the program were consistent with its original goals, and to evaluate the impact of the NDPA on NIH and its funding of high-risk research. The outcome evaluation was designed to follow the research achievements of the first two cohorts of NDPA awardees (FY 2004–2005). The main report provides aggregate and anonymous data on the awardees and their research outcomes. This companion volume provides detailed information and follows a case study approach for each awardee.

Case studies were performed for each of the awardees in order to determine whether their research was indeed pioneering, and to examine the impact of their NDPA-funded research on their students, their institutions, the NIH, and the greater research community. A cross-sectional case study approach was used for the outcome evaluation due to the inherent difficulties of measuring pioneering research.

Several data sources informed the case studies:

1. Detailed interviews were conducted with each of the awardees;
2. STPI asked external experts in the awardees' fields to conduct a review of the awardees' post-award research accomplishments (hereafter referred to as the "expert review" or the "experts");[3]

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[1] *See* the Roadmap Initiative website for more details: http://nihroadmap.nih.gov/overview.asp.

[2] The NIH Director's Pioneer Award Program press release, January 20, 2004. Available online at http://nih.gov/news/pr/jan2004/od-20.htm.

[3] The expert review was organized by STPI, and completely differs from the panel of reviewers who interviewed the finalists during the application process.

3. The awardees' application data, including their original NDPA proposals, application scores, and progress reports for each year of the funding period were obtained by the NIH;
4. Web-based NDPA materials such as the Request for Applications (RFA), the Program Announcements (PA) and the web profiles of the NDPA awardees were used;
5. Full records of the awardees' publications before and after receiving the NDPA were downloaded from the database Web of Science, and were used to conduct the bibliometric analyses in the case studies. Web of Science and NIH RePORTER were used to identify which articles were attributed to NDPA funding.

Each Pioneer case study follows a similar five-section structure:

Section 1, Research Summary, provides background information on each awardee's history as a researcher, describes the NDPA proposal, outlines the research the awardee had been performing before receiving the award, and summarizes the activities and outcomes of the Pioneer under the NDPA. Sources of information for this section were: NDPA application essays, awardee progress reports, and awardee publications. Awardees were asked to edit and approve their research summaries. Research summaries were edited and approved by the Pioneer awardees. These research summaries were also provided to the experts who reviewed the awardees' accomplished research.

Section 2, NDPA Reviewer Selection Panel Opinions, describes the commentary the NDPA panel of reviewers provided during the application process. During the application and selection process, finalists were invited to interview before a panel of reviewers, and the panel wrote a summary statement to aid the NIH director in his selection of awardees. The summary statement intended to explain the candidate's appropriateness for the Pioneer Award mechanism. This section provides insight into how the panel defined "pioneering research" and identified potential "pioneers." The summary statements written by the panel of reviewers were obtained from the NIH, along with the applications and reviewer scores.

Section 3, Nature of Project Risks and Outcomes, characterizes the pioneering nature of the awardees' research. As part of this outcome evaluation, three experts per awardee were asked to assess whether the research they reviewed was pioneering. Furthermore, the experts and the awardees themselves characterized the proposal risks and outcomes of the research of each Pioneer. Proposal risks were characterized using a typology suggested by former NSF Director Rita Colwell:[4]

- Conceptual Risk: Fundamental ideas of the project are at odds with the prevailing wisdom.

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

- Technical Risk: Proposals require equipment, techniques, or approaches that either have not been tried or are assumed to be extraordinarily difficult (i.e., crystallization of a membrane protein).
- Experience Risk: Investigators are proposing to work outside their previously demonstrated areas of expertise.
- Multidisciplinary Risk: Proposals entail unprecedented combinations of disciplines or have criteria of success that involve viewing the results from an unfamiliar multidisciplinary perspective.

Potential creative outcomes were characterized using a typology by Thomas Heinze:[5]

- New Idea: The project may result in the formulation of new ideas that open up a new cognitive frame or bring theoretical claims to a new level of sophistication (i.e., theory of special relativity).
- New Phenomenon: The project may result in the discovery of new empirical phenomena that stimulate new theorizing (i.e., the observation of biodiversity spurred the theory of evolution).
- New Methodology: The project may develop new methodologies by which theoretical problems could be empirically tested (i.e., factor analysis generated the theory on mental abilities).
- New Technology: The project may invent novel instruments that open up new research perspectives and domains (i.e., scanning tunneling microscopy opened up the field of nanotechnology).
- New Framework: The project may synthesize formerly dispersed existing ideas into general theoretical laws that enable analyses of diverse phenomena within a common cognitive frame (i.e., general systems theory was a combination of biology, cybernetics, and sociology).

Section 4, Value of the NDPA Program, illustrates how the awardees and experts perceive the value of the NDPA program. Awardees considered value from the perspective of how the NDPA changed the way they conduct research. Experts discussed value in the context of how the Pioneer Award is adding value to the NIH research portfolio and changing the culture of NIH.

Section 5, Descriptive Bibliometrics, describes the outcome of bibliometric analyses to compare the research performed before and after the award and to characterize the publications attributed to NDPA funding. The bibliometric analysis was separated into four categories:

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[5] Thomas Heinze and Gerrit Bauer. 2007. "Characterizing creative scientists in nano-S&T: Productivity, multidisciplinarity, and network brokerage in a longitudinal perspective." *Scientometrics* 70(3): 811-830. doi: 10.1007/s11192-007-0313-3.

productivity, impact, interdisciplinarity, and collaboration. Awardee productivity is captured through the number of original publications and the publication rate.

The impact of awardee research was estimated through the citations to awardee publications and journal impact factors. Citation analyses include number of citations, age-weighted citation rate (AWCR),[6] and h-index.[7] Journal impact factors are taken from Eigenfactor.org, a free website that provides *Eigenfactor* scores based on the concept that a journal is influential "if it is cited often by other influential journals."[8] The *Eigenfactor* ranking system also claims to account for the prestige of a citing journal and differences in citation patterns among disciplines. To facilitate easier comparisons of impact factors between the pre- and post-NDPA periods, analyses were performed on the *Eigenfactor* percentiles of the journals in which awardees published. Impact was estimated by counting the number of publications in journals at or above the 98th *Eigenfactor* percentile. *Eigenfactor* scores at the 98th percentile and above encompass prestigious disciplinary and multidisciplinary journals such as: *Nature*, *Science*, *Neuron*, *Cell*, *Blood*, *Journal of Biological Chemistry*, *European Journal of Neuroscience*, *Bioinformatics*, and *Journal of the American Chemical Society*.[9]

Interdisciplinarity was assessed by examining the fields in which awardees published and the fields cited by awardees. The broad field categories in this volume are called "macro-disciplines."[10] Indicators of interdisciplinarity used in this report include: the number and categories of macro-disciplines in which awardees publish and cite, maps of science, and integration (I) and specialization (S) scores. A map of science is a visual representation of the

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[6] While the AWCR normalizes for the number of years since publication, it can never fully adjust for the effects of time on citation patterns. It takes time for an article to be identified as important in its field, so new articles have the inherent disadvantage of being less read, and therefore less cited. Additionally, it takes time for research influenced by awardee research to cite the awardee research in a publication. Furthermore, after an article is cited for the first few times, the number of places where a potential citing researcher may find it increases dramatically; this renders the citation of older and more established articles much more likely.

[7] Citations to review articles were excluded from the citation analyses because they are highly cited documents and often cited without reference to analysis in the review. Other bibliometric analyses draw from all original publications: journal articles, reviews, meeting abstracts, and proceedings papers.

[8] *See* http://eigenfactor.org/methods.htm, accessed November 18, 2010. *Eigenfactor scores* were not found for several of the Pioneers' sources. Reasons for this may include: the journal is new and *Eigenfactor scores* rely on the five previous years' citation data, the source is not a journal, the source is not a journal that is registered with ISI, or the source no longer exists.

[9] Based on 2008 *Eigenfactor* value percentiles, Eigenfactor.org.

[10] The 18 "Macro-disciplines" to which this report refers were identified by Leydesdorff and Rafols using factor analysis. They compared two nearly decomposable matrices created using the factor analysis; one matrix consisted of citing data, which is based on the patterns of subject categories citing journals, while the other matrix consisted of cited data, which is based on the subject categories of the cited references of a journal set. The subject categories, upon which the analysis and 14 of the macro-disciplines are based, are those defined by Thomson ISI in the Science Citation Index. They performed a similar analysis to identify 4 more macro-disciplines based on the Thomson ISI Social Science Citation Index.

Loet Leydesdorff and Ismael Rafols. (2009). "A global map of science based on the ISI subject categories." *Journal of the American Society for Information Science and Technology*, 60(2), 348–362.

relationships among scientific disciplines. Cited references were overlaid onto a map of science in order to characterize research focus and scope. Maps of science were created for only five of the awardees because it was found that they did not provide a unique dimension of analysis for our purposes.[11] Integration (I) and specialization (S) scores are quantitative measures of interdisciplinarity. Integration scores measure the "extent to which a research article cites diverse subject categories."[12] When applied to a publication set, it may refer to the diversity and distribution of the body of knowledge from which the publication set draws. Specialization "considers the spread of subject categories in which the body of research…is published."[13] Collaboration was examined through the lens of co-authorship. Indicators used to measure collaboration included the median number of authors on a group of publications and the number of unique authors in a researcher's publishing network.

[11] Each node represents a different ISI subject category. Lines span the nodes that represent related subject categories. Spatially, nodes that are closer to each other are more closely related, but distortions may have occurred by changing the dimensions of the image. The labels on the image refer to macro-disciplines. They are shown in preference to the labels of all of the subject categories for ease of reading.

[12] A. L. Porter, A. S. Cohen, D. Roessner, and M. Perreault. 2007. Measuring researcher interdisciplinarity. Scientometrics, 72(1), pp. 117–149.

[13] Higher integration scores represent an integration of a greater diversity of research knowledge while higher specialization scores are indicative of a tight focus on one or a few subfields. Further information on I and S scores can be found in the literature review of the main report.

2. Aggregate Analyses

Table 1, Figure 1, and Table 2 summarize the qualitative analyses, expert review, and bibliometric analyses, respectively, for the group of awardees profiled in these case studies.

Table 1. Pioneers at a Glance: Qualitative Analyses

Pioneer	Research Area[a]	What did the awardees propose to do with the NDPA funds in their applications?[b]	How did the proposal differ from the research conducted by Pioneers before receiving the award?[b]	How did the actual NDPA research differ from the NDPA proposals?[b]	What have the NDPA funds allowed awardees to do that would not be possible with traditional funding sources? (Pioneer)[c]	What are the applications of awardee research to the diagnosis and treatment of disease? (Pioneer)[c]	In what ways has the NDPA played a role in changing the awardees' research fields over the past five years? (Experts)[d]
Abbott	Quantitative and mathematical biology	Test a specific hypothesis or set of hypotheses	Broaden the focus of their research to a grander systems level	Broad research goals were met or continue to progress	• Follow a natural research trajectory • Take a long term view • Spend more time on lab research	Awareness of potential long-term applications	• NDPA work has influenced other researchers • Too early to tell • Connected formerly disparate research fields
Chandler	Molecular and cellular biology	Pursue and open-ended research objective	Apply previous research methods and ideas to new biomedical issues	Original plan evolved into the research conducted under the NDPA	• Undertake resource-intensive projects • Take a long term view	Awareness of potential long-term applications	• Changed prevailing wisdom/ provided novel perspective • Major contributor
Cline	Molecular and cellular biology	Develop a new technology or approach to research	Broaden the focus of their research to a grander systems level	Original plan evolved into the research conducted under the NDPA	• Follow a natural research trajectory • Take a long term view	Studies with implications for disease treatment and diagnosis underway	• No significant contributions • NDPA work has influenced other researchers
Cosmides	Behavioral and social sciences	Test a specific hypothesis or set of hypotheses	Conduct new experiments that support their existing hypotheses	Broad research goals were met or continue to progress	• Follow a natural research trajectory • Take a long term view • Spend more time on lab research	Research already having an impact	• Increased the research field's visibility • Connected formerly disparate research fields

Pioneer	Research Area[a]	What did the awardees propose to do with the NDPA funds in their applications?[b]	How did the proposal differ from the research conducted by Pioneers before receiving the award?[b]	How did the actual NDPA research differ from the NDPA proposals?[b]	What have the NDPA funds allowed awardees to do that would not be possible with traditional funding sources? (Pioneer)[c]	What are the applications of awardee research to the diagnosis and treatment of disease? (Pioneer)[c]	In what ways has the NDPA played a role in changing the awardees' research fields over the past five years? (Experts)[d]
Daley	Molecular and cellular biology	Develop a new technology or approach to research	Remain in the same field but proposed a project with a distinctly different, lateral (in scope), focus	Original plan evolved into the research conducted under the NDPA	• Follow a natural research trajectory • Take a long term view • Spend more time on lab research	Discoveries of health-related applications within 10 year timeframe	• Major contributor
de Lange	Molecular and cellular biology	Develop a new technology or approach to research	Broaden the focus of their research to a grander systems level	Original plan evolved into the research conducted under the NDPA	• Undertake resource-intensive projects • Follow a natural research trajectory	Awareness of potential long-term applications	• Major contributor
Deisseroth	Physiological and integrative systems	Develop a new technology or approach to research	Apply previous research methods and ideas to new biomedical issues	Broad research goals were met or continue to progress	• Follow a natural research trajectory • Take a long term view	Studies with implications for disease treatment and diagnosis underway	• Major contributor • Developed new techniques
Harbury	Instrumentation and engineering	Develop a new technology or approach to research	Apply previous research methods and ideas to new biomedical issues	Broad research goals were met or continue to progress	• Follow a natural research trajectory • Spend more time on lab research	Discoveries of health-related applications within 10 year timeframe	• Too early to tell • No significant contributions
Hellinga	Quantitative and mathematical biology	Develop a new technology or approach to research	Apply previous research methods and ideas to new biomedical issues	Original plan evolved into the research conducted under the NDPA	• Follow a natural research trajectory	Awareness of potential long-term applications	• No significant contributions

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Jarvis	Behavioral and social sciences	Test a specific hypothesis or set of hypotheses	Conduct new experiments that support their existing hypotheses	Broad research goals were met or continue to progress	• Follow a natural research trajectory • Take a long term view • Spend more time on lab research • Improve their labs	Awareness of potential long-term applications	• Connected formerly disparate research fields • Major contributor
McCune	Pathogenesis and epidemiology	Test a specific hypothesis or set of hypotheses	Conduct new experiments that support their existing hypotheses	Broad research goals were met or continue to progress	• Undertake resource-intensive projects • Follow a natural research trajectory	Studies with implications for disease treatment and diagnosis underway	• Changed prevailing wisdom/ provided novel perspective
McKnight	Molecular and cellular biology	Pursue and open-ended research objective	Broaden the focus of their research to a grander systems level	Broad research goals were met or continue to progress	• Undertake resource-intensive projects • Follow a natural research trajectory • Improve their labs	Discoveries of health-related applications within 10 year timeframe	• Major contributor • Increased the research field's visibility
Mirkin	Other	Develop a new technology or approach to research	Apply previous research methods and ideas to new biomedical issues	Broad research goals were met or continue to progress	• Follow a natural research trajectory	Studies with implications for disease treatment and diagnosis underway	• No significant contributions • Major contributor
Phillips	Quantitative and mathematical biology	Pursue and open-ended research objective	Apply previous research methods and ideas to new biomedical issues	Broad research goals were met or continue to progress	• Take a long term view • Spend more time on lab research • Improve their labs	Awareness of potential long-term applications	• Connected formerly disparate research fields

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Quake	Instrumentation and engineering	Develop a new technology or approach to research	Apply previous research methods and ideas to new biomedical issues	Broad research goals were met or continue to progress	• N/A	N/A	• Major contributor
Rando	Molecular and cellular biology	Pursue and open-ended research objective	Broaden the focus of their research to a grander systems level	Original plan evolved into the research conducted under the NDPA	• Undertake resource-intensive projects • Follow a natural research trajectory • Take a long term view • Spend more time on lab research	Studies with implications for disease treatment and diagnosis underway	• NDPA work has influenced other researchers
Smith	Quantitative and mathematical biology	Develop a new technology or approach to research	Apply previous research methods and ideas to new biomedical issues	Broad research goals were met or continue to progress	• Follow a natural research trajectory • Take a long term view • Spend more time on lab research • Improve their labs	Research already having an impact	• Major contributor • No significant contributions
Tononi	Physiological and integrative systems	Test a specific hypothesis or set of hypotheses	Conduct new experiments that support their existing hypotheses	Broad research goals were met or continue to progress	• Take a long term view • Spend more time on lab research • Improve their labs	Discoveries of health-related applications within 10 year timeframe	• Major contributor • Developed new techniques

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Waterman	Quantitative and mathematical biology	Pursue and open-ended research objective	Broaden the focus of their research to a grander systems level	Original plan evolved into the research conducted under the NDPA	• Follow a natural research trajectory • Improve their labs	N/A	• N/A
Wolfe	Molecular and cellular biology	Pursue and open-ended research objective	Apply previous research methods and ideas to new biomedical issues	Broad research goals were met or continue to progress	• Follow a natural research trajectory • Spend more time on lab research	Research already having an impact	• NDPA work has influenced other researchers • Too early to tell • Connected formerly disparate research fields
Xie	Instrumentation and engineering	Develop a new technology or approach to research	Remain in the same field but proposed a project with a distinctly different, lateral (in scope), focus	Broad research goals were met or continue to progress	• Follow a natural research trajectory • Take a long term view • Spend more time on lab research	Discoveries of health-related applications within 10 year timeframe	• Major contributor
Yuan	Molecular and cellular biology	Test a specific hypothesis or set of hypotheses	Remain in the same field but proposed a project with a distinctly different, lateral (in scope), focus	Original plan evolved into the research conducted under the NDPA	• Follow a natural research trajectory • Spend more time on lab research	Studies with implications for disease treatment and diagnosis underway	• No significant contributions • NDPA work has influenced other researchers

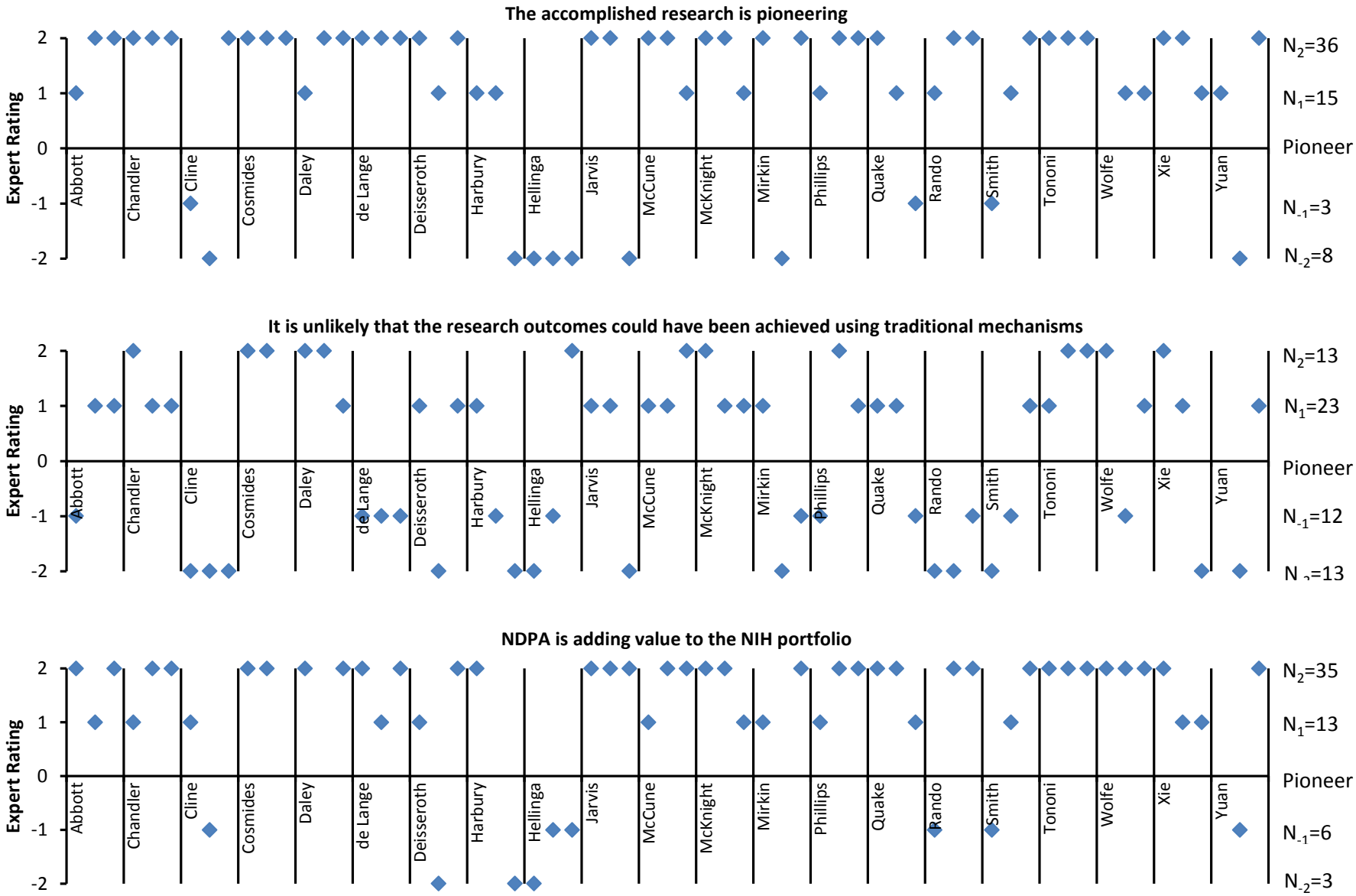
Sources:

[a] Awardee applications to the NDPA.

[b] Awardee applications to the NDPA, publications in Web of Science, Pioneer interviews, Expert review.

[c] Pioneer interviews.

[d] Expert review.



Source: Expert review.

Notes: Experts were asked to score these questions on a rating scale: –2 is strongly disagree, –1 is moderately disagree, 1 is moderately agree, and 2 is strongly agree.

Figure 1. Pioneers at a Glance: Expert Review

Table 2. Pioneers at a Glance: Bibliometrics

	Career-Long Metrics			Pre-NDPA and Post-NDPA				Attributed to NDPA Funding		
Pioneer	Number of Publications (Total)	Number of Citations (Total)	H-index	Number of Publications (Pre-NDPA)	Number of Publications (Post-NDPA)	Number of Citations (Pre-NDPA	Number of Citations (Post-NDPA)	Publication Year of First NDPA-Attributed Publication	Number of Publications (Attributed to NDPA)	Number of Citations (Attributed to NDPA)
Abbott	134	10,380	54	31	17	1,896	277	2009	2	22
Chandler	76	6,609	31	15	13	448	255	2008	1	32
Cline	82	4,319	34	20	21	1,140	329	2007	4	32
Cosmides	41	2,294	18	15	8	356	101	2006	5	30
Daley	240	9,640	44	73	137	4,448	2,902	2008	24	580
de Lange	111	14,953	61	27	24	3,375	721	2008	5	103
Deisseroth	68	4,283	27	8	45	987	1,026	2008	10	199
Harbury	32	2,325	17	11	9	348	97	2007	5	58
Hellinga	70	2,649	31	27	16	1,216	147	2006	8	34
Jarvis	59	2,404	23	14	19	1,049	189	2006	8	142
McCune	130	7,855	43	40	32	3,057	596	2007	17	315
McKnight	97	20,881	53	13	13	2,005	362	2009	3	11
Mirkin	461	28,238	72	157	232	16,293	5,803	2006	45	661
Phillips	76	1,866	24	26	34	781	484	2006	12	149
Quake	106	7,078	41	48	52	5,115	1,415	2006	13	265
Rando	93	3,434	30	41	19	1,385	546	2009	3	18
Smith	21	1,235	13	6	12	749	389	2007	8	371
Tononi	198	4,642	37	58	87	1,567	807	2007	17	251
Wolfe	44	750	15	19	22	577	100	2005	10	74
Xie	136	7,125	43	54	58	3,257	2,172	2007	8	313
Yuan	156	18,617	57	33	49	2,217	740	2006	7	134

Source: Web of Science, NIH RePORTER.

3. Case Studies

A. Larry Abbott (2004)

1. Research Summary

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 conductances 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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers believed that Abbott had evidence of a pioneering past, particularly when considering his switch from physics to neuroscience earlier in his career. While his proposal on neural circuit dynamics was an extension of his current work, the panel believed that there was still a high risk of failure involved. The panel was "enthusiastic that Dr. Abbott [embodied] the traits and qualities of a pioneer."

3. Nature of Project Risks and Outcomes

Both the Pioneer and the three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 3 and Table 4).

a. Typology of Project Risks

Table 3. Characterization of Unique Project Risk (Abbott)

Please indicate which of the following risks are applicable to the NDPA-funded project	Abbott	Expert 1	Expert 2	Expert 3
Conceptual risk	x	x	x	x
Technical risk		x	x	
Experience risk	x			x
Multidisciplinary risk	x			x
None of these risks				

Source: Pioneer interview, Expert review.

At least two of three experts thought Abbott's work contained conceptual and technical risks. Abbot himself believed his work included conceptual, experience, and multidisciplinary risks.

Abbott was able to comment on the relationship between his project and the risk typology mentioned above. While he said that his work on understanding "input-driven brains" did not operate under new assumptions or ideas, Abbott mentioned that the framework was "not conventional," and this was the aspect that made his work risky. He also explained that the techniques he used in his proposal were not risky because they were already known, "especially in the mathematics community."

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Abbott's research:

> Studying networks with random synaptic connectivity could be viewed as novel and controversial in neuroscience, depending on one's prior beliefs about randomness.
>
> The advantage of randomness in networks (Abbott's hypothesis) is counterintuitive and not at all obvious even after one has seen examples."
>
> The work is truly interdisciplinary, incorporating sophisticated theory and mathematics, but also providing serious connection to and adherence to the constraints of experimental data.

Experts noted primarily the way in which Abbott's research substantiated a new hypothesis that was vastly different from current models (i.e., "the advantage of randomness in networks"), and the interdisciplinary nature of his work (i.e., "theory and mathematics", "theoretical neuroscience and…computer science").

b. Typology of Potential Outcomes

Table 4. Characterization of Potential Pioneering Outcomes (Abbott)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Abbott	Expert 1	Expert 2	Expert 3
New Idea	x	x	x	x
New Phenomenon	x	x		
New Methodology	x			
New Technology			x	
New Framework		x	x	x
None of these outcomes				

Source: Pioneer interview, Expert review

At least two of three experts believed Abbott's research had the potential to advance new ideas and form the underlying basis for a new framework. Abbott thought his research had the potential to result in the formulation of new ideas, the observation of new phenomena, and the development of new methodology.

Abbott remarked that the NDPA allowed him to develop "a descriptive framework" based on the theoretical models he had developed prior to the project. With newfound understanding, he foresees the next step as applying the models to experiments.

Below is a selection of comments from experts that justify their evaluations of the potential pioneering outcomes of Abbott's research:

> The work on balanced excitation/inhibition has elevated this concept…to a much more substantial hypothesis…The work on the olfactory system has synthesized several lines of experimental and theoretical work, including normalization models and randomized sparse networks.
>
> New theoretical ideas and methods about the dynamics of neural networks were developed…the work established some bridge between theoretical neuroscience and related work in computer science on random networks.
>
> How networks on the edge of chaos can nonetheless be sensitive enough to process input and achieve stable patterns of activity is likely to be broadly relevant across brains of different species… The paper is likely to be an important contribution to our theoretical understanding of how recurrent neural nets work—these are networks present in many important regions of all brain (e.g., the hippocampus in humans).

His presentation of new hypotheses and synthesis of information from multiple fields seemed to be the underlying explanation for how Abbott was considered pioneering.

c. Assessing Whether the Research Was Pioneering

The experts were also asked to rate whether Abbott's research was pioneering. Two experts strongly agreed and one expert moderately agreed that Abbott's research was pioneering. Below is a selection of comments from experts that justify their ratings:

> Of the three papers included in the packet, the olfactory paper is most pioneering. It represents new work for the PI, and develops important bridges between disparate types of model, applied to a system (olfaction) that has defied modeling efforts in the past.
>
> Histogram equalization (the main idea in the Luo paper) has already been proposed in the context of sensory systems (Simon Laughlin, in the fly visual system). However, it is certainly novel in the context of the olfactory system.
>
> Sparse coding in the mushroom body has already been explored extensively both experimentally and computationally by Gilles Laurent's lab, making it difficult to say it was truly pioneering research.

The olfactory paper given to reviewers was considered to be the most pioneering because of its implications for a model in the olfactory system.

4. Value of the NDPA Program

a. Pioneer Perspective

Abbott stated that the NDPA gave him the freedom in his research. From now on, he "will probably be more adventurous" by performing the "no turning back even without that source of funding" kind of research. He appreciated the ability "to try something hard and go through the period when you know you are kind of lost." He also expressed that the NDPA enabled him to be more flexible; he stated that "on a regular grant, you don't get a long enough detour" to follow the course of your research. In Abbott's opinion, the NDPA was essentially "a vision statement" with which he was able to go forward and study. He "didn't have a plan" and his opinion, "if a theorist… [has] the next five years planned, they generally have a boring project." In his case, "there was a period when [his lab was] building these wrong models," but since they were not funded through "a conventional grant," they didn't worry about having holes of apparent inactivity in their CVs. If he had not gotten the Pioneer Award, Abbott noted that he would have progressed on the project more slowly or tried to get an NSF grant because "NSF has a…more broad-minded science objective."

b. Expert Perspective

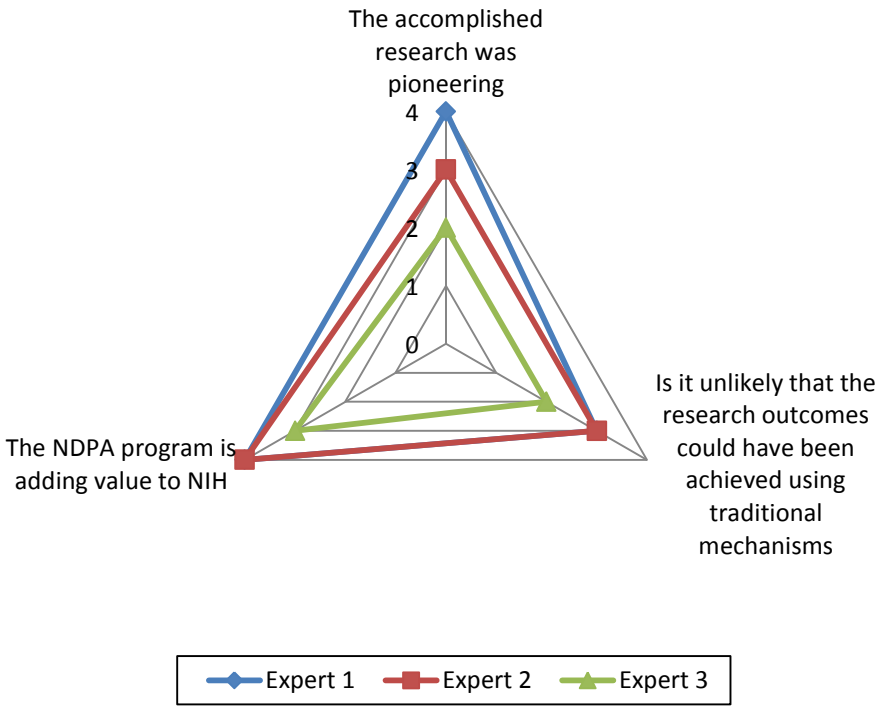
Experts were asked to rate whether Abbott's results were a unique output of the Pioneer Award and whether the Pioneer Award is adding value to NIH (Figure 2).

Two experts moderately agreed and one expert moderately disagreed that it is unlikely that Abbott's research outcomes could have been achieved under traditional funding mechanisms. Two experts strongly agreed and one moderately agreed that the NDPA is adding value to NIH. Below is a selection of comments from reviewers about the value of the NDPA program:

> If the goal was to push science into newer frontiers not achievable with other funding mechanisms, I'm not sure this has necessarily been achieved here. Theory/computational work does not need too much more than support for personnel and computing power and freedom from distractions. Although I believe the Pioneer Award helped Abbott…it's not clear they would not have been achieved by more traditional NIH mechanisms.
>
> The research was not necessarily tied to a particular experimentalist's research program, but could potentially have impact on many experimentalists. Some of this research might have been difficult to fund by traditional mechanisms.
>
> Certainly some of this work could have been done under traditional grant mechanisms. But I believe that quite a bit of it resulted from giving the PI the freedom to pursue new connections and ideas. This is especially important for theorists who…are able to notice and rapidly explore the relationships between seemingly disparate experimental findings.

> 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…without unwavering support for at least five years.

Experts were mixed about whether Abbott's research could have been pursued under traditional funding mechanisms, but they were generally in agreement that the NDPA gives PIs the potential to push the boundaries of current science.



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 2. Experts' Opinions of the NDPA (Abbott)

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Abbott received the Pioneer Award in 2004, the pre-NDPA range refers to activity between 1999 and 2004, while the post-NDPA range refers to activity between 2005 and 2010.

a. Productivity

Abbott published a total of 134 original articles over the 32 years of his research career for an average rate of 4.19 original publications per year (Table 5). During the pre-NDPA period,

Abbott published 31 original publications for a rate of 5.17 per year. During the post-NDPA period, he published 17 publications for a rate of 2.83 per year. [14]

Table 5. Summary of Publication Activity (Abbott)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	31	17	2	134
Number of Years	6	6	N/A	32
Publication Rate	5.17	2.83	N/A	4.15

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Abbott published more original works during the pre-NDPA period as compared to the post-NDPA one. The drop in his post-NDPA publication rate may or may not be NDPA-related. It should be noted that Abbott moved his lab from Brandeis to Columbia during his NDPA funding period; this move may have affected his ability to publish as productively as he had in the past.

Of the 17 articles Abbott published in the period after receiving the award, only two were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 6.

Table 6. Publications Attributed to NDPA Funding (Abbott)

Title	Journal	Year Published
Gating multiple signals through detailed balance of excitation and inhibition in spiking networks	Nature Neuroscience	2009
HCN hyperpolarization-activated cation channels inhibit EPSPs by interactions with M-type K+ channels	Nature Neuroscience	2009

Source: Web of Science, NIH RePORTER.

[14] In his interview, Abbott noted that he believed he has always published at about the same rate.

b. Impact

1) Citation Analyses

For the full length of his career, as of August 2010, Abbott's 130 original publications excluding reviews had been cited a total of 10,380 times. In the post-NDPA period, Abbott published 16 publications that had received a total of 277 citations by August 2010. Two of those 16 publications were attributed to NDPA funding and they received a total of 22 citations.

Total number of citations and age-weighted citation rate do not display unexpected results. Abbott is cited fewer times per publication in the post-NDPA period than either the full career or pre-NDPA publication sets.

Statistics on Abbott's publications set are displayed in Table 7.

Table 7. Summary of Citation Analyses (Abbott)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (130 pubs)	10,380	25.48	54
Pre-NDPA (30 pubs)	1,896	13.82	N/A
Post-NDPA (16 pubs)	277	7.69	N/A
Attributed to NDPA Funding (2 pubs)	22	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science.

2) Journal Impact Factors

Abbott published 31 publications in thirteen different sources during the pre-NDPA period and 17 publications in twelve different sources during the post-NDPA period. Detailed information on Abbott's most published-in journals for the pre- and post-NDPA periods are displayed in Table 8 and Table 9, respectively.

Table 8. Most Published-in Journals in the Pre-NDPA Period, 1999–2004 (Abbott)

Number of Publications	Source	2008 Eigenfactor score	Eigenfactor percentile
9	Neurocomputing	0.010435	79.48
4	Journal of Neurophysiology	0.1296	98.71
3	Journal of Neuroscience	0.521789	99.87
3	Nature Neuroscience	0.196657	99.3
3	Neural Computation	0.018975	87.78

Source: Eigenfactor.org, Journal names came from Web of Science.

Table 9. Most Published-in Journals in the Post-NDPA Period, 2005–2010 (Abbott)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
3	Nature Neuroscience	0.196657	99.3
2	Journal of Neurophysiology	0.1296	98.71
2	Journal of Neuroscience	0.521789	99.87
2	Neuron	0.28702	99.62
1	Annual Review of Neuroscience	0.046113	95.21
1	Cortical Function: A View From The Thalamus	N/A	N/A
1	Journal of Computational Neuroscience	0.00494	64.27
1	Network-Computation in Neural Systems	0.002336	44.64
1	Neural Computation	0.018975	87.78
1	Pharmacopsychiatry	0.004111	59.46
1	Physical Review Letters	1.2816	99.95
1	Proceedings of the National Academy of Sciences of The United States of America	1.69817	99.99

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 14 of Abbott's 31 publications, 45.16%, were in journals at or above the 98th percentile (Table 10). In the post-NDPA period, 11 of Abbott's 17 publications, 64.71% were in journals of the same caliber. Both of Abbott's NDPA-attributed publications had Eigenfactor values above the 98th percentile.

Table 10. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Abbott)

Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (31 pubs)	14	45.16%
Post-NDPA (17 pubs)	11	64.17%
Attributed to NDPA Funding (2 pubs)	2	100.00%

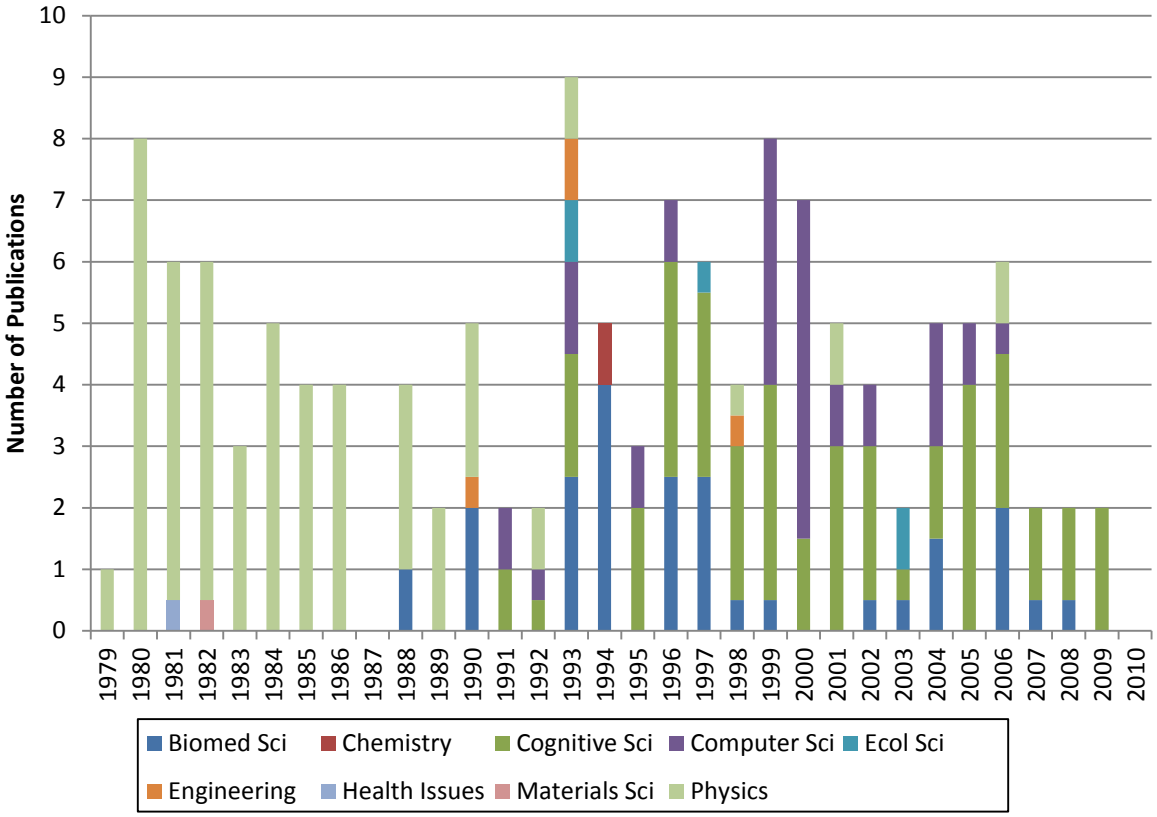
Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data is from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Abbott's 134 publications over the duration of his career can be categorized into a total of nine different macro-disciplines. He published in five macro-disciplines in the pre-NDPA period with 31 publications, and four macro-disciplines in the post-NDPA period with 17 publications. The distribution of Abbott's publications into macro-disciplines for the full length of his career is displayed in Figure 3.

Abbott began his career firmly in Physics by studying quantum mechanics. Over the course of his career, however, he began to move into Biomedical Science, Cognitive Science, and Computer Science as he performed quantitative computations on neural networks. By the time of his receipt of the NDPA, Abbott had moved almost entirely away from Physics and into those three fields.



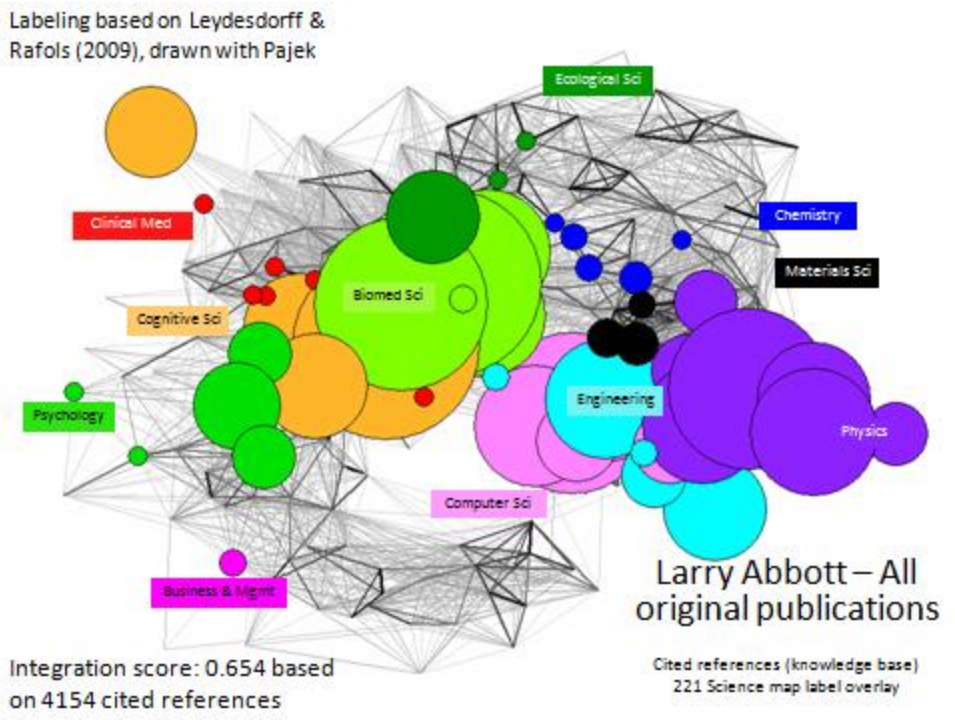
Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 3. Distribution of Publications into Macro-disciplines over Time (Abbott)

2) Body of Knowledge Cited

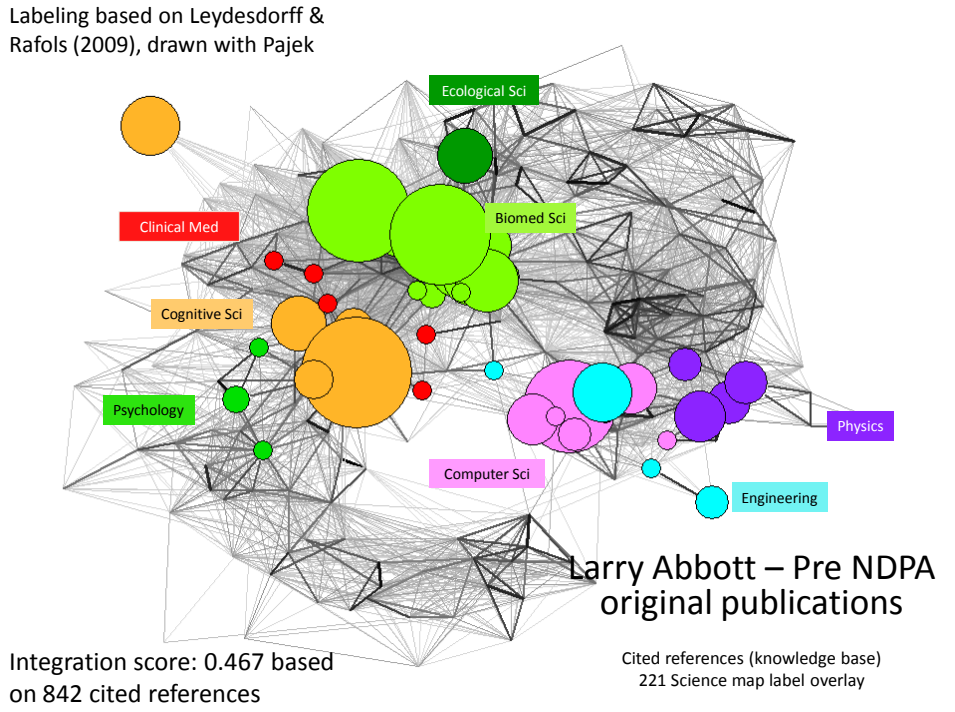
Abbott cited thirteen different macro-disciplines in the 4,154 references of his 134 career publications. This included eight macro-disciplines in the 842 references of his 31 pre-NDPA publications and ten macro-disciplines in the 812 references of his 17 post-NDPA publications.

The subject categories of references cited in Abbott's publications were overlaid onto a map of science. The range of Abbott's cited references for his full career, pre-NDPA period, and post-NDPA period are shown in Figure 4, Figure 5, Figure 6, respectively.



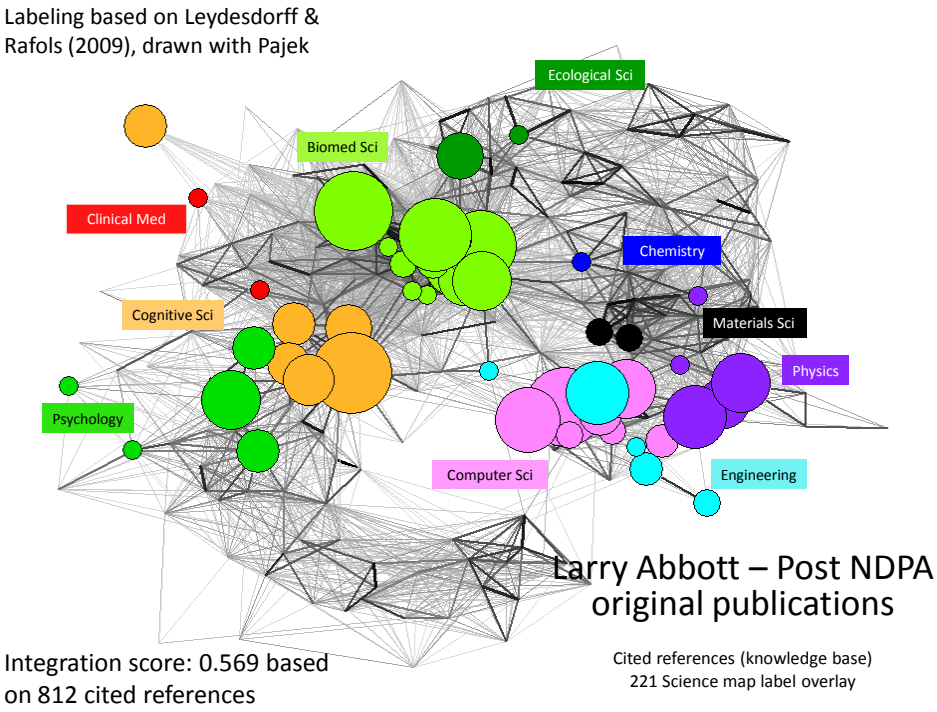
Note: Visualization by Pajek, Source: Web of Science

Figure 4. Map of Science Overlay for Cited References of All Original Publications (Abbott)



Note: Visualization by Pajek, Source: Web of Science

Figure 5. Map of Science Overlay for Cited References of Pre-NDPA Publications (Abbott)



Note: Visualization by Pajek, Source: Web of Science

Figure 6. Map of Science Overlay for Cited References of Post-NDPA Publications (Abbott)

3) Integration and Specialization Scores

For the publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The scores for Abbott are shown in Table 11.

Table 11. Integration and Specialization Scores (Abbott)

	Full Career (4154 cited references)	Pre-NDPA (842 cited references)	Post-NDPA (812 cited references)
Integration	0.654	0.467	0.569
Specialization	0.293	0.464	0.548

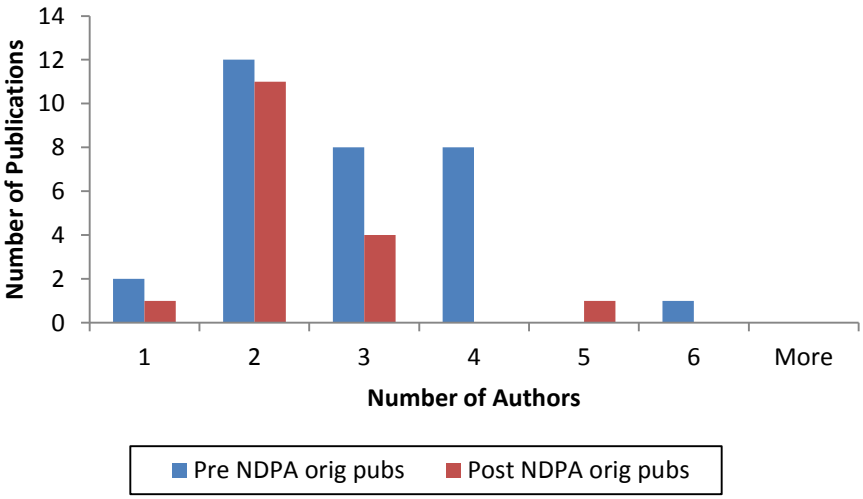
Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, Abbott changed his publication and citation activity over time. A "Renaissance integrator" over the length of his career with a high I and a low S score, Abbott was more of a "Grazer" in his pre-NDPA period and a "Disciplinarian" during his post-NDPA period.[15]

[15] Porter et al. (2007) Measuring researcher interdisciplinarity.

d. Collaboration

The median number of total authors in Abbott's original publications set was two. In the pre-NDPA period, this median was three and post-NDPA the median returned to two. A comparison of the pre- and post-NDPA data of the total number of authors may be seen in Figure 7.



Source: Web of Science.

Figure 7. Distribution of Number of Authors in Original Publication Set (Abbott)

The number of unique authors in a researcher's publishing network is another metric that captures collaboration patterns. Abbott has published with approximately 94 unique individuals throughout his full career. In the pre-NDPA period, he co-authored with 29 researchers, and in the post-NDPA period, he collaborated with 16 researchers. Over his two NDPA-attributed publications, Abbott published with three other unique authors.

B. Vicki Chandler (2005)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers believed that Chandler had displayed evidence of a pioneering past in her discoveries and characterizations of paramutation in maize. They considered her proposal an extension of her current work in that she desired to study the role of paramutation in humans. The panel, however, was "enthusiastic" that the project had potential for a high impact breakthrough, and that it would have human implications in terms of "understanding…certain human genetic diseases."

3. Nature of Project Risks and Outcomes

Both the Pioneer and the three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 12 and Table 13).

a. Typology of Project Risks

Table 12. Characterization of Unique Project Risk (Chandler)

Please indicate which of the following risks are applicable to the NDPA-funded project	Chandler	Expert 1	Expert 2	Expert 3
Conceptual risk	x	x	x	x
Technical risk		x		
Experience risk	x	x	x	x
Multidisciplinary risk	x	x	x	x
None of these risks				

Source: Pioneer interview, Expert review

Three out of three experts agreed that Chandler's research contained conceptual, experience, and multidisciplinary risks. Chandler herself believed her NDPA proposal encompassed those same risks.

In her interview, Chandler remarked that her hypothesis that epigenetic mechanisms may contribute to "heritable changes in gene expression" is at odds with the prevailing idea that "all gene regulation is monitored by SNPs" and that diseases may be found by "looking at nuclear type changes." Chandler also believed that although she continued to study genetics in her NDPA proposal, "human genetics is…different from plant genetics," and the shift required her to "read [new] literature and…collaborate and interact with [new] people," all of which took "an immense amount of…time."

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Chandler's research:

> Paramutation was thought to be an obscure phenomenon restricted to plants for which there was no mechanistic explanation. The applicant has found that tandem repeats and RNA interference regulate trans-allelic silencing, an unprecedented window into the phenomenon.
>
> The NDPA award permitted Dr. Chandler, renown for her expertise in plant genetics, to work in the area of mammalian genomics and perhaps even disease."
>
> Chandler is one of only a very few who could have brought the disciplines of plant biology, mammalian biology, genetics, epigenetics, and molecular biology all into focus at once.

Experts acknowledged that Chandler's work has questioned existing genetic theories and combined work from multiple fields (i.e., plant biology, mammalian biology, genetics, epigenetics, molecular biology).

b. Typology of Potential Outcomes

Table 13. Characterization of Potential Pioneering Outcomes (Chandler)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Chandler	Expert 1	Expert 2	Expert 3
New Idea	x	x	x	x
New Phenomenon	x	x	x	x
New Methodology		x		x
New Technology				
New Framework	x	x	x	x
None of these outcomes				

Source: Pioneer interview, Expert review

At least two of three experts believed Chandler's research had the potential to advance new ideas, discover new empirical phenomena, develop a new methodology, and form the underlying basis for a new framework of thinking. Chandler agreed with the experts about advancing new ideas, discovering new empirical phenomena, and forming a new framework.

To qualify her outcome typology responses, Chandler stated that the discovery that "small RNAs coming from noncoding tandem repeats in humans could lead to gene silencing" was a new empirical phenomenon that resulted from her research.

Below is a selection of comments from experts that justify their evaluations of the potential pioneering outcomes of Chandler's research:

> "Chandler has produced new technology for genome analysis and RNAi-based functional studies, both of which have helped her field to address questions that were previously not within range."
>
> "Researchers tend to think of gene regulation and gene mutation/ alteration…as separate phenomena, but Dr. Chandler's work on paramutation has helped to bring these two fields together."
>
> "[Studying] the link between RNAi, tandem repeats and paramutation…is likely to have a major impact on diseases that depend on loss of heterozygosity, in particular cancer."

Experts thought Chandler had developed new technology to perform her research (i.e., for genome analysis and RNAi-based functional studies). They also recognized that her research may have human disease implications into the understanding of the heredity of certain diseases (i.e., cancer).

c. Assessing Whether the Research Was Pioneering

The experts were asked whether they believed Chandler's research was pioneering. All three experts strongly agreed that Chandler's research was pioneering. Below is a selection of comments from experts about why Chandler's research was or was not pioneering:

> The research has led to several reviews, papers, and clinical collaborations on the role of paramutation in human disease, most notably cancer, that were simply non-existent until this research was performed. This project is clearly leading the way.
>
> Her paper, Ames et al.…is focused on mammalian sequences, but the findings and questions raised by this paper can be applied to many other species. Although not entirely new, her studies have also expanded our understanding of several other fields, including gene silencing, RNA interference, chromatin, gene evolution, inheritance, and much more.

The experts thought Chandler's work raised awareness of paramutation in human disease and expanded understanding of multiple sub-fields of genetics.

4. Value of the NDPA Program

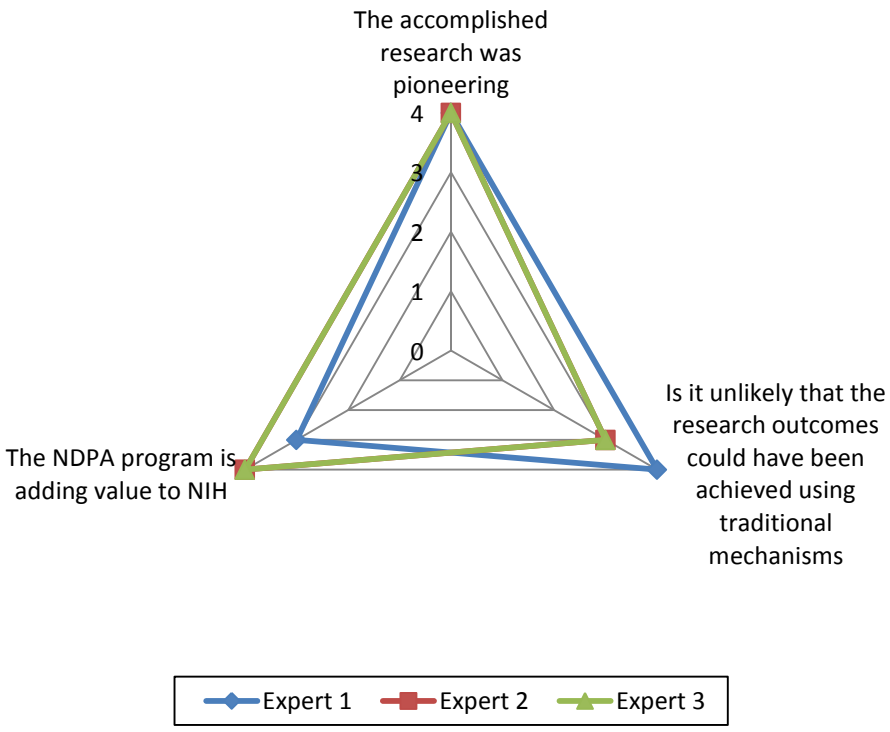
a. Pioneer Perspective

Chandler evaluated the value of the NDPA program in a number of different ways. She explained that the NDPA funds allowed her to worry less about publishing since there was no pressure to produce outputs in order to have a "chance of a renewal." Chandler also stated that the NDPA allowed her to perform research that was exploratory and resource-intensive; her lab "wouldn't have been able to make [that] kind of progress" because the "the kinds of experiments [they] did—gene sequencing, mechanistic experiments using transgenic maize and mice lines—cost a fortune." The human aspect of Chandler's research would not have been performed or

performed at a much slower rate without the NDPA because the lab had to be set up for "human cell culture," and she had to "hire people that had [human genetics] expertise."

b. Expert Perspective

Experts were asked to rate whether Chandler's results were a unique output of the Pioneer Award and whether the Pioneer Award is adding value to NIH (Figure 8).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 8. Experts' Opinions of the NDPA (Chandler)

One expert strongly agreed and two experts moderately agreed that it is unlikely that Chandler's research outcomes could have been achieved using traditional mechanisms. Two experts strongly agreed and one expert moderately agreed that the NDPA program is adding value to NIH. Below is a selection of comments from reviewers about the value of the NDPA program:

> "Conventional study sections are finding it harder and harder to fund exploratory research…The NDPA represents a relatively modest investment in pioneering research that would not otherwise have been competitive."
>
> In this instance, the work done was slow and high risk. This type of block [of] five year funding enables such work to be done."

> "These awards have greatly raised the profile of interdisciplinary research...In my experience, it is very difficult to persuade funding agencies to embrace this particular combination of effort and this is one of the few examples that I know."
>
> "A program like this…encourages other younger scientists of this ilk to see that there is a path forward and that this type of innovative science is held in high regard by the nation…The R01 application process ends up with an overemphasis on the details…and feasibility…it forces scientists to think small."

Experts commented that the value of the NDPA is in its funding of exploratory and interdisciplinary research. One reviewer also believes that the NDPA sets a good example for younger researchers to see that innovation is highly valued in the scientific community and the nation.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Chandler received the Pioneer Award in 2005, the pre-NDPA range refers to activity between 2001 and 2005, while the post-NDPA range refers to activity between 2006 and 2010.

a. Productivity

Chandler published a total of 76 original articles over the 31 years of her research career, giving her an average of 2.45 original publications per year (Table 14). In the pre-NDPA period, she published 15 original articles for an average rate of 3 publications per year. In the post-NDPA period, she published 13 original articles for an average rate of 2.6 publications per year.

Table 14. Summary of Publication Activity (Chandler)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	15	13	2	76
Number of Years	5	5	N/A	31
Publication Rate	3	2.6	N/A	2.451613

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Chandler published more pre-NDPA compared to the post-NDPA period, but the difference is slight. Two of Chandler's 13 post-NDPA publications were attributed to NDPA funding,

which suggests that her post-NDPA publication rate may have been sustained by non-NDPA research. The publications attributed to Pioneer Award funding are listed in Table 15.

Table 15. Publications Attributed to NDPA Funding (Chandler)

Title	Journal	Year Published
Distinct size distribution of endogenous siRNAs in maize: Evidence from deep sequencing in the mop1-1 mutant	Proceedings of the National Academy of Sciences of the United States of America	2008
Paramutation in maize: RNA mediated trans-generational gene silencing	Current Opinion In Genetics & Development	2010

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout her career, as of August 2010, Chandler's 67 publications excluding reviews had been cited a total of 6,609 times. In the post-NDPA period, Chandler published 12 publications that had received 255 citations by August 2010. Two of the 12 publications were attributed to NDPA funding, and they had already received 32 citations.

It is surprising that the age-weighted citation rate for the post-NDPA publication set is higher than that for the pre-NDPA publication set. The barriers to comparing citations between different time periods, discussed in the introduction, did not inhibit the number of citations to Chandler's post-NDPA, and more particularly, NDPA-attributed research. This suggests that the research is having an important impact on the scientific community.

Statistics on citations to Chandler's research are shown in Table 16.

Table 16. Summary of Citation Analyses (Chandler)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (67 pubs)	6,609	23.48	31
Pre-NDPA (12 pubs)	448	7.26	N/A
Post-NDPA (12 pubs)	255	8.06	N/A
Attributed to NDPA Funding (1 pub)	32	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science

2) Journal Impact Factors

Chandler published 15 publications in eleven different sources during the pre-NDA period and 13 publications in eight different sources during the post-NDPA period. Detailed information on Chandler's most published-in journals of the pre- and post-NDPA periods is provided in Table 17 and Table 18, respectively.

Table 17. Most Published-in Journals in the Pre-NDPA Period, 2001–2005 (Chandler)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
4	Plant Physiology	0.129651	98.72
2	Genetics	0.120362	98.58
1	Cold Spring Harbor Symposia on Quantitative Biology	0.007464	73.2
1	Genes & Development	0.278064	99.59
1	Homology Effects	N/A	N/A
1	Journal of Biological Chemistry	1.32919	99.96
1	Maydica	0.000746	21.2
1	Nature Reviews Genetics	0.107603	98.26
1	Plant Cell	0.121567	98.62
1	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
1	RNA Interference	N/A	N/A

Source: Eigenfactor.org, Journal names came from Web of Science

Table 18. Most Published-in Journals in the Post-NDPA Period, 2006–2010 (Chandler)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
3	Genetics	0.120362	98.58
3	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
2	In Vitro Cellular & Developmental Biology-Animal	0.001837	38.4
1	BMC Plant Biology	N/A	N/A
1	Cell	0.671695	99.89
1	Current Opinion in Genetics & Development	0.044997	95
1	Nature	1.76345	100
1	PLOS Genetics	0.060832	96.76

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 11 of Chandler's 15 publications, 73.33%, were in journals at or above the 98th percentile (Table 19). In the post-NDPA period, 8 of Chandler's 17 publications, 61.54%, were in journals at or above the 98th percentile. One of two NDPA-attributed publications had an Eigenfactor value above the 98th percentile.

Table 19. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Chandler)

Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (15 pubs)	11	73.33%
Post-NDPA (17 pubs)	8	61.54%
Attributed to NDPA Funding (2 pubs)	1	50.00%

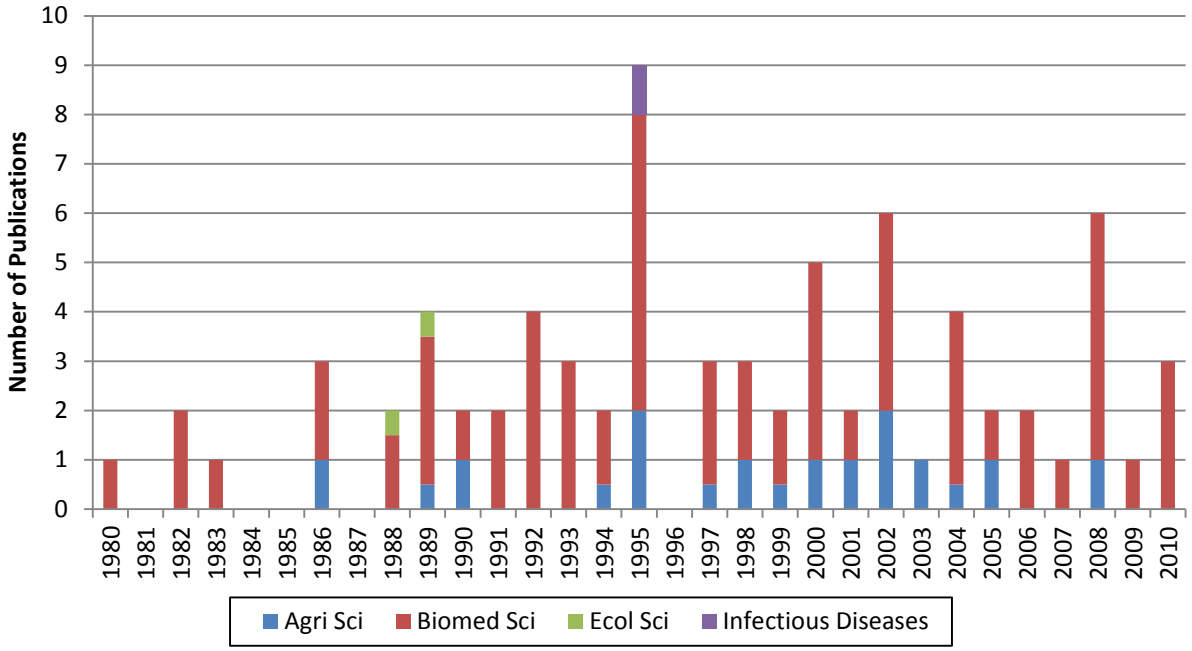
Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data is from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Chandler's 76 publications over the course of her career can be categorized into a total of four different macro-disciplines. During the pre- and post-NDPA periods, she published in the

same two macro-disciplines with 15 and 13 articles respectively. The distribution of Chandler's publications into macro-disciplines for the full length of her career is in Figure 9.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 9. Distribution of Publications into Macro-disciplines over Time (Chandler)

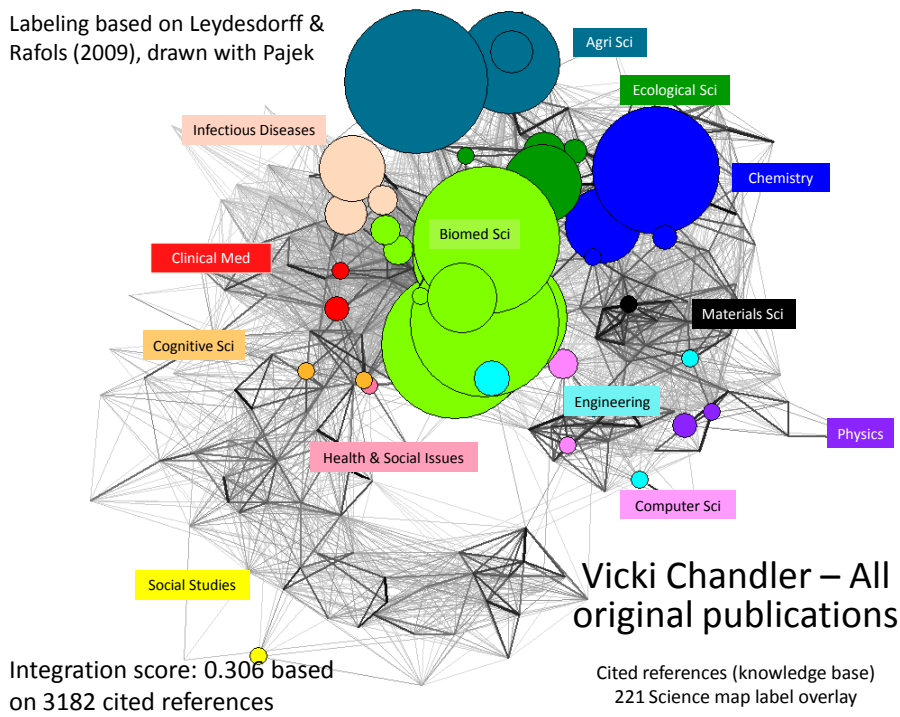
Chandler has spent her entire career firmly in Biomedical Science and Agricultural Science with her work regarding maize and paramutation. The NDPA did not change in which macro-disciplines she published, primarily because her shift in research focus from plant to animal genetics would have continued to fall under Biomedical Science.[16]

2) Body of Knowledge Cited

Chandler cited thirteen different macro-disciplines in the 3,182 references of her 76 career publications. This included nine macro-disciplines in the 750 cited references of her 15 pre-NDPA publications and eleven macro-disciplines in the 478 cited references of her 13 post-NDPA publications.

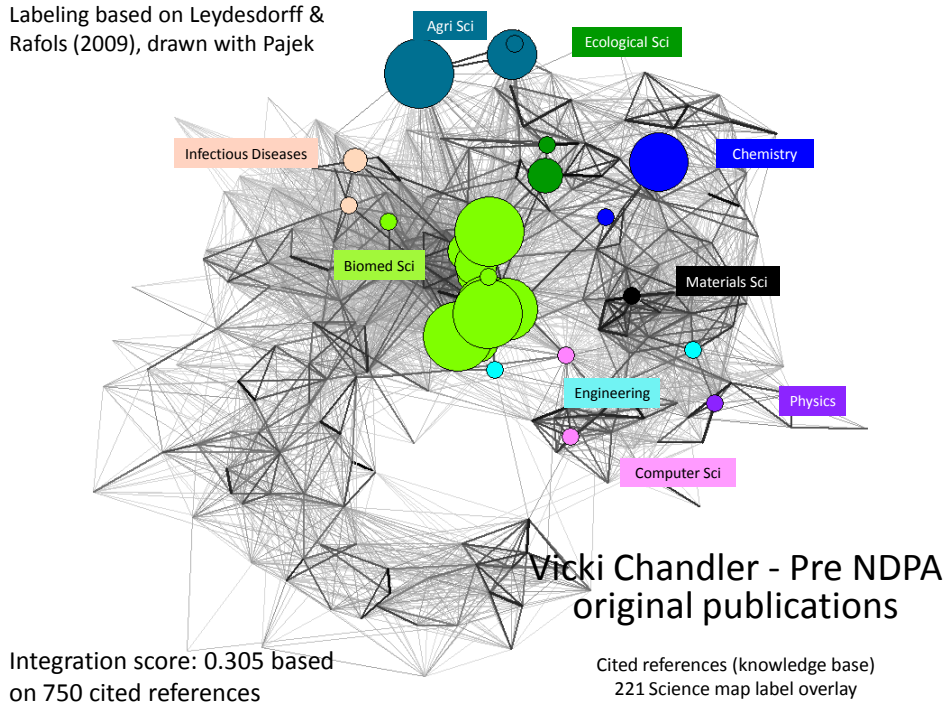
The range of Chandler's cited references can be visualized more clearly over the three time periods with maps of science (Figure 10, Figure 11, and Figure 12).

[16] Chandler and the STPI expert reviewers noted, however, that Chandler did shift fields from plant genetics to human genetics after the receipt of the NDPA. Such a shift is not likely to register on the broader macro-discipline scale because both fields are within the biomedical and agriculture sciences (Section XX).



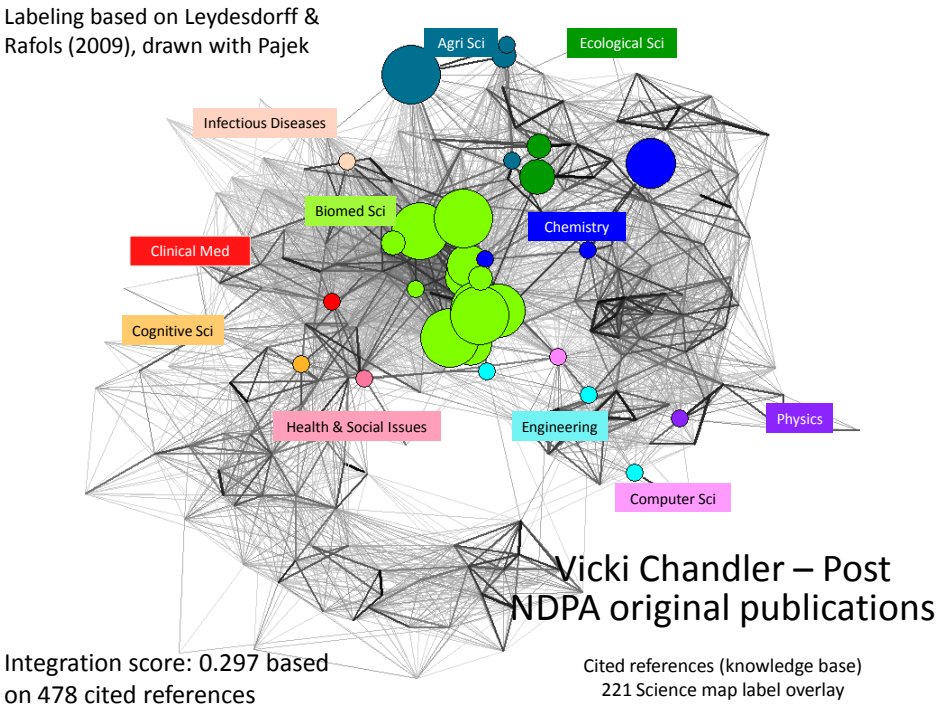
Note: Visualization by Pajek, Source: Web of Science

Figure 10. Map of Science Overlay for Cited References of All Publications (Chandler)



Note: Visualization by Pajek, Source: Web of Science

Figure 11. Map of Science Overlay for Cited References of Pre-NDPA Publications (Chandler)



Note: Visualization by Pajek, Source: Web of Science

Figure 12. Map of Science Overlay for Cited References of Post-NDPA Publications (Chandler)

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The scores for Chandler are shown in Table 20.

Table 20. Integration and Specialization Scores (Chandler)

	Full Career (3182 cited references)	Pre-NDPA (750 cited references)	Post-NDPA (478 cited references)
Integration	0.306	0.305	0.297
Specialization	0.699	0.657	0.819

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

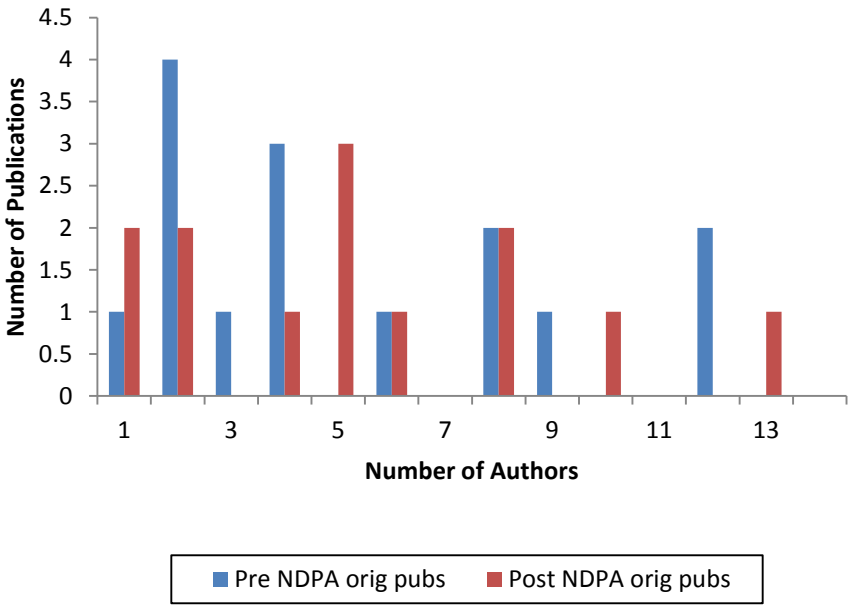
Compared to the other Pioneers, Chandler remains a "Disciplinarian" throughout her career and during the pre- and post-NDPA periods.[17] Despite her shift in focus from plants to humans with regard to paramutation, her underlying research is about genetics. In that manner, she has stayed firmly in her field. She appears to have had a jump in S score during the post-NDPA

[17] Porter et al. (2007) Measuring researcher interdisciplinarity.

period. Since she decreased her research in plants during this period, there is a lower likelihood that the journals in which she published could have been categorized as ecological or agricultural. A decrease in the instances of these subject categories could have caused an increase in her S score.

d. Collaboration

The median number of total authors in Chandler's publication set was 3.5. During the pre-NDPA period, the median was four, and during the post-NDPA period, the median was five.[18] Graphics depicting Chandler's collaborations may be seen in Figure 13.



Source: Web of Science

Figure 13. Distribution of Number of Authors in Original Publication Set (Chandler)

The number of unique authors in a researcher's publishing network is another metric that captures collaboration patterns. Chandler has published with approximately 275 unique individuals throughout her career. In the pre-NDPA period, she collaborated with 47 researchers, in the post-NDPA period, she collaborated with 44 researchers. Over her one NDPA-attributed publication, Chandler published with 12 other unique authors.

[18] During her interview, Chandler noted that she had to seek out new collaborators for her NDPA project since she was jumping into the field of human genetics without having had much experience doing that type of work.

C. Hollis Cline (2005)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers believed that Cline proposed an innovative approach that combined several existing methods for "mapping neural circuits…using a system of transferring specific protein constructs from one neuron to another across a synapse." The panel was "very enthusiastic" that her work had the potential for a high impact breakthrough that "[changes] the way people look at the brain."

3. Nature of Project Risks and Outcomes

Both the Pioneer and the three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 21 and Table 22).

a. Typology of Project Risks

Table 21. Characterization of Unique Project Risk (Cline)

Please indicate which of the following risks are applicable to the NDPA-funded project	Cline	Expert 1	Expert 2	Expert 3
Conceptual Risk				
Technical Risk	x	x	x	x
Experience Risk	x	x		x
Multidisciplinary Risk	x			x
None of these risks				

Source: Pioneer interview, Expert review

At least two of three experts thought Cline's work contained technical and experience risks. Cline's opinions of her research corroborated these assessments and went beyond to include multidisciplinary risk.

In her interview, Cline provided more detail in characterizing the unique risks of her research. She explained that before the techniques used in her NDPA project, "nobody knew how to identify these [synaptic] proteins." Cline also explained that her project required knowledge beyond her expertise because her lab had never before worked with "rabies [viruses]" nor used "serial section [electron microscopy] to reconstruct individual cells" and determine which cells were connected. Cline qualified her belief that her project was multidisciplinary in explaining that she used multiple methods- 3-D electron microscopy, rabies viruses in Xenopus neurons, and another "biochemistry strategy"- to study her original hypothesis. She emphasized that the formation of new collaborations

with labs with different expertise has been an important part of addressing the risks of her project.

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Cline's research:

> "The development of the tools the researcher intended to generate for the xenopus was not straightforward and involved considerable risk, and it was not clear that the resources proposed could be obtained… As it turned out, these resources were not feasible as originally proposed."
>
> "The research proposed was also somewhat of a departure from the researcher's previous areas of expertise…particularly in interpreting the organization of neuronal circuits as opposed to single neuronal cells, which was the researcher previous area of expertise. On the other hand, the research proposed was in many ways a natural follow-up to…previous lines of study."
>
> "The addition of membrane targeted HRP and electron microscopy is a unique technology that will be very useful…Electron microscopy was not Dr. Cline's original expertise, so developing a whole new approach in this arena was truly unique."

Experts recognized Cline's project incorporated technical risks (i.e., her original failed approach) and expanded beyond her expertise (i.e., study of neuronal circuits).

b. Typology of Potential Outcomes

Table 22. Characterization of Potential Pioneering Outcomes (Cline)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Cline	Expert 1	Expert 2	Expert 3
New Idea	x		x	x
Discovery of a new empirical phenomena	x	x	x	x
New Methodology	x	x		x
New Technology	x			
New Framework	x		x	
None of these outcomes				

Source: Pioneer interview, Expert review

At least two of three experts believed Cline's research had the potential to advance new ideas, result in the discovery of new phenomena, and develop new methodology. Chandler thought her research had the potential to result in the formulation of new ideas, the discovery of new phenomena, the development of new methodology, the invention of new technology, and the synthesis of a new framework.

Cline commented on her characterization of the potential pioneering outcomes of her proposal. She believes that the proposal idea could result in the formulation of new ideas and theoretical concepts if "the circuit mapping [works]." Cline noted that her project could result in the invention of novel instruments "in terms of molecular biological instruments [and] reagents" rather than new equipment or techniques.

Below is a selection of comments from experts that explain their evaluations of the potential pioneering outcomes of Cline's research:

> "These data provide a link between a classic signaling pathway outside the brain and well-studied neurophysiological and neurodevelopmental processes. The link between these two elements was new. The methods and individual topics (insulin receptor signaling, dendritic plasticity) themselves were not."
>
> "The most significant advancement achieved…in the context of this NDPA was the development of new tools for quantitative neuroanatomical analysis. In particular, the new methods developed will likely greatly facilitate the quantitative analysis of the development and plasticity of neuritic processes."
>
> "Other attempts cited by the researcher…for studying connected cells in functional circuits either involve methods that have already been tested and proven efficient in other systems… or are still at a very incipient stage of development."

It is surprising that no experts agreed that her proposal could generate new technologies since there was unanimous agreement about the technical risks of her project. Experts noted that her data resulted in the advancement of new ideas (i.e., link between classic signaling pathways and neurodevelopmental processes) and the development of new methodologies (i.e., quantitative neuroanatomical analysis).

c. Assessing Whether the Research Was Pioneering

The experts were asked to rate whether they believed Cline's research was pioneering. Only one of three experts strongly agreed that Cline's research was pioneering. The other two experts moderately and strongly disagreed with that statement. This negative assessment is likely due to the failure of Cline's original idea. Below is a selection of comments from experts about why Cline's research was or was not pioneering:

> "The resulting methodology for examining functionally connected neuronal cells is either not as radically different from previous methods…or is still at an early stage...The novel method for combining time-lapse imaging and electron microscopy is potentially very important and in some ways more of a novel tool. However, it does not address the question of the organization of interconnected cells, one of the main

> questions in the original proposal. In several respects, therefore, the technical improvements achieved represent an important but somewhat incremental progress in methodology."
>
> "The research accomplished under the NDPA was solid, and in the case of the insulin receptor signaling work on dendritic plasticity, mechanistically novel. There was little by way of transformative biology or technology that resulted."

The failure of Cline's NDPA proposal led her to return to research that was similar to her previous work, which seems to have caused reviewers to disagree with the statement that her work was pioneering.

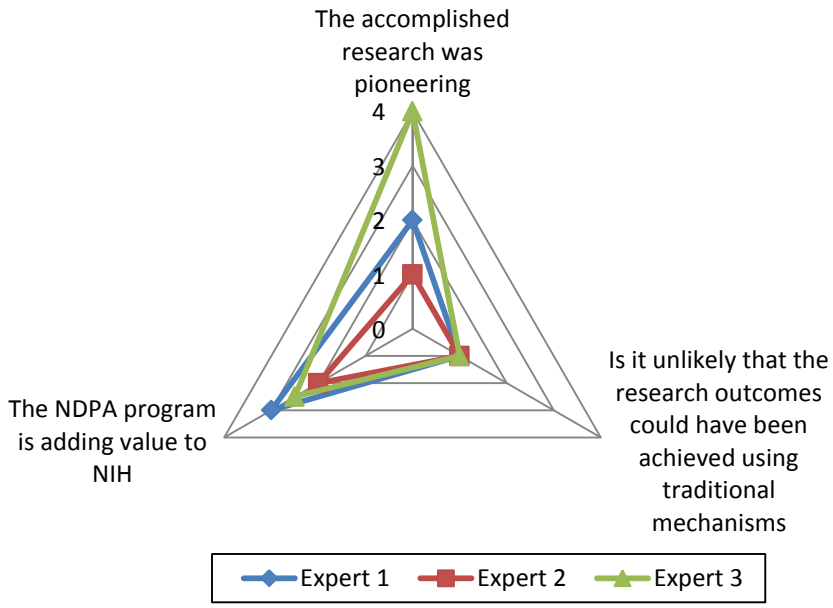
4. Value of the NDPA Program

a. Pioneer Perspective

In the interview, Cline commented that the NDPA allowed her to take a long-term view, and be flexible because with "traditional grants…you have very clear things…to accomplish." With the NDPA funds, she had more freedom to initiate collaborations and divert post-docs to side projects. Cline also thought the NDPA allowed her to undertake new and multiple strategies and even fail. The "amount of money for a long enough period that you could…regroup and think of an alternate…[strategy]" if the first idea failed. The flexibility of the funds encouraged her creativity because she did not have to "do [preliminary] work and publish…without income to support the work." Her lab was able to "start using a new technique in the lab" that could be incorporated into "different types of exploration and hopefully grant income." Without having received the NDPA, Cline would have only been able to commit "a fraction of the effort" to this project because it was so risky. If anything, the idea would have been pursued "serially, not in parallel" with her other research.

b. Expert Perspective

Experts were additionally asked to rate whether Cline's results were a unique output of the Pioneer Award and whether the Pioneer Award is adding value to NIH (Figure 14).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 strongly agree. Source: Expert review.

Figure 14. Experts' Opinions of the NDPA (Cline)

All three experts believed that Cline's research outcomes could have been achieved under traditional funding mechanisms. One expert moderately disagreed, one was neutral, and one moderately agreed that the NDPA is adding value to NIH. Below is a selection of comments from reviewers about the value of the NDPA program:

> "It is typically very hard for researchers to obtain funding for projects that attempt to develop radically new resources/tools/approaches. The NDPA program can be a very important way of facilitating that process, even though not all projects may necessarily achieve the goals as originally proposed. That level of risk has to be part of the equation if one wants to promote efforts leading to new scientific breakthroughs."

> "From what I have seen, and consistent with this current NDPA, is that initially proposed projects are innovative but subside into the mainstay programs of the funded laboratory… Relative to the impact of a typical HHMI Investigator, or Max Planck Director I would rate the NDPA results as less impactful at this point."

> "I'm not so sure that this mechanism is needed because truly outstanding and pioneering research is also accomplished through the traditional RO1 and renewed RO1 mechanisms… It's conceivable that having more money all at once leads to some innovation that wouldn't occur if it were obtained on renewed grant applications."

One expert reviewer thought the NDPA was valuable for projects trying to develop new tools and approaches. Two reviewers thought that, while the NDPA is funding innovative work, many of the projects could have been funded with R01s and that the NDPA is not as influential as other "innovative" grant mechanisms, such as those at HHMI.

5. Descriptive Bibliometrics

Terms included in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Cline received the Pioneer Award in 2005, her pre-NDPA range is from 2001 to 2005, and her post NDPA range is from 2006 to 2010.

a. Productivity

Cline has published a total of 82 original articles over the 30 years of her research career. For this duration, she has an average of 2.73 original publications per year (Table 23). Cline published 20 original articles in her pre-NDPA period for an average rate of 4 original publications per year. She published 21 original articles in her post-NDPA period for an average rate of 4.2 original publications per year.

Table 23. Summary of Publication Activity (Cline)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	20	21	4	82
Number of Years	5	5	N/A	30
Publication Rate	4	4.2	N/A	2.733333

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Cline published at approximately the same rate before and after receiving the NDPA. Of her 21 post-NDPA publications, four were attributed to NDPA funding. These publications are listed in Table 24.

Table 24. Publications Attributed to NDPA Funding (Cline)

Title	Journal	Year Published
Convergence of Multisensory Inputs in Xenopus Tadpole Tectum	Developmental Neurobiology	2009
Endogenous dopamine suppresses initiation of swimming in prefeeding zebrafish larvae	Journal of Neurophysiology	2008
Refining the roles of GABAergic signaling during neural circuit formation	Trends in Neurosciences	2007
Visual Deprivation Increases Accumulation of Dense Core Vesicles in Developing Optic Tectal Synapses in Xenopus laevis	Journal of Comparative Neurology	2010

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout her career, as of August 2010, Cline's 73 original publications excluding reviews have been cited a total of 4,319 times. In the post-NDPA period, Cline published 18 articles that had received 329 citations by August 2010. The four publications that were attributed to the NDPA had received a total of 32 citations.

Cline's citation analyses are not surprising results. As the publication sets refer to more recent time periods, the number of citations decreases.

A summary of the citation analyses is shown in Table 25.

Table 25. Summary of Citation Analyses (Cline)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (73 pubs)	4,319	19.71	34
Pre-NDPA (16 pubs)	1,140	11.21	N/A
Post-NDPA (18 pubs)	329	8.87	N/A
Attributed to NDPA Funding (4 pubs)	32	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Cline published 20 original publications in twelve different sources in the pre-NDPA period and 21 original publications in twelve different sources in the post-NDPA period. Detailed data on Cline's most published-in journals for the pre- and post-NDPA periods are shown in Table 26 and Table 27.

Table 26. Most Published-in Journals in the Pre-NDPA period, 2001–2005 (Cline)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
5	Neuron	0.28702	99.62
3	Current Opinion in Neurobiology	0.054066	96.16
3	Journal of Comparative Neurology	0.066163	97.06
1	Differentiation	0.009707	78.1
1	Embo Reports	0.064317	96.96
1	Journal of Neurobiology	0.018742	87.68
1	Journal of Neuroscience	0.521789	99.87
1	Nature	1.76345	100
1	Nature Neuroscience	0.196657	99.3
1	Nature Reviews Neuroscience	0.113991	98.43
1	Real-Time Imaging	0.001702	39.9
1	Science	1.58309	99.98

Source: Eigenfactor.org, Journal names came from Web of Science

Table 27. Most Published-in Journals in the Post-NDPA Period, 2006–2010 (Cline)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
5	Journal of Neuroscience	0.521789	99.87
3	Developmental Neurobiology	N/A	N/A
2	Journal of Neurophysiology	0.1296	98.71
2	Neuron	0.28702	99.62
2	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 10 of Cline's 20 publications, 50%, were in journals at or above the 98th percentile (Table 28). In the post-NDPA period, 13 of Cline's 21 publications, 61.90%, were in journals at or above the 98th percentile.

Table 28. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Cline)

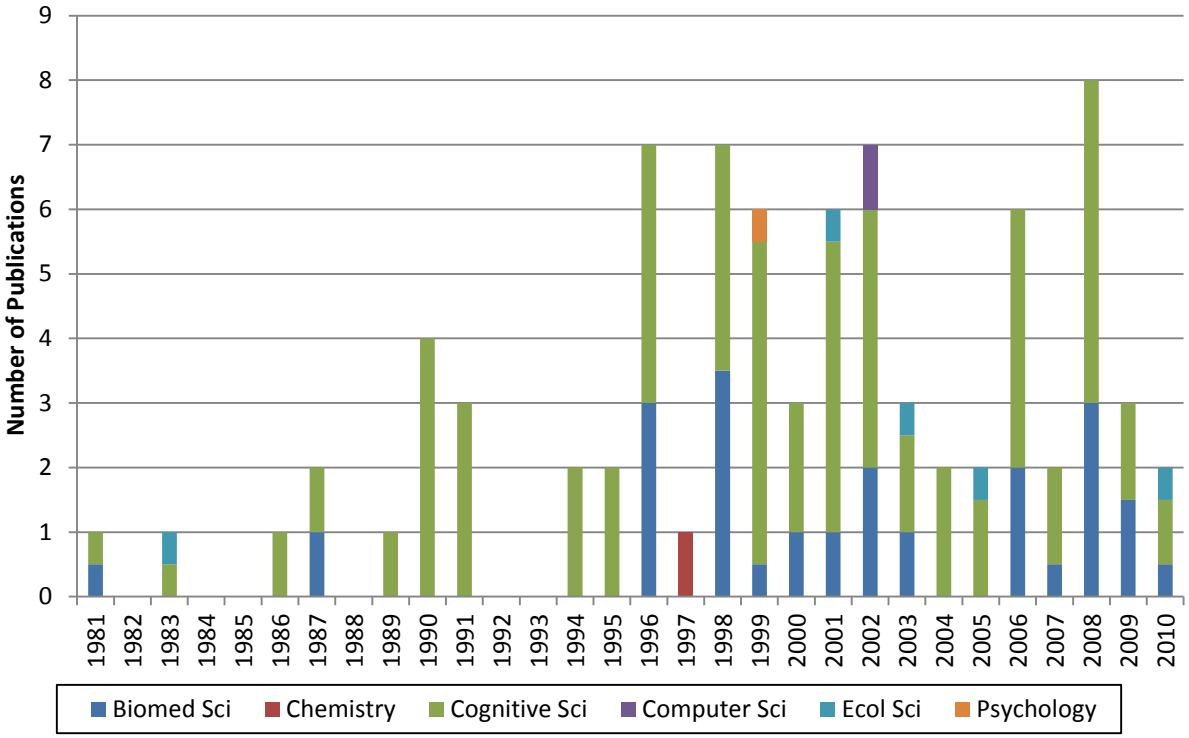
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (20 pubs)	10	50.00%
Post-NDPA (21 pubs)	13	61.90%
Attributed to NDPA Funding (4 pubs)	1	25.00%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data is from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Cline's 82 publications over the duration of her career can be categorized into a total of six different macro-disciplines. She published in four macro-disciplines over her 20 pre-NDPA publications and three macro-disciplines over her 21 post-NDPA publications. The distribution of Cline's publications into macro-disciplines over the course of her career may be seen in Figure 15.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

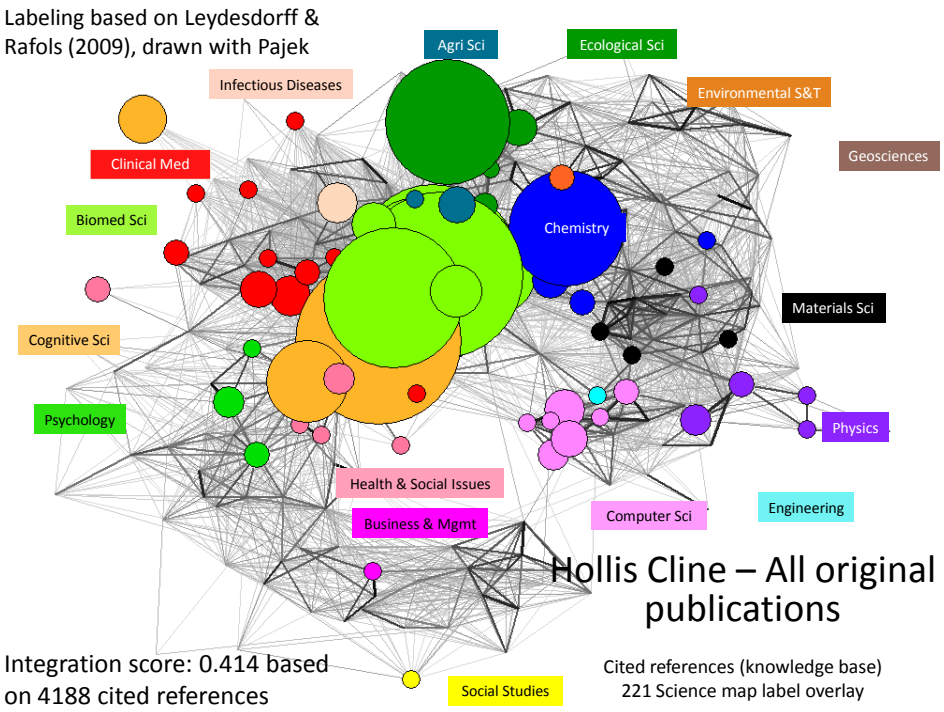
Figure 15. Distribution of Publications into Macro-disciplines over Time (Cline)

Cline began her career in Cognitive Science by studying the behavior of single neuron cells and has continued to publish in that field to the present day. In the latter half of her career, she published more frequently in Biomedical Science. Due to the inherent interdisciplinary nature of the field of neuroscience, however, there may not actually have been a shift in research focus at this time period. The increase in Biomedical Science does indicate, however, a shift in where Cline published because macro-disciplines pertain to the classification of journals.

2) Body of Knowledge Cited

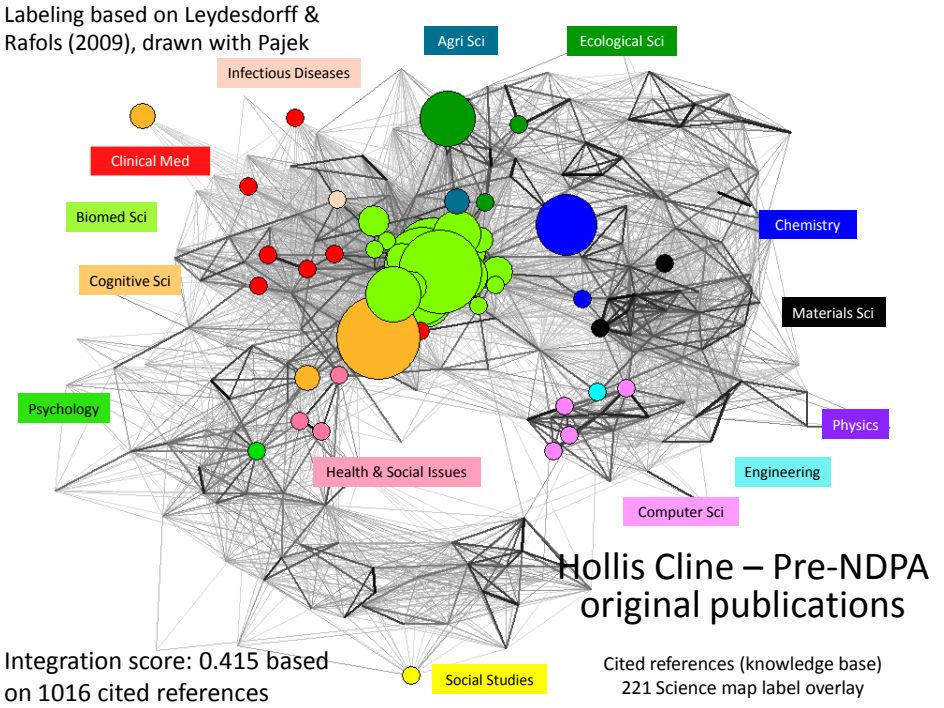
Cline cited sixteen different macro-disciplines in the 4,188 references of her 82 career publications. This included thirteen macro-disciplines in the 1,016 references of her 20 pre-NDPA publications and ten macro-disciplines in the 1,212 references of her 21 post-NDPA publications.

The spread of the subject categories of Cline's cited references for her full career, pre-, and post-NDPA period were overlaid onto Maps of Science that are displayed in Figure 16, Figure 17, and Figure 18.



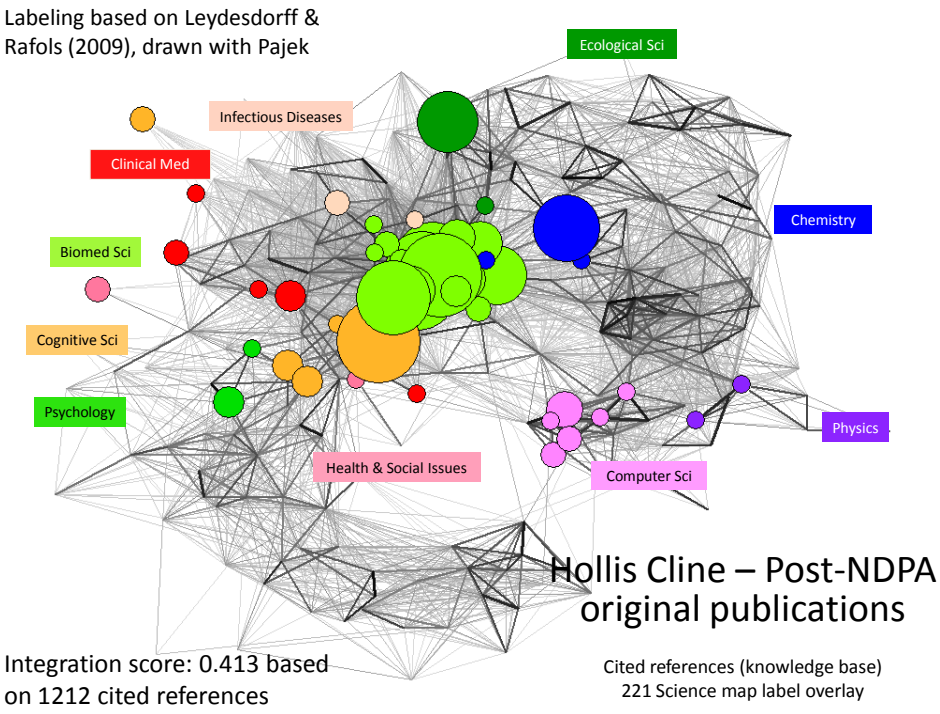
Note: Visualization by Pajek, Source: Web of Science

Figure 16. Map of Science Overlay for Cited References of All Original Publications (Cline)



Note: Visualization by Pajek, Source: Web of Science

Figure 17. Map of Science Overlay for Cited References of Pre-NDPA Publications (Cline)



Note: Visualization by Pajek, Source: Web of Science

Figure 18. Map of Science Overlay for Cited References of Post-NDPA Publications (Cline)

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The scores for Cline are displayed in Table 29.

Table 29. Integration and Specialization Scores (Cline)

	Full Career (4,188 cited references)	Pre-NDPA (1,016 cited references)	Post-NDPA (1,212 cited references)
Integration	0.414	0.415	0.413
Specialization	0.607	0.532	0.634

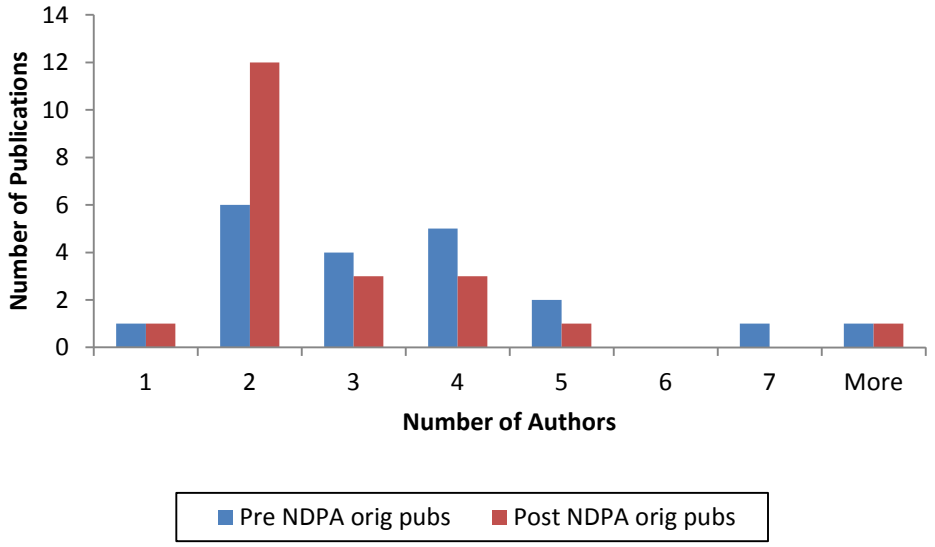
Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, Cline may be considered a "Disciplinarian" for her full career, pre-NDPA period, and post-NDPA period.[19] While her specific research was different in her NDPA proposal, the shift in focus from single neuronal cells to neuronal networks likely does not constitute a large change in fields.

[19] Porter et al. (2007) Measuring researcher interdisciplinarity.

d. Collaboration

The median number of total authors in Cline's career publication set is three. The pre-NDPA median was three and the post-NDPA median was two. A comparison of the pre- and post-NDPA distributions of the total number of authors for Cline can be seen in Figure 19.



Source: Web of Science

Figure 19. Distribution of Number of Authors in Original Publications Set (Cline)

The number of unique authors in a researcher's publishing network is another metric that captures collaboration patterns. Cline has published with approximately 114 unique individuals throughout her full career. In the pre-NDPA period, she published with 30 researchers, and in the post-NDPA period, she co-authored with 57 researchers. Over her four NDPA-attributed publications, Cline published with four other unique authors.

D. Leda Cosmides (2005)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers thought Cosmides had a bold and intriguing vision that had the potential for a high impact on the field of "cognitive psychology." The panel thought she had an innovative approach in her "quantitative approach to motivational behavior," but they had "mixed views" about the implementation of her project and its "integration…into other aspects of behavioral and biomedical research."

3. Nature of Project Risks and Outcomes

Both the Pioneer and the three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 30 and Table 31).

a. Typology of Project Risks

Table 30. Characterization of Unique Project Risk (Cosmides)

Please indicate which of the following risks are applicable to the NDPA-funded project	Cosmides	Expert 1	Expert 2	Expert 3
Conceptual risk	x	x	x	
Technical risk	x			
Experience risk		x		
Multidisciplinary risk	x	x	x	x
None of these risks				

Source: Pioneer interview, Expert review

At least two of three experts thought Cosmides's work contained conceptual and multidisciplinary risks. Cosmides herself corroborated these assessments and added that technical risk was also involved.

In her interview, Cosmides commented on the risks of her research proposal. Regarding the technical risks of her project, Cosmides explained that her hypothesis required that her group "figure out how to approach it…and to develop…instruments." For instance, her survey methodology, experiment set-up, and quantitative methods are new and untried techniques in her field. Cosmides qualified her belief that her project involved an experience risk by saying that knowledge was required beyond her previous expertise because her lab was "developing a whole new framework for thinking about motivation." They "had to develop [the knowledge]."

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Cosmides's research:

> "The central theoretical notion in this research program, an Internal Regulatory Variable, had never been considered previously as a critical component in explaining human motivation…The field affect and motivation has been averse to postulating any internal mechanisms."
>
> "Behavioral and neural sciences have been averse to studying highly emotion-laden human faculties like kinship, anger, dominance, and sexual attraction and repulsion… Cosmides is among the first researchers to overcome the squeamishness of the rest of the field concerning these incredibly important yet under-studied topics."
>
> "Cosmides…seeks to integrate modern evolutionary biology with psychology and neuroscience -not just the throwaway pseudo-evolutionary biology that people evolved to run away from tigers, but sophisticated analyses of the logic of adaptive problems."
>
> "We should expect all systems to be geared towards optimizing an organism's decision-making. She and Tooby proposed new models and predictions from this functional perspective. This required their unique combination of expertise in biological anthropology, cognitive psychology and social psychology."

Experts lauded the integration of multiple areas of study in Cosmides's research (i.e., evolutionary biology, psychology, neuroscience) and appreciated her boldness in studying concepts that researchers have been hesitant to question (i.e., kinship, anger, dominance, sexual attraction and repulsion).

b. Typology of Potential Outcomes

Table 31. Characterization of Potential Pioneering Outcomes (Cosmides)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Cosmides	Expert 1	Expert 2	Expert 3
New Idea	x	x	x	x
Discovery of new empirical phenomenon	x	x	x	
New Methodology	x			
New Technology	x			
New Framework	x	x	x	x
None of these outcomes				

Source: Pioneer interview, Expert review

At least two of three experts believed Cosmides's research had the potential to advance new ideas, discover new phenomena, and synthesize new frameworks. Cosmides herself thought that her research had the potential to result in new ideas, new phenomena, new methodology, new technology and a new framework.

Cosmides explained the ways in which her research had the potential to produce pioneering outcomes. The new empirical phenomena that she believes may be discovered include "[internal] regulatory variables" and evidence of "certain emotions…having a re-calibrational function." This could change the way "anger and guilt and gratitude" are understood and have "clinical implications for various kinds of therapies." Cosmides used the example of "welfare trade-off ratios" as an example of a new methodology that she used to look at internal regulatory variables. The new technologies she believes may result from her NDPA project are "measuring instruments" for understanding human motivations.

Below is a selection of comments from experts that justify their evaluations of the potential pioneering outcomes of Cosmides's research:

> "Cosmides has opened up promising research programs on four topics that are central to human psychology and health but have almost never been studied in the lab: incest, anger, dominance, and kin altruism. In each case she has provided both a computational theory…AND a set of laboratory techniques by which they may be investigated."
>
> "Cosmides and [her] colleagues uncovered new phenomena (e.g. correlations between physical strength, anger and politics, or the existence of a 'kin-detection' estimation process in human minds)."
>
> "Cosmides' research is now demonstrating, through a series of empirical studies, the extent to which this new conception of cognition as motivation is relevant to understanding human emotion, as well as such disparate

domains as mating, political attitudes and the detection of violations of social norms."

Reviewers praised the unique framework that Cosmides proposed to look at psychological issues (i.e., computational theory).

c. Assessing Whether the Research Was Pioneering

The experts were also asked to rate whether Cosmides's research was pioneering. All three experts strongly agreed that Cosmides's research was pioneering. Below is a selection of comments from experts that explain their opinions:

> "Kinship detection is a matter of old interest, but lacks empirical evidence. This research has opened new alleys. It also changes the perspective on aggression."

> "Cosmides and Tooby were already pioneers in this field—but the NDPA allowed their lab to switch gears, and run much more extensive empirical studies. This has revitalized the field in the sense that many junior scientists are now working in this now much more visible field."

The experts believed that Cosmides's Pioneer project opened new doors by presenting a new quantitative framework for understanding human motivation.

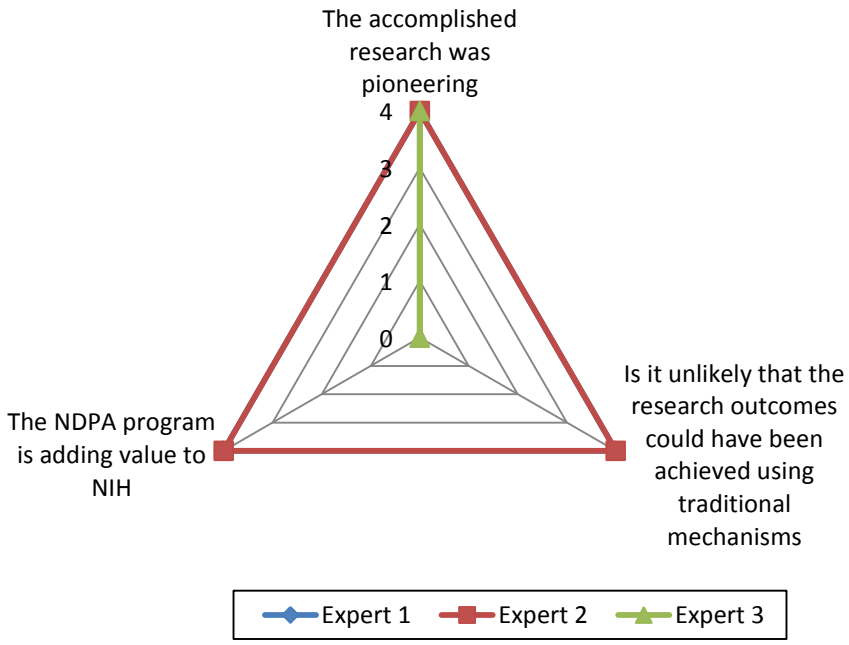
4. Value of the NDPA Program

a. Pioneer Perspective

Cosmides characterized the value of the NDPA program in a few different ways. She explained that it induced creative thinking as compared to the "regular granting system…because you have to already know a huge amount about your project in order to justify it to a panel." Since there is "no panel for NIH or NSF [for] … evolutionary psychology," her idea would never have been funded. The money allowed her to be flexible, and accelerate the pace of her research which normally would have taken "four times as long." She was able to perform research in new and multiple areas such as "visual attention." Cosmides noted that the NDPA also relieved her and her graduate students of their teaching duties so they could "focus on the research more."

b. Expert Perspective

Experts were additionally asked to rate whether Cosmides's results were a unique output of the Pioneer Award and whether the Pioneer Award is adding value to NIH (Figure 20).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 20. Experts' Opinions of the NDPA (Cosmides)

Two experts strongly agreed that Cosmides' research likely would not have been funded through traditional mechanisms. They also thought the NDPA was adding value to NIH. One reviewer declined to comment on these two questions because "as a European researcher, [he or she] was not aware enough of the funding instruments of the NIH." Below is a selection of comments from reviewers about the value of the NDPA program:

> "Cosmides in particular has faced high hostility from certain sectors, because the application of evolutionary biology to psychology and neuroscience has been politically controversial and simply unconventional. I do not think this research would have been funded by ordinary NIH channels. The fact that her work, once funded, got published in the highest quality journals, and received substantial press coverage, vindicates the rationale for the program, which is that there are a great deal of overlooked and underfunded, yet groundbreaking and scientifically solid research ideas that NIH mechanism as constituted are likely to miss."

> "There is a vast amount of research being funded by NIH that consists of minor variations around a small number of questions and experimental paradigms. The development of new theories that could seed the next generation of research questions, identify new topics to study, and integrate disparate findings into a framework that would be useful to

practitioners, has been hampered by the dynamics of the conventional review process."

"Scientific innovation often comes from non-traditional connections between phenomena in different fields—or from some scholar's decision to adopt entirely new tools to tackle a standard question. These are not usually funded through existing programs. NIH is very special in having actually done something substantial about that problem."

Experts praised the non-traditional methods (i.e., computational methods) and disciplines (i.e., evolutionary biology, psychology, neuroscience) that she integrated in her work.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Cosmides received the Pioneer Award in 2004, the pre-NDPA range refers to activity between 2001 and 2005, while the post-NDPA range refers to activity between 2006 and 2010.

a. Productivity

Cosmides published a total of 41 original articles over the 28 years of her research career, giving her an average of 1.46 publications per year (Table 32). In the pre-NDPA period, Cosmides published 15 original publications for a rate of 3 articles per year. In the post-NDPA period, Cosmides published 8 original publications for a rate of 1.6 per year.

Table 32. Summary of Publication Activity (Cosmides)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	15	8	5	41
Number of Years	5	5	N/A	28
Publication Rate	3	1.6	N/A	1.464286

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Cosmides published almost twice as many publications in her pre-NDPA period than in her post-NDPA period. Cosmides indicated in her interview that the NDPA funds supported her entire lab and allowed them to focus seriously on the research. The

development of new quantitative methods for studying affect and motivation may explain the lowered publication rate during the post-NDPA period.

Of the eight articles Cosmides published in the post-NDPA period, five were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 33.

Table 33. Publications Attributed to NDPA Funding (Cosmides)

Title	Journal	Year Published
Adaptive specializations, social exchange, and the evolution of human intelligence	Proceedings of the National Academy of Sciences of the United States of America	2010
Formidability and the logic of human anger	Proceedings of the National Academy of Sciences of the United States of America	2009
Human adaptations for the visual assessment of strength and fighting ability from the body and face	Proceedings of the Royal Society B-Biological Sciences	2009
Relative status regulates risky decision making about resources in men: evidence for the co-evolution of motivation and cognition	Evolution And Human Behavior	2008
Theory of mind broad and narrow: Reasoning about social exchange engages ToM areas, precautionary reasoning does not	Social Neuroscience	2006

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, Cosmides's 35 original publications excluding reviews had been cited a total of 2,294 times. In the post-NDPA period, Cosmides published 8 articles that had received a total of 101 citations by August 2010. The five articles attributed to NDPA funding had received a total of 30 citations.

Considering the near-term nature of the evaluation, the age-weighted citation rate values for the pre- and post-NDPA periods are similar. The articles that Cosmides published in the period after the award appear to be making a large impact on the scientific community.

Detailed information on her citations is shown in Table 34.

Table 34. Summary of Citation Analyses (Cosmides)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (35 pubs)	2,294	12.92	18
Pre-NDPA (10 pubs)	356	6.31	N/A
Post-NDPA (8 pubs)	101	5.53	N/A
Attributed to NDPA Funding (5 pubs)	30	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science

2) Journal Impact Factors

Cosmides published 15 publications in nine different sources during the pre-NDPA period and 8 publications in eight different sources during the post-NDPA period. Detailed information on Cosmides's most published-in journals for the pre- and post-NDPA time periods, respectively, is shown in Table 35 and Table 36.

Table 35. Most Published-in Journals in the Pre-NDPA period, 2001–2005 (Cosmides)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
5	Social Cognition	0.003738	57.12
3	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
1	Current Opinion in Neurobiology	0.054066	96.16
1	Evolution and Human Behavior	0.008166	74.99
1	Journal of Research in Personality	0.007341	73.09
1	Proceedings of The Royal Society of London Series B-Biological Sciences	0.100438	98.17
1	Psychological Bulletin	0.034533	93.21
1	Psychological Review	0.026458	91.17
1	Trends in Cognitive Sciences	0.053226	96.06

Source: Eigenfactor.org, Journal names came from Web of Science

Table 36. Most Published-in Journals in the Post-NDPA period, 2006–2010 (Cosmides)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
3	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
1	Evolution and Human Behavior	0.008166	74.99
1	Nature	1.76345	100
1	Proceedings of The Royal Society B-Biological Sciences	0.100438	98.17
1	Social Cognition	0.003738	57.12
1	Social Neuroscience	N/A	N/A

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 4 of Cosmides's 15 publications, 26.67%, were in journals at or above the 98th percentile (Table 37). In the post-NDPA period, 5 of Cosmides's 8 publications, 64.17%, were in journals of the same caliber. All three of her NDPA-attributed publications had Eigenfactor values above the 98th percentile.

Table 37. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Cosmides)

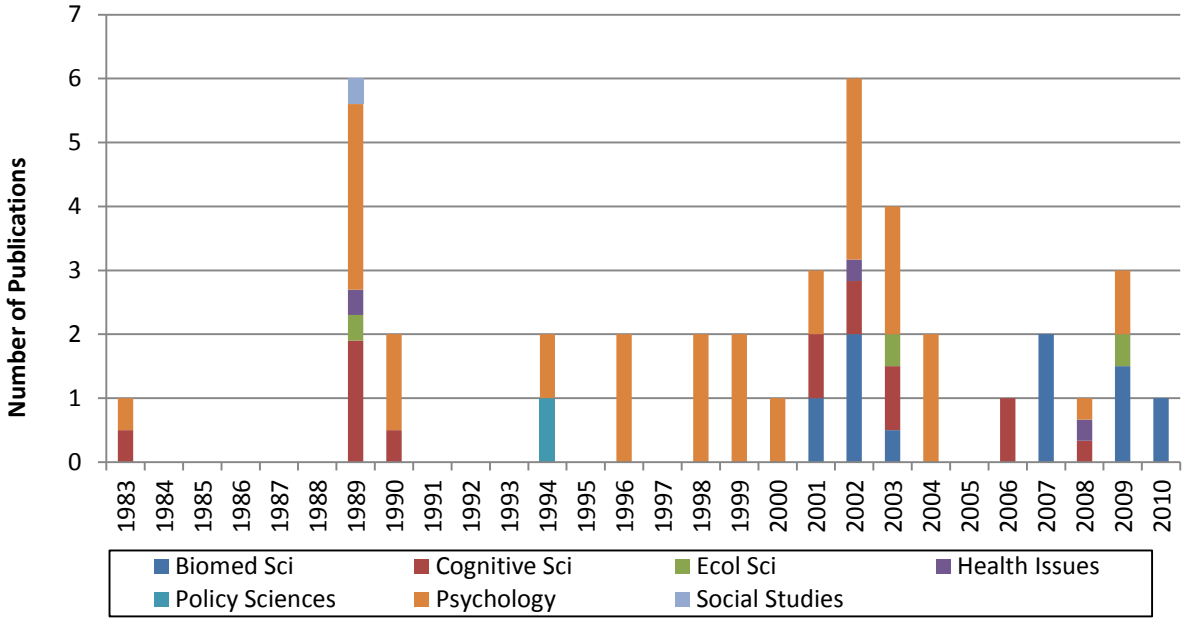
	Number of Publications	Percentage of Publications
Pre-NDPA (15 pubs)	4	26.67%
Post-NDPA (8 pubs)	5	62.50%
Attributed to NDPA Funding (5 pubs)	3	60.00%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data is from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Over the duration of her career, Cosmides's 41 publications may be categorized into a total of seven different macro-disciplines. She published in five macro-disciplines in the pre-NDPA period with 15 publications and five in the post-NDPA period with 8 publications. The distribution of Cosmides's publications into macro-disciplines for the full length of her career is displayed in Figure 21.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

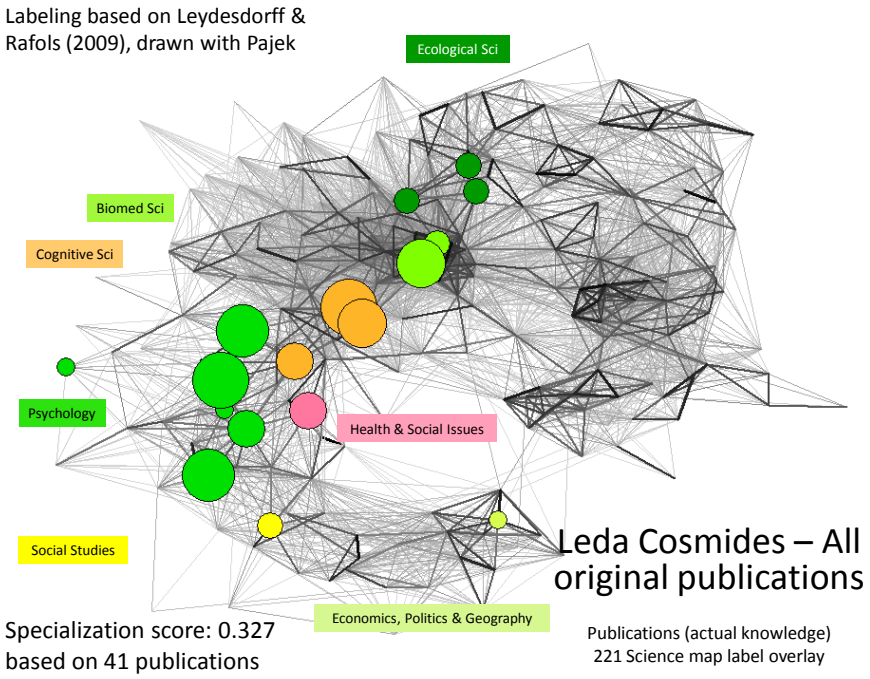
Figure 21. Distribution of Publications into Macro-disciplines over Time (Cosmides)

Cosmides has been highly multidisciplinary throughout her career, publishing primarily in journals categorized under Psychology, Cognitive Science, and Biomedical Science. Her work in emotion, reason, and motivation created a new field called evolutionary psychology that incorporates all of these macro-disciplines. The Biomedical Science focus emerged in the years leading up to her NDPA award, which may reflect the consideration of her previous research for clinical use.

2) Body of Knowledge Cited

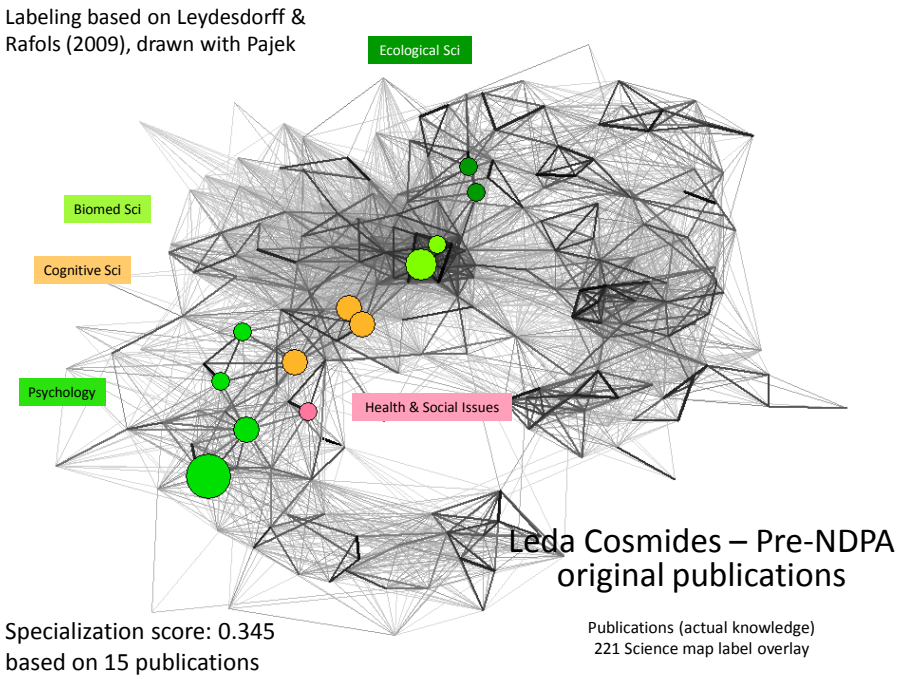
Cosmides cited eighteen different macro-disciplines in the 2,463 cited references of her 41 total career publications. This included sixteen macro-disciplines in the 1,121 cited references of her 15 pre-NDPA articles and fifteen macro-disciplines in the 433 cited references of her 8 post-NDPA articles. The range of the macro-disciplines of her cited

references may be visualized via the following maps of science overlays (Figure 22, Figure 23, and Figure 24).



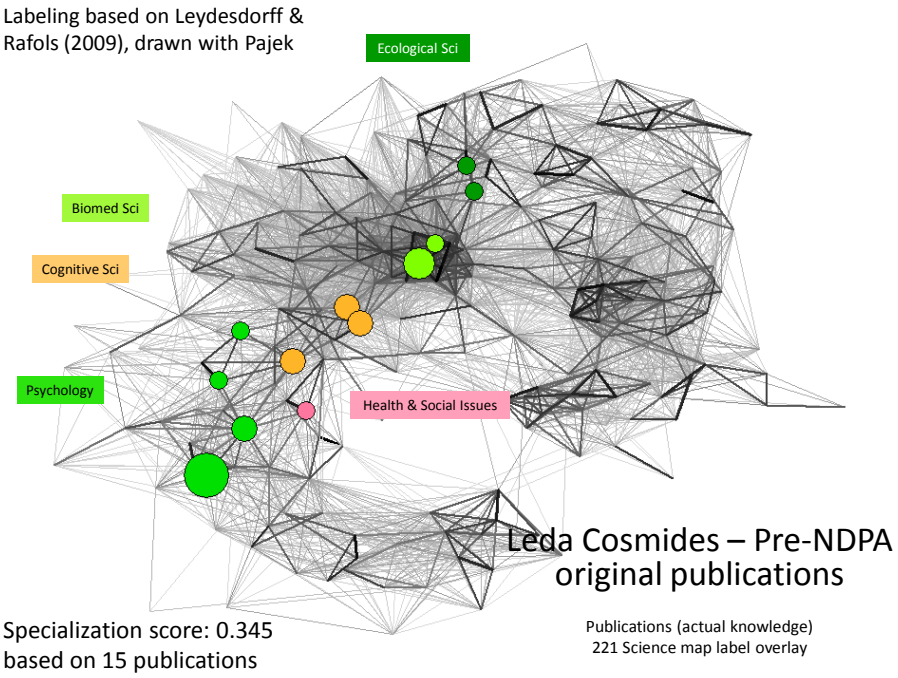
Note: Visualization by Pajek, Source: Web of Science

Figure 22. Map of Science Overlay for Cited References of All Original Publications (Cosmides)



Note: Visualization by Pajek, Source: Web of Science

Figure 23. Map of Science Overlay for Cited References of Pre-NDPA Publications (Cosmides)



Note: Visualization by Pajek, Source: Web of Science

Figure 24. Map of Science Overlay for Cited References of Post-NDPA Publications (Cosmides)

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. Detailed information for Cosmides is shown in Table 38.

Table 38. Integration and Specialization Scores (Cosmides)

	Full Career (2,463 cited references)	Pre-NDPA (1,121 cited references)	Post-NDPA (433 cited references)
Integration	0.700	0.658	0.713
Specialization	0.327	0.345	0.378

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

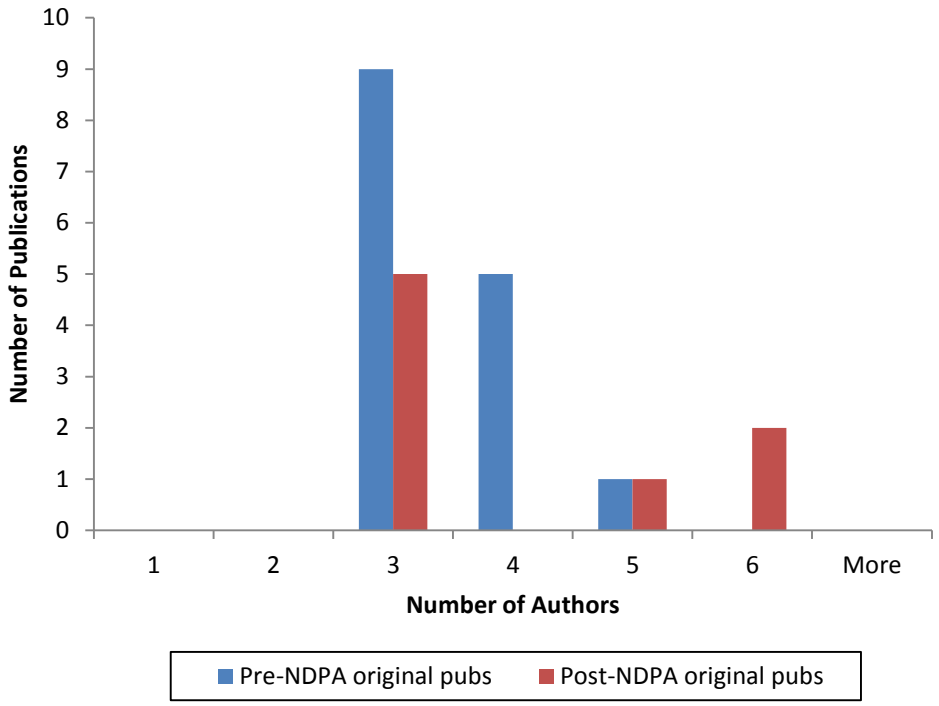
Compared to other Pioneers, Cosmides has been a "Renaissance integrator" for her full career and for the pre- and post-NDPA time periods.[20] These I and S scores correlate with what she and experts have said about the incorporation of multiple fields into her research, and they corroborate the information visualized in the cited reference and

[20] Porter et al. (2007) Measuring researcher interdisciplinarity.

publication set Maps of Science. Cosmides pulls from many knowledge areas to accomplish her research and consequently publishes her work in a wide range of areas.

d. Collaboration

The median number of total authors in Cosmides's publication set was three for her full career, pre-, and post-NDPA time periods. Information on the distribution and patterns of her co-authorship may be seen in Figure 25.



Source: Web of Science

Figure 25. Distribution of Number of Authors in Original Publication Set (Cosmides)

The number of unique authors in a researcher's publishing network is another metric that captures collaboration patterns. Cosmides has published with approximately 33 unique individuals throughout her full career. In the pre-NDPA period, she collaborated with 19 researchers. In the post-NDPA period, she collaborated with 16 researchers. Over her five NDPA-attributed publications, Cosmides published with nine other unique authors.

E. George Daley (2004)

1. Research Summary

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 Ph.D. in 1989 from the Massachusetts Institute of Technology where he worked in the lab 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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers believed Daley had evidence of a productive past in "blood cell cancer biology and differentiation." His proposal to "[reprogram] oocytes produced from mouse embryonic stem cells" was innovative because it moved him into a "new field of reproductive biology" and had a high risk of failure. Although his proposal was an extension of his current work, it had potential for a high-impact breakthrough. The panel was "very enthusiastic" about his project.

3. Nature of Project Risks and Outcomes

Both the Pioneer and the three STPI-found experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 39 and Table 40).

a. Typology of Project Risks

Table 39. Characterization of Unique Project Risk (Daley)

Please indicate which of the following risks are applicable to the NDPA-funded project	Daley	Expert 1	Expert 2	Expert 3
Conceptual risk			x	
Technical risk	x		x	
Experience risk	x	x	x	
Multidisciplinary risk	x	x	x	x
None of these risks				

Source: Pioneer interview, Expert review

At least two of three experts thought Daley's work contained experience and multidisciplinary risks. Daley himself thought his work contained technical, experience, and multidisciplinary risks.

In terms of the risks of his research, Daley that his proposal had an experience risk because he "didn't know a thing about microRNAs" before it began. In terms of the conceptual risk, Daley remarked that "there was a lot of wisdom hoping that this could be done," so that type of risk did not necessarily apply to his research.

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Daley's research:

> "George Daley's research…pioneered the reprogramming of somatic cells back into pluripotent cells, creating a way to generate patient-specific pluripotent cells for further study and treatment."
>
> "Demonstrating that lin 28 is a germline oncogene in mice and humans was a real leap forward, and involved an unprecedented combination of perspectives."
>
> "The concept that it might be possible to change the phenotype of cells was emerging but had never been demonstrated…Many researchers in related fields held it to be impossible to induce the change when the research began."

Experts thought Daley's proposal (i.e., reprogramming of somatic cells to pluripotent cells) had combined unique approaches and perspectives.

b. Typology of Potential Outcomes

Table 40. Characterization of Potential Pioneering Outcomes (Daley)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Daley	Expert 1	Expert 2	Expert 3
New Idea		x	x	x
New Phenomenon	x		x	
New Methodology	x		x	
New Technology				
New Framework	x	x	x	
None of these outcomes				

Source: Pioneer interview, Expert review

At least of two of three experts believed Daley's research could result in the formulation of new ideas and the synthesis of a new framework. Daley thought his research might lead to the discovery of new phenomena, the development of new methodology, and the synthesis of a new framework.

He also commented on the pioneering outcomes of his work. Daley explained that there was a "remarkable growth phenotype" and the possibility of "early puberty" in the "transgenic mice with *LIN-28*" that his lab studies. This discovery led to his lab's discussion of "a whole new way of thinking about *LIN-28*, so…there [would certainly be] new theories there." The new methodology in his research is the "iPS work." Daley noted that while his lab did not develop novel instruments, they "developed collaborations with people who were developing new technology" around "methylation and methylomics."

Below is a selection of comments from experts that justify their evaluations of the potential pioneering outcomes of Daley's research:

> "George was…among the first to generate iPS cells from human somatic cells, and the first to use this method to generate iPS cells from human disease cells."
>
> "His linking of early tissue development genes and oncogenesis, although often predicted, turned out to be true in fact. Both of these lines of research appear to be highly translational, and could result in therapies for both male sterility and germline tumors."
>
> "The opportunities…provided by the use of iPS cells are of the very greatest importance. It has also lead already to research to make the next step along this pathway by changing cells directly from one phenotype to another, in this case from fibroblast to neurons."

Reviewers believed Daley had demonstrated empirical phenomena that had been though impossible (i.e., reprogramming somatic cells to pluripotent cells). They also remarked on the important opportunities for human therapies that Daley's research has generated (i.e., cancer, male sterility).

c. Assessing Whether the Research Was Pioneering

The experts were asked whether they believed Daley's research was pioneering. Two experts strongly agreed and one moderately agreed that Daley's research was pioneering. Below is a selection of explanatory comments from experts about the pioneering nature of Daley's research:

> "George Daley's recent work is truly pioneering in the field, allowing for the realization of the dream of generating patient-specific pluripotent cells, which can then be used to study the disease model, to screen drugs against the disease, and to perform cell-based therapy to treat the related diseases."
>
> "Daley had the right idea for looking for reprogramming to pluripotency, but others did NT and iPS first. Daley applied these ideas and brought original ideas to the problems of specification of the germline and the hematopoietic lineages from in vitro pluripotent stem cell lines."

All three experts believed that Daley's research was pioneering. While he performed important discovery work, the experts found his application of previously-known ideas to disease models to be his most pioneering work.

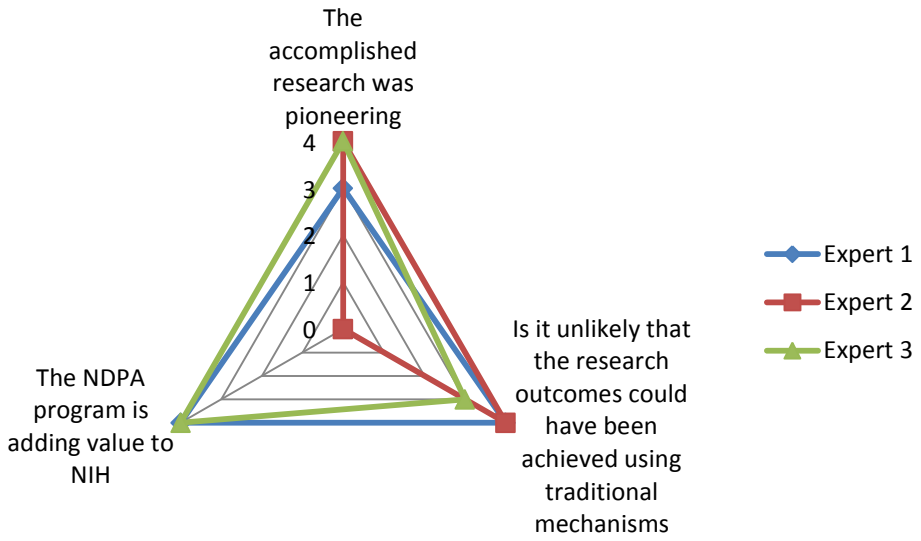
4. Value of the NDPA Program

a. Pioneer Perspective

Daley described the value of the NDPA program in several ways. For one, it allowed him to *take a long-term view* because if head to work according to "NIH study section deliverables…[he] would have been on the cusp of not getting…that work funded or certainly not renewed." He also stressed how the NDPA enabled him to *be flexible*. For instance, his lab "would have almost certainly not pursued to as great a degree the Lin-28 work" because of lack of funding. The NDPA allowed him to give "one graduate student …a long leash to pursue a couple of sort of crazy ideas,…one of which was aimed at understanding biomedical forces and the ability to generate blood, the idea being that the heartbeat was actually the signal for blood development in…embryo." Furthermore, the NDPA facilitated Daley's *undertaking of multiple projects and strategies*. The research he was doing "generated such incredibly exciting offshoots" and "without that money [he] would have had to refocus and change directions into much more predictable areas." Normally, "you're doing what can be done, not what you hope could be done."

b. Expert Perspective

Experts were additionally asked to rate the value of the NDPA program in terms of the research it is funding and in terms of what it brings to the NIH portfolio (Figure 26).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 26. Experts' Opinions of the NDPA (Daley)

All three experts strongly believed that it was unlikely that Daley's research would have been funded using traditional mechanisms. The reviewers believe that while the standard R01-type mechanisms inherently fund only conservative research, the NDPA mechanism is a step in the right direction for supporting creative research. Two believed the NDPA was adding value to NIH. One reviewer declined to comment citing their lack of familiarity with NIH's current portfolio. Below is a selection of comments from reviewers about the value of the NDPA program:

> "While the 'bedrock' funding mechanisms such as R01 support the majority of research, it is obvious such mechanisms and the review processes lean toward supporting conservative research instead of very creative research.
>
> "The program encourages researchers to be ambitious and provides generous funding to allow them to make rapid progress."
>
> "I am convinced that the classical NIH peer review system is just a shadow of what it was 20-25 years ago. Then…it was expert review. Now it is simply…a rare few experts, many average scientists in the field, and a few who have no measurable accomplishments. Added to that is the current…admonition to the reviewers that the primary objective of review is to judge whether THE PROPOSED EXPERIMENTS WILL WORK… it is rare in the genesis of scientific discovery that the proposed experiments work as listed at one point in time."

Experts generally agreed that Daley's research likely would not have been funded through traditional mechanisms because it was ambitious and creative. Two experts strongly agreed and one declined to respond that the NDPA is adding value to NIH.

5. Descriptive Bibliometrics

Terms included in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Daley received the Pioneer Award in 2004, his pre-NDPA range is from 1999 to 2004, and his post-NDPA range is from 2005 to 2010.

a. Productivity

Daley has published a total of 240 original articles over the 30 years of his research career, giving him an average of 8 original publications per year (Table 41). In the pre-NDPA period, Daley published 73 articles for a rate of 12.17 per year, and in the post-NDPA period, Daley published 137 articles for a rate of 22.83 articles per year.

Table 41. Summary of Publication Activity (Daley)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	73	137	24	240
Number of Years	6	6	N/A	30
Publication Rate	12.16667	22.83333	N/A	8

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Daley published many more original works in the post-NDPA period than in the pre-NDPA period. Of the 137 articles he published after the award, 24 were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 42.

Table 42. Publications Attributed to NDPA Funding (Daley)

Title	Journal	Year Published
A role for Lin28 in primordial germ-cell development and germ-cell malignancy	Nature	2009
Activation of tyrosine kinases by mutation of the gatekeeper threonine	Nature Structural & Molecular Biology	2008
AP24163 Inhibits the Gatekeeper Mutant of BCR-ABL and Suppresses In vitro Resistance	Chemical Biology & Drug Design	2010
Autologous blood cell therapies from pluripotent stem cells	Blood Reviews	2010
Biomechanical forces promote embryonic haematopoiesis	Nature	2009
Bone-marrow adipocytes as negative regulators of the haematopoietic microenvironment	Nature	2009
Cross-regulation of the Nanog and Cdx2 promoters	Cell Research	2009
Disease Models from Pluripotent Stem Cells Turning Back Time in Disease Pathogenesis?	Hematopoietic Stem Cells VII, Annals of the New York Academy of Sciences	2009
Disease-specific induced pluripotent stem cells	Cell Research	2008
Down's syndrome suppression of tumour growth and the role of the calcineurin inhibitor DSCR1	Nature	2009
Enhanced plating efficiency of trypsin-adapted human embryonic stem cells is reversible and independent of trisomy 12/17	Cloning and Stem Cells	2008
From Fibroblasts to iPS Cells: Induced Pluripotency by Defined Factors	Journal of Cellular Biochemistry	2008
Generation of Functional Human Hepatic Endoderm from Human Induced Pluripotent Stem Cells	Hepatology	2010
Generation of human-induced pluripotent stem cells	Nature Protocols	2008
Generation of induced pluripotent stem cells from human blood	Blood	2009
Hematopoietic Development From Human Induced Pluripotent Stem Cells	Blood	2009
Hematopoietic Development from Human Induced Pluripotent Stem Cells	Hematopoietic Stem Cells VII, Annals of the New York Academy of Sciences	2009
ICSBP-mediated immune protection against BCR-ABL-induced leukemia requires the CCL6 and CCL9 chemokines	Blood	2009
Knockdown of Fanconi anemia genes in human embryonic stem cells reveals early developmental defects in the hematopoietic lineage	Blood	2010
Lin28 promotes transformation and is associated with advanced human malignancies	Nature Genetics	2009
Lin28a transgenic mice manifest size and puberty phenotypes identified in human genetic association studies	Nature Genetics	2010
Live cell imaging distinguishes bona fide human iPS cells from partially reprogrammed cells	Nature Biotechnology	2009
Ras-MAPK signaling promotes trophectoderm formation from embryonic stem cells and mouse embryos	Nature Genetics	2008
Surface antigen phenotypes of hematopoietic stem cells from embryos and murine embryonic stem cells	Blood	2009

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, Daley's 219 original publications excluding reviews had been cited a total of 9, 640 times. In the post-NDPA period, Daley published 126 articles that had received 2,902 citations by August 2010. Of the 126 post-NDPA articles, 24 were attributed to NDPA funding and they received a total of 580 citations.

Daley's post-NDPA age-weighted citation rate is higher than that for his pre-NDPA period. His research after the Pioneer Award, particularly his research attributed to NDPA funding, has had a lot of impact on the scientific community. His most-cited article that was attributed to the NDPA had received 235 citations since being published in 2008.

Table 43 presents the citation analyses for Daley's publication sets.

Table 43. Summary of Citation Analyses (Daley)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (219 pubs)	9,640	32.48	44
Pre-NDPA (67 pubs)	4,448	21.74	N/A
Post-NDPA (126 pubs)	2,902	30.07	N/A
Attributed to NDPA Funding (24 pubs)	580	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science

2) Journal Impact Factors

Daley published 73 original articles in thirty-two different sources in the pre-NDPA time period, and 137 original articles in fifty different sources in the post-NDPA period. Detailed information on Daley's most published-in journals for the pre- and post-NDPA time periods are shown in Table 44 and Table 45.

Table 44. Most Published-in Journals in the Pre-NDPA Period, 1999-2004 (Daley)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
27	Blood	0.462532	99.82
5	Oncogene	0.259466	99.54
3	Cell	0.671695	99.89
3	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
2	Biotechnology and Bioengineering	0.037731	93.82
2	Circulation	0.482604	99.84
2	Experimental Hematology	0.024601	90.43
2	Leukemia	0.059435	96.61
2	Nature	1.76345	100
2	Nature Genetics	0.321781	99.68
2	Stem Cells	0.060358	96.71

Source: Eigenfactor.org, Journal names came from Web of Science

Table 45. Most Published-in Journals in the Post-NDPA Period, 2005-2010 (Daley)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
38	Blood	0.462532	99.82
10	Experimental Hematology	0.024601	90.43
8	Nature	1.76345	100
7	Cell Stem Cell	N/A	N/A
4	Cell	0.671695	99.89
4	Nature Biotechnology	0.147052	98.94
4	Nature Genetics	0.321781	99.68

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 52 of Daley's 73 publications, 70.27%, were in journals at or above the 98th percentile (Table 46). In the post-NDPA period, 84 of Daley's 137 publications, 61.76%, were in journals of the same caliber. Of the 24 NDPA-attributed publications, 16 were published in journals at the 98th percentile or above.

Table 46. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Daley)

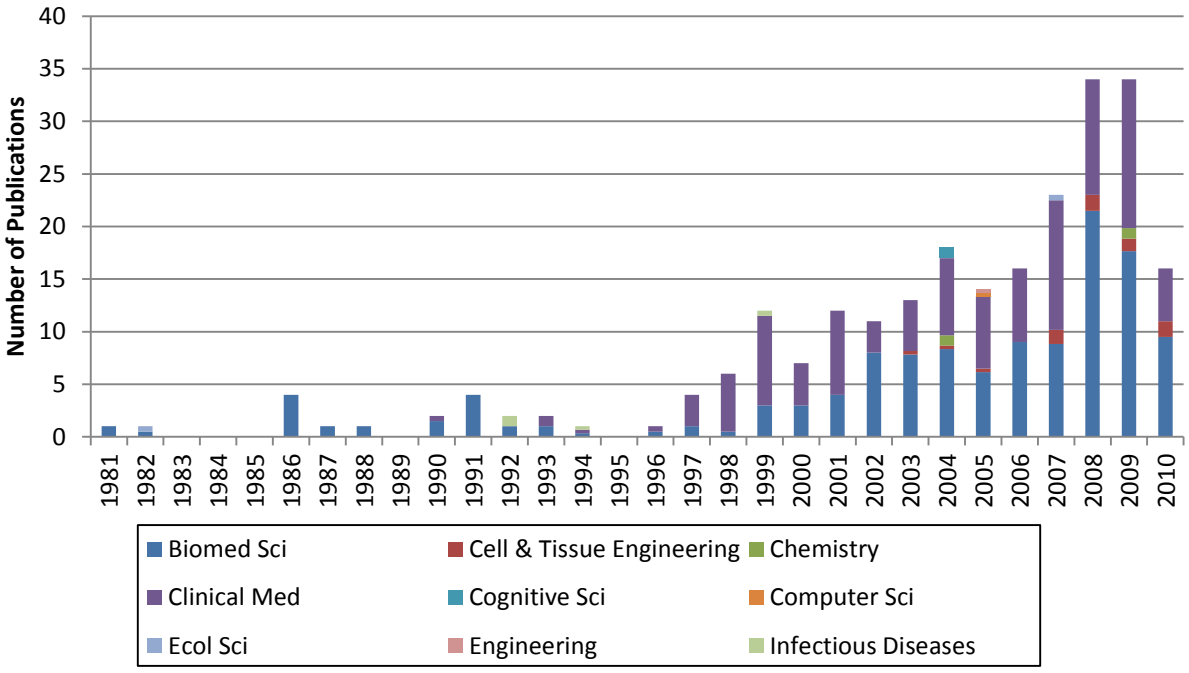
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (73 pubs)	52	70.27%
Post-NDPA (137 pubs)	84	61.76%
Attributed to NDPA Funding (24 pubs)	16	66.67%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data is from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Daley's 240 publications over the duration of his career can be categorized into a total of nine different macro-disciplines. He published in six disparate macro-disciplines in the pre-NDPA period with 73 publications, and seven in the post-NDPA period with 137 publications. The distribution of Daley's publications into macro-disciplines for the full length of his career may be seen in Figure 27.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 27. Distribution of Publications into Macro-disciplines over Time (Daley)

Daley has spent most of his career in Biomedical Science and Clinical Medicine with his work on cell reprogramming and its applications to tissue regeneration and other diseases. The broader applications of his work can be seen with his dabbling in Cell & Tissue Engineering and Infectious Diseases.

2) Body of Knowledge Cited

Daley cited fifteen different macro-disciplines in the 7,134 cited references of his 240 career publications. This included twelve macro-disciplines in the 2,469 cited references of his 73 pre-NDPA publications and fourteen macro-disciplines in the 3,847 cited references of his 137 post-NDPA publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The scores for Daley are shown in Table 47.

Table 47. Integration and Specialization Scores (Daley)

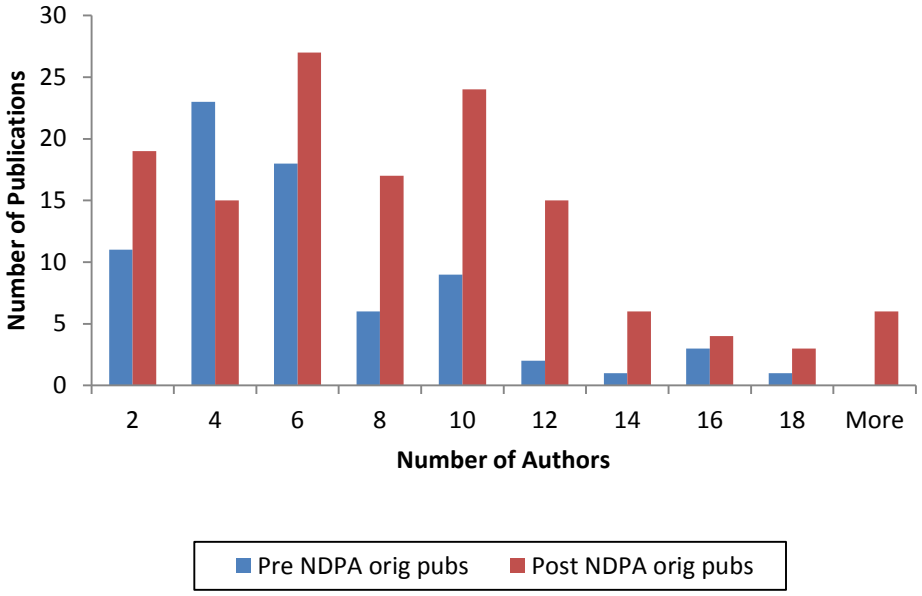
	Full Career (7134 cited references)	Pre-NDPA (2469 cited references)	Post-NDPA (3847 cited references)
Integration	0.408	0.417	0.409
Specialization	0.635	0.615	0.666

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, Daley appears to be a "Disciplinarian" for all three time ranges. Regardless of the changes in his publishing patterns, Daley continued to publish in and draw knowledge from similar fields.

d. Collaboration

The median number of total authors in Daley's publication set was six. In the pre-NDPA period, the median was five, while in the post-NDPA period, the median was seven. A comparison of the pre- and post-NDPA distributions of the total number of authors can be seen in Figure 28.



Source: Web of Science

Figure 28. Distribution of Number of Authors in Original Publication Set (Daley)

The number of unique authors in a researcher's publishing network is another metric that captures collaboration patterns. Daley has published with approximately 94 unique individuals throughout his full career. In the pre-NDPA period, he published with 199 researchers, and in the post-NDPA period, he published with 515 researchers. Over his 24 NDPA-attributed publications, Daley published with 133 other unique authors.

F. Titia de Lange (2005)

1. Research Summary

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 which 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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers believed that de Lange proposed a new and innovative approach to studying "the initiation of the DNA damage pathway in mammalian cells based on disruption of telomeres to expose new DNA ends," which was a departure from her previous work. The panel believed that her project required substantial technological developments before a high impact breakthrough could result from her "field-enabling" research. The panel was "very enthusiastic" about the potential of her project.

3. Nature of Project Risks and Outcomes

Both the Pioneer and the three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 48 and Table 49).

a. Typology of Project Risks

Table 48. Characterization of Unique Project Risk (de Lange)

Please indicate which of the following risks are applicable to the NDPA-funded project	de Lange	Expert 1	Expert 2	Expert 3
Conceptual risk			x	
Technical risk	x		x	
Experience risk	x	x		x
Multidisciplinary risk	x			x
None of these risks				

Source: Pioneer interview, Expert review

Two experts thought de Lange's research contained an experience risk. De Lange indicated that her research incorporated technical, experience, and multidisciplinary risks.

In her interview, de Lange explained that the technique she proposed for studying DNA damage response, the rapid uncapping of telomere ends, had never before been studied. In fact, the chemical techniques she first used in her attempt to "inhibit telomere function" did not work, so a ts mutant had to be developed instead. Her project also

required her to build knowledge in DNA damage response, so an experience risk was involved.

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of de Lange's research:

> "The time-lapse microscopy analysis of uncapped telomeres…are novel in the field and probably had to be first established in the de Lange lab."
>
> "One fundamental idea…is that the outcome of DNA damage signaling is cell cycle arrest. De Lange revealed an unexpected role for DNA damage signaling and chromatin mobility in DNA repair."
>
> "The detailed insights demonstrated by Dr. de Lange's work…go beyond the expected or standard expertise of a telomere biologist and would have required an extensive immersion in the general genomic DNA damage response."
>
> "The idea of using controlled telomere inactivation as a mode of inducing site-specific DNA damage as a model for the general DNA damage response is a novel one that stands slightly 'outside the box.'"

Experts recognized the novelty of de Lange's approach to studying DNA damage response (i.e., in using telomere inactivation).

b. Typology of Potential Outcomes

Table 49. Characterization of Potential Pioneering Outcomes (de Lange)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	de Lange	Expert 1	Expert 2	Expert 3
New Idea		x	x	x
New Phenomenon	x			x
New Methodology	x			x
Invention of a new technology				
New Framework				x
None of these outcomes				

Source: Pioneer interview, Expert review

At least two of three experts found that de Lange's research had the potential to result in the formulation of new ideas. De Lange believed her research could result in the discovery of new phenomena and the development of new methodologies.

Below is a selection of comments from experts that justify their evaluations of the potential pioneering outcomes of de Lange's research:

> "De Lange's work advanced the ideas that DNA damage signaling and chromatin mobility facilitate DNA repair."

> "The discovery that 53BP1 associates with uncapped telomeres, making them highly mobile, was completely unexpected… The concept that the dynamic behavior of dysfunctional telomeres or DNA double strand breaks may facilitate nonhomologous DNA end joining is new and probably very important."

> "The proposed research certainly revealed new information, on the cell cycle dependence of different types of responses to dysfunctional telomeres, the individual contributions of each telomere component to control of local DNA damage responses, the notion that DNA damage does not necessarily lead to overt nucleosome disruption in the vicinity (although I disagree that the technique devised could distinguish the terminal nucleosome on the chromosome—this is a technical issue that may be addressable), the role of specific proteins in controlling the ability of chromosome ends to move within the nucleus and the consequences of this movement for telomeric events."

They also found that her results relating to DNA damage signaling, chromatin mobility, and the contributions of telomere components in the control of local DNA damage responses were new and pioneering outcomes.

c. Assessing Whether the Research Was Pioneering

The experts were also asked to rate whether de Lange's research was pioneering. All three experts strongly agreed that de Lange was pioneering. Below is a selection of comments from experts about why de Lange's research was or was not pioneering:

> "Titia de Lange has pioneered the structural and functional analysis of mammalian telomeres…She has dissected the mechanisms of telomere fusions that occur upon loss of shelterin function (this grant). Without her amazing work the telomere field would be much less advanced."

> "The idea that telomeres must be distinguished from sites of damage triggered the inception of the telomere concept, but the idea of using controlled telomeric de-protection as a framework for understanding the DNA damage response in general was pioneering."

> "De Lange has not been satisfied to use the 'blunt' tools like overexpressed proteins and dominant negative alleles for her studies, but rather has developed the types of tools that have been largely confined in the past to studies in genetically amenable systems like yeast."

All three experts acknowledged that de Lange's work contributed greatly to the understanding of telomeres and that she developed refined tools to enhance her research.

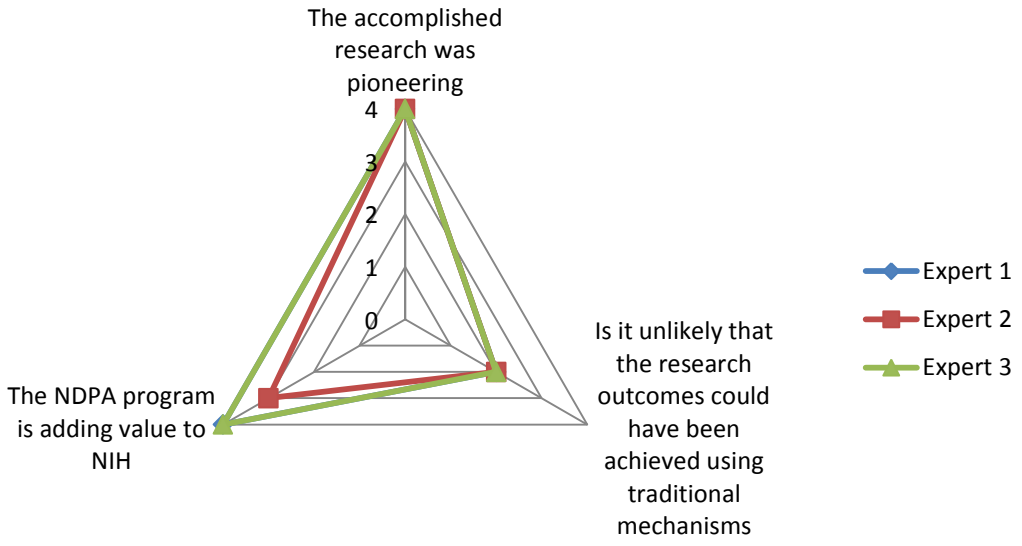
4. Value of the NDPA Program

a. Pioneer Perspective

De Lange explained that the NDPA funds allowed her to *take a long-term view* and *be flexible* because her kind of research varies a lot. The duration of five years and the large amount was necessary for her project. She also explained that the award *induced creative thinking*; the possibility of getting the money engendered her Pioneer project idea. The money also enabled her to perform *resource-intensive projects*. Her lab would neither have been able to perform the screen because it cost one dollar per compound, nor pay as easily for the mice with which they work. Furthermore, the other approaches taken for her project took a lot of time and three post-docs; they might not have been able to find funding for parts of those projects. If she had not been funded, she would have attempted to perform parts of the research, but would have been unable to do the screening and focus as much time on the idea.

b. Expert Perspective

Experts were additionally asked to rate the value of the NDPA program in terms of the research it is funding and in terms of what it brings to the NIH portfolio (Figure 29).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 29. Experts' Opinions of the NDPA (de Lange)

All three experts moderately disagreed that it is unlikely that the research outcomes could have been achieved using traditional mechanisms. Two experts strongly agreed and one expert moderately agreed that the NDPA is adding value to NIH. Below is a selection of comments from reviewers about the value of the NDPA program:

> "The research proposed herein may have also been deemed sufficiently likely to succeed by a normal NIH study section…Nonetheless, I think Dr. de Lange is the perfect example of a pioneer who continues to push the boundaries…She should not be saddled to a constant process of fundraising nor limited to performing only those experiments that are guaranteed to succeed and/or to do so quickly."

> "It sounds like this is more trying to get 'high-risk' research that might not get funded. In this case, I really don't know if this research wouldn't have been funded through more traditional mechanisms."

> "Very innovative research necessarily is of higher risk as the outcome and success of experiments is less predictable…The impact of it may often surpass the results obtained with more conventional approaches."

The experts somewhat disagreed that de Lange's research could not have been funded through traditional mechanisms, but they all agreed that the NDPA is adding value to the NIH portfolio because it is important to fund innovative research.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since de Lange received the Pioneer Award in 2005, the pre-NDPA range refers to activity between 2001 and 2005, while the post-NDPA range refers to activity between 2006 and 2010.

a. Productivity

De Lange published a total of 111 original articles over the 29 years of her research career, giving her an average of 3.83 original publications per year (Table 50). In the pre-NDPA period, de Lange published 27 original publications for a rate of 5.4 original publications per year. In the post NDPA period, she published 24 original publications for a rate of 4.8 publications per year.

Table 50. Summary of Publication Activity (de Lange)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	27	24	5	111
Number of Years	5	5	N/A	29
Publication Rate	5.4	4.8	N/A	3.827586

The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science

De Lange published slightly more in the pre-NDPA period than in the post-NDPA period. Of the 27 articles de Lange published in the period after receiving the award, five were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 51.

Table 51. Publications Attributed to NDPA Funding (de Lange)

Title	Journal	Year Published
53BP1 promotes non-homologous end joining of telomeres by increasing chromatin mobility	Nature	2008
Cell cycle control of telomere protection and NHEJ revealed by a ts mutation in the DNA-binding domain of TRF2	Genes & Development	2008
How Telomeres Solve the End-Protection Problem	Science	2009
No overt nucleosome eviction at deprotected telomeres	Molecular and Cellular Biology	2008
Persistent Telomere Damage Induces Bypass of Mitosis and Tetraploidy	Cell	2010

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation analyses

Throughout her career, as of August 2010, de Lange's 102 original publications excluding reviews had been cited a total of 14,953 times. In the post-NDPA period, de Lange published 22 publications that had received a total of 721 citations by August 2010. Five of those 22 publications were attributed to NDPA funding and they received a total of 103 citations.

Of the 2004 and 2005 Pioneers, de Lange had the second highest h-index, a metric which speaks to her impact as well as productivity. Half of the papers de Lange published in the pre-NDPA period had over 100 citations, which contributed substantially to her high h-index value.

The statistics on this publication set are displayed in Table 52.

Table 52. Summary of Citation Analyses (de Lange)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full career (102 pubs)	14,953	36.76	61
Pre-NDPA (24 pubs)	3,375	20.26	N/A
Post-NDPA (22 pubs)	721	14.70	N/A
Attributed to NDPA Funding (5 pubs)	103	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

De Lange published 27 publications in eighteen different sources in the pre-NDPA time period and 24 publications in eleven different sources in the post-NDPA period. Detailed information on de Lange's most published-in journals in both time periods can be found in Table 53 and Table 54.

Table 53. Most Published-in Journals in the Pre-NDPA Period, 2001-2005 (de Lange)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
4	EMBO Journal	0.283977	99.6
3	Current Biology	0.252795	99.5
3	Genes & Development	0.278064	99.59
2	Journal of Biological Chemistry	1.32919	99.96
2	Molecular Cell	0.285021	99.61

Source: Eigenfactor.org , Journal names came from Web of Science

Table 54. Most Published-in Journals in the Post-NDPA Period, 2006-2010 (de Lange)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
4	Cell	0.671695	99.89
4	Genes & Development	0.278064	99.59
4	Molecular and Cellular Biology	0.322537	99.7
3	Science	1.58309	99.98
2	Journal of Biological Chemistry	1.32919	99.96
2	Nature	1.76345	100

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 25 of de Lange's 27 publications, 92.59%, were in journals at or above the 98th percentile (Table 55). In the post-NDPA period, 22 of de Lange's 24 publications, 91.67%, were in journals of the same caliber. All of de Lange's NDPA-attributed publications had Eigenfactor values above the 98th percentile.

Table 55. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (de Lange)

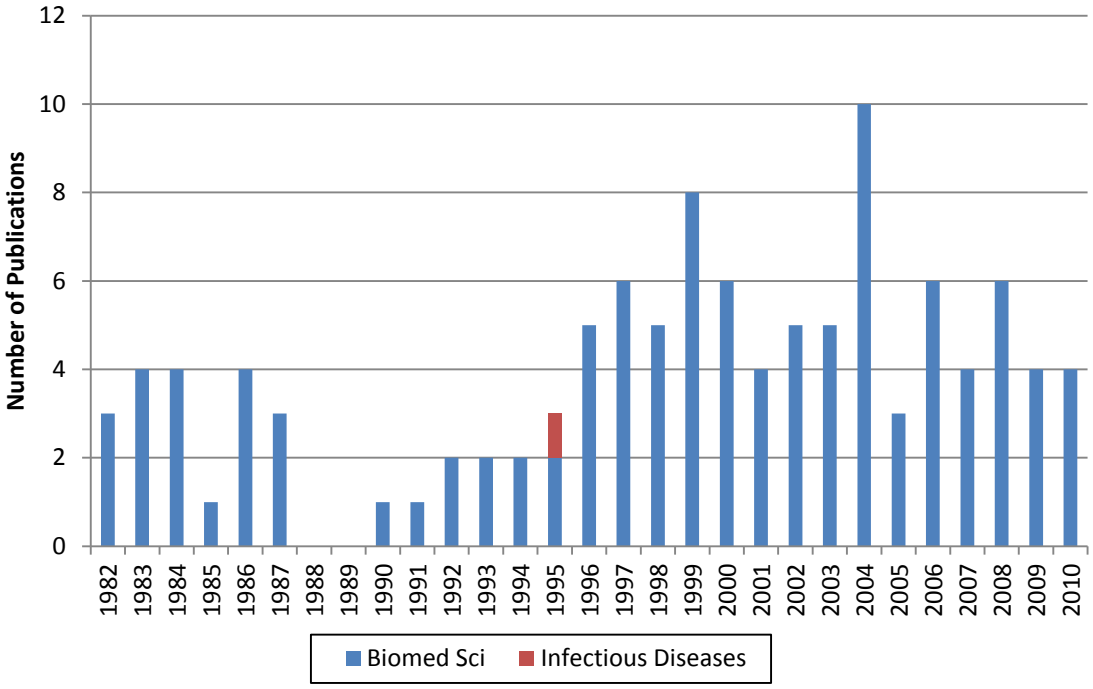
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (27 pubs)	25	92.59%
Post-NDPA (24 pubs)	22	91.67%
Attributed to NDPA Funding (5 pubs)	5	100.00%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data is from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

De Lange published in a total of two macro-disciplines over 111 original publications of her career. She published in one macro-discipline in both her pre- and post-NDPA periods with 27 and 24 publications respectively. The distribution of her publications into macro-disciplines may be seen in Figure 30.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one.

Figure 30. Distribution of Publications into Macro-disciplines over Time (de Lange)

De Lange remained in Biomedical Science throughout the duration of her career with her research on telomeres. Compared to the Pioneers, she had the lowest number of macro-disciplines represented by her publications.

2) Body of Knowledge Cited

De Lange cited thirteen different macro-disciplines over the 5,075 references of her 111 career publications. This included ten macro-disciplines in the 1,372 references of her 27 pre-NDPA publications and nine macro-disciplines in the 1,177 references of her 24 post-NDPA publications.

d. Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The scores for de Lange are shown in Table 56.

Table 56. Integration and Specialization Scores (de Lange)

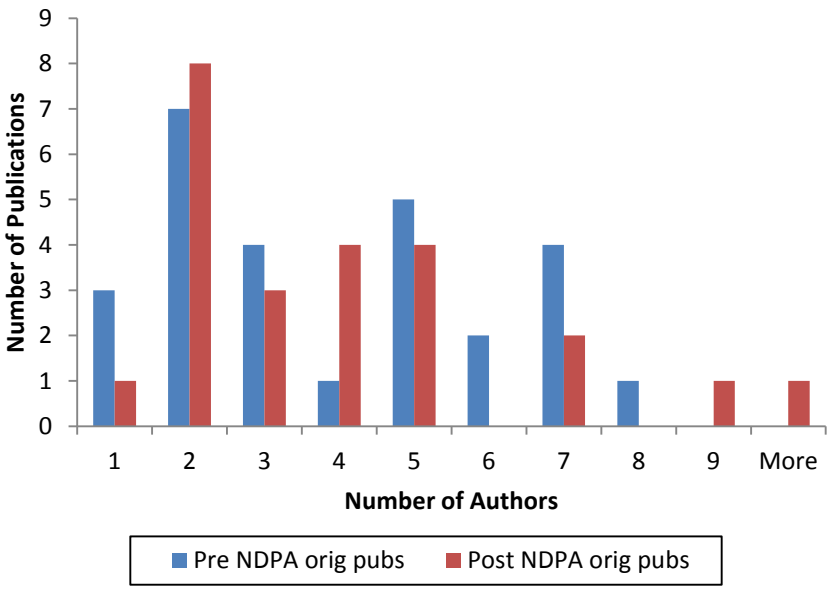
	Full Career (5075 cited references)	Pre-NDPA (1372 cited references)	Post-NDPA (1177 cited references)
Integration	0.248	0.262	0.254
Specialization	0.868	0.882	0.873

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, de Lange is a strict "Disciplinarian" for all three time periods. Based on her continuing work on her continuous work in molecular genetics, this assessment of her research seems valid.

e. Collaboration

The median number of total authors in de Lange's publication set was four. In the pre-NDPA period, this median was three, and in the post-NDPA period, the median was 3.5. The distribution of publication authors and the authorship patterns are displayed in Figure 31.



Source: Web of Science

Figure 31. Distribution of Number of Authors in Original Publications (de Lange)

The number of unique authors in a researcher's publishing network is another metric that captures collaboration patterns. De Lange has published with approximately 195 unique individuals throughout her full career. She published with 57 researchers in the

pre-NDPA period and 52 researchers in the post-NDPA period. Over her five NDPA-attributed publications, she published with seven other people.

G. Karl Deisseroth (2005)

1. Research Summary

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.[21]

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 US 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.

2. NDPA Reviewer Panel Opinions

The panel of reviewers stated that Deisseroth proposed an innovative approach to research the development of technology that induced "action potentials in a controllable manner based on light." While the panel noted the project's potential for a high-impact breakthrough, there was "substantial concern" about obstacles to the technology's application.

3. Nature of Project Risks and Outcomes

Both the Pioneer and the three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 57 and Table 58).

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

a. Typology of Project Risks

Table 57. Characterization of Unique Project Risk (Deisseroth)

Please indicate which of the following risks are applicable to the NDPA-funded project	Deisseroth	Expert 1	Expert 2	Expert 3
Conceptual risk				
Technical risk	x	x	x	x
Experience risk	x			x
Multidisciplinary risk	x	x		x
None of these risks				

Source: Pioneer interview, Expert review

At least two of three experts agreed that Deisseroth's proposal incorporated technical and multidisciplinary risks. Deisseroth himself thought his proposal had technical, experience, and multidisciplinary risks.

In his interview, Deisseroth commented on the nature of the risks in his proposal. He explained that while the study of psychiatric disease through inherent chemical imbalances was and is the prevailing wisdom, his use of optogenetics is a different, yet not competing, perspective. He also believed that his proposal forced him into a new area of study, plant biology.

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Deisseroth's research:

> "This research thus requires a unique and highly integrative approach to the nervous system, spanning molecular, cellular, systems and behavioral levels. Many of the experiments demonstrated by Deisseroth were considered impossible for generations, and have opened up entirely new avenues of inquiry."
>
> "The goal to develop a general method to optically control activity of specific neuronal populations with single-spike temporal resolution was a bold and unique concept. While there was proof of principle support for such a technology, the more systematic testing of such techniques…required the freedom provided by the NDPA program."
>
> "The expertise needed to meet the evolving goals of this project required flexible access to a wide variety of potentially changing co-investigators (physiology, engineering, systems neuroscience, disease pathophysiology)."

The reviewers believed Deisseroth's research presented a unique idea (i.e., to "optically control activity of specific neuronal populations with single-spike temporal resolution") and a multidisciplinary risk (i.e., use of "physiology, engineering, systems neuroscience, disease pathophysiology").

b. Typology of Potential Outcomes

Table 58. Characterization of potential pioneering outcomes (Deisseroth)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Deisseroth	Expert 1	Expert 2	Expert 3
New Idea	x	x	x	x
New Phenomenon	x		x	x
New Methodology	x	x	x	x
Invention of a new technology	x	x	x	x
New Framework	x	x		x
None of these outcomes				

Source: Pioneer interview, Expert review

At least two of three experts believed Deisseroth's research had the potential to achieve all five typology outcomes: formulate new ideas, discover new phenomena, develop a new methodology, invent new technology, and synthesize a new framework.

Deisseroth also remarked on the potential outcomes of his research project and the ways in which they are pioneering. His proposal to use circuit dynamics to understand disease is a new idea in the study of psychiatry. His lab developed new instruments that combined optics and electronics to perform the research. He also developed a new framework for studying psychiatric diseases. In his interview, Deisseroth likened his new framework for the study of diseases like depression to the study of heart disease, an area where many factors, genetic and environmental, are recognized as contributors to the disease. His use of neural circuit dynamics is intended to help determine the multiple potential contributors to such psychiatric diseases.

Below is a selection of comments from experts that justify their evaluations of the potential pioneering outcomes of Deisseroth's research:

> "The tools have been made available to the general neuroscience community, with impact on both basic studies of synaptic physiology and models of disease pathophysiology and treatment mechanisms. One such example is the new view of mechanisms mediating DBS effects in Parkinson's disease—a study that could only be done because of the availability of these new methods."

> "As described above, the work carried out by the Deisseroth lab has not only provided a novel set of molecular tools and experimental strategies, but also important new results which have deepened our understanding of neural circuits and how they drive behavior. The overall approach…should lead to a re-evaluation of many existing theories of brain function."

> "These tools are likely to have improved our understanding of DBS effects in other neuropsychiatric disorders and allow the more general dissection and testing of specific neural circuits in animal models of such disorders, as proposed in the original application."

His work has health applications (i.e., Parkinson's) and has changed theories of brain function (i.e., study of neural circuits and disorders).

c. Assessing Whether the Research Was Pioneering

In addition to characterizing the associated risks and identifying the potential outcomes of the research, experts were also asked to assess whether the accomplished work was pioneering. Two strongly agreed and one moderately agreed that Deisseroth's research outcomes were pioneering. Below is a selection of comments from experts about why Deisseroth's research was or was not pioneering:

> "These methods have changed the face of neurophysiology. This is paradigm shifting new technology."

> "The pioneering nature of the research, and its importance for advancing our understanding of basic brain function and neurological disease, cannot be underestimated."

> "The tools have had a major impact. On the other hand, another group without Pioneer support came up with similar technology."

All three experts believed Deisseroth's research was pioneering because they will change the way brain function is understood and neurological diseases are studied. One expert, however, stated that another group had invented similar technology without Pioneer support.

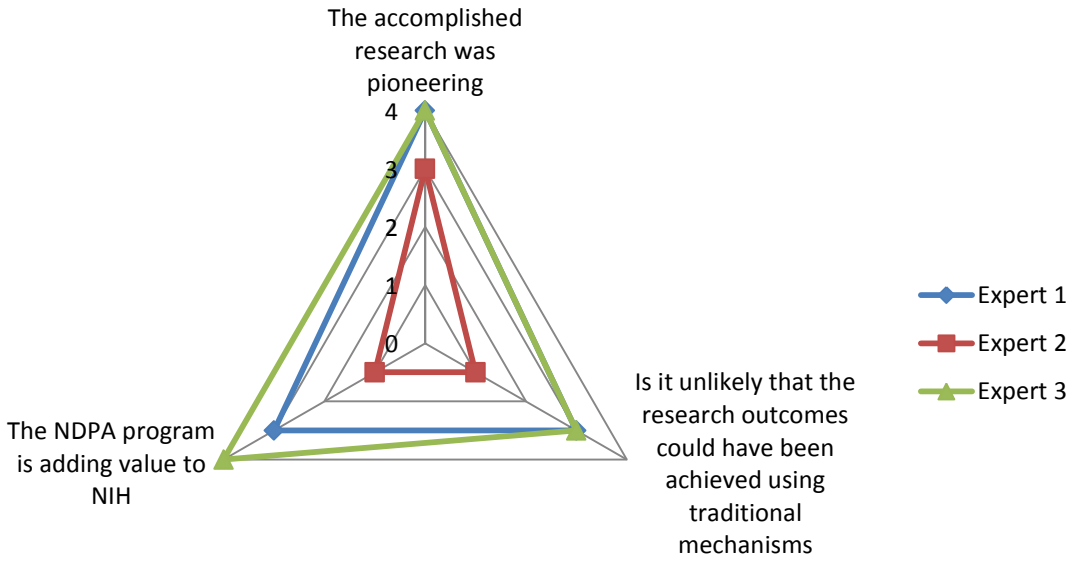
4. Value of the NDPA Program

a. Pioneer Perspective

Deisseroth explained that the NDPA induced creative thinking in his research because it has "allowed [them] to do things" that have "changed his thinking and gotten [him] more excited about tinkering." The NDPA funds have "pushed [him] to play." Without the NDPA funds, Deisseroth would have attempted the project on a smaller scale and at a slower pace. His lab "wouldn't have been able to do both technology development and application," and "it would have been a very much a pale shadow of currently this, it would have been somewhat transferable and much, much smaller."

b. Expert Perspective

Experts were asked to rate whether Deisseroth's results were a unique output of the Pioneer Award and whether the Pioneer Award is adding value to NIH (Figure 32).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 32. Experts' Opinions of the NDPA (Deisseroth)

Two experts moderately agreed and one expert strongly disagreed that it is unlikely that the research outcomes could have been achieve using traditional mechanisms. One strongly agreed, one moderately agreed, and one strongly disagreed with the statement that the NDPA is adding value to NIH. Below is a selection of comments from reviewers about the value of the NDPA program:

> "Such flexibility allowed him to not only address potential methods to excite, inhibit, alter tracts as well as neurones, impact biochemical signaling rather than just action potential initiation, etc., but to test their potential application in a wide range of biological systems (cells, culture, freely moving animals; direct injections, molecular probes). Such a wide range of experiments would be considered overly ambitious if proposed using any other grant mechanism."

> "This particularly application exemplifies what is possible when a brilliant scientist has the resources and time to think through a problem without restrictions."

> "The NDPA program serves an absolutely crucial role in the NIH portfolio. It identifies, highlights and supports the most outstanding biomedical researchers, and gives them the freedom to pursue high-risk,

high-reward research that is difficult to evaluate support using the conventional NIH funding model."

"While the many of the same tools could have been developed (indeed were developed) without Pioneer support…at least Deisseroth did something novel and published beautiful papers with it. I know of several other Pioneer Awardees about whom the same cannot be said. Many in the field would prefer to see Pioneer money placed back into the general budget to fund R01 grants."

Two reviewers thought the NDPA was valuable for supporting ambitious and high-risk proposals. One reviewer thought that R01s were producing the same outputs as the NDPA, and that the Pioneer money should go back to the R01 mechanism.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Deisseroth received the Pioneer Award in 2005, the pre-NDPA range refers to activity between 2001 and 2005, while the post-NDPA range refers to activity between 2006 and 2010.

a. Productivity

Deisseroth has published a total of 68 original articles over the 20 years of his research career, giving him an average of 3.4 articles per year (Table 59). In the pre-NDPA period, Deisseroth published 8 original articles for an average of 1.6 articles per year. In the post-NDPA period, he published 45 articles for an average of 9 articles per year.

Table 59. Summary of Publication Activity (Deisseroth)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of publications	8	45	10	68
Number of years	5	5	N/A	20
Publication rate	1.6	9	N/A	3.4

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

The difference between his pre- and post-NDPA publishing activity was drastically increased as compared to differences seen with other Pioneers. This difference suggests that the NDPA greatly promoted Deisseroth's research career.

Of the 45 articles Deisseroth published in the period after receiving the award, 10 were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 60.

Table 60. Publications Attributed to NDPA Funding (Deisseroth)

Title	Journal	Year Published
Bi-stable neural state switches	Nature Neuroscience	2009
Driving fast-spiking cells induces gamma rhythm and controls sensory responses	Nature Neuroscience	2009
eNpHR: a Natronomonas halorhodopsin enhanced for optogenetic applications	Brain Cell Biology	2008
Global and local fMRI signals driven by neurons defined optogenetically by type and wiring	Nature Neuroscience	2010
Optical Deconstruction of Parkinsonian Neural Circuitry	Science	2009
Optogenetic interrogation of neural circuits: technology for probing mammalian brain structures	Nature Protocols	2010
Sleep Homeostasis Modulates Hypocretin-Mediated Sleep-to-Wake Transitions	Journal of Neuroscience	2009
Targeted optogenetic stimulation and recording of neurons in vivo using cell-type-specific expression of Channelrhodopsin-2	Nature Protocols	2010
Temporally precise in vivo control of intracellular signalling	Nature	2009
Ultrafast optogenetic control	Nature Neuroscience	2010

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, Deisseroth's 65 original publications excluding reviewers had been cited a total of 4,283 times. In the post-NDPA period, Deisseroth published 44 publications that had received a total of 1,026 citations by August 2010. Ten of the 44 publications were attributed to NDPA funding and they received a total of 199 citations.

Deisseroth's age-weighted citation rate is higher in the post-NDPA period than in the pre-NDPA period. This suggests that his post-NDPA work is having a much greater

impact than his previous work. The higher rate is also likely due to the greater number of publications he had in the post-NDPA period.

Table 61 shows the statistics on this publication set.

Table 61. Summary of Citation Analyses (Deisseroth)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (65 pubs)	4,283	25.19	27
Pre-NDPA (6 pubs)	987	11.21	N/A
Post-NDPA (44 pubs)	1,026	18.46	N/A
Attributed to NDPA Funding (10 pubs)	199	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Deisseroth published 8 publications in five different sources in the pre-NDPA period and 45 publications in twenty-three different sources in the post-NDPA period. Detailed information on Deisseroth's most published-in journals for both time periods are shown in Table 62 and Table 63.

Table 62. Most Published-in Journals in the Pre-NDPA Period, 2001-2005 (Deisseroth)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
2	Nature Neuroscience	0.196657	99.3
2	Neuron	0.28702	99.62
2	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
1	Current Opinion in Neurobiology	0.054066	96.16
1	Trends in Neurosciences	0.06325	96.88

Source: Eigenfactor.org, Journal names came from Web of Science

Table 63. Most Published-in Journals in the Post-NDPA Period, 2006-2010 (Deisseroth)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
7	Nature	1.76345	100
5	Journal of Neuroscience	0.521789	99.87
4	Science	1.58309	99.98
3	Nature Neuroscience	0.196657	99.3
2	Biological Psychiatry	0.113895	98.42
2	Brain Cell Biology	N/A	N/A
2	Current Biology	0.252795	99.5
2	Journal of Neural Engineering	N/A	N/A
2	Nature Protocols	0.032379	92.72
2	Neuroscience Research	0.01428	84.67
2	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, Deisseroth published six times (75%) in journals with an *Eigenfactor* percentile of greater than or equal to 98. In the post-NDPA period, he published 28 times (62%) in journals with an *Eigenfactor* percentile of greater than or equal to 98.

Table 64. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Deisseroth)

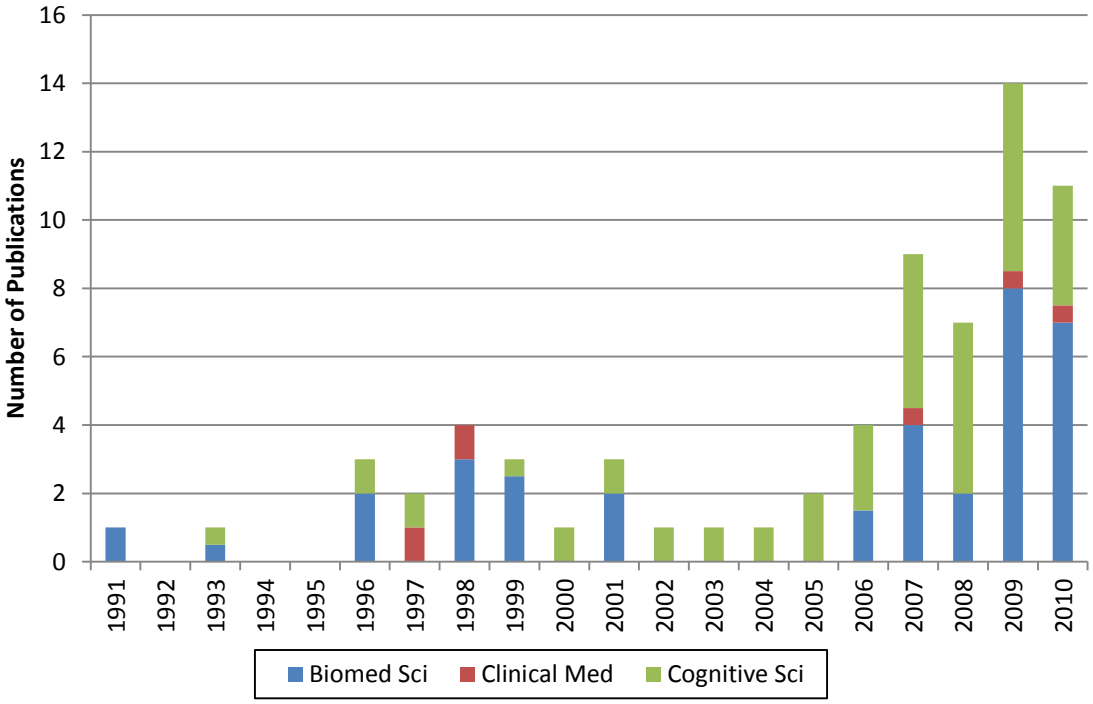
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (8 pubs)	6	75.00%
Post-NDPA (45 pubs)	28	62.22%
Attributed to NDPA Funding (10 pubs)	7	70.00%

Source: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data is from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Deisseroth's 68 publications over the length of his career can be categorized into a total of three macro-disciplines. He published in two macro-disciplines over his 8 pre-NDPA publications and three macro-disciplines over his 45 post-NDPA publications. The distribution of Deisseroth's work into macro-disciplines is displayed in Figure 33.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 33. Distribution of Publications into Macro-disciplines over Time (Deisseroth)

Deisseroth published steadily in both Biomedical Science and Cognitive Science journals with his work in neurobiology and psychiatry. It does not appear that he entered new macro-disciplines after receiving the NDPA.

2) Body of Knowledge Cited

Deisseroth cited fourteen different macro-disciplines in the 2,474 references of his 65 career publications. This included ten macro-disciplines in the 405 references of his 8 pre-NDPA publications and fourteen macro-disciplines in the 1,574 references of his 45 post-NDPA publications.

3) Integration and Specialization Scores

For the publication dataset of the Pioneers, the mean I score is 0.572 and the mean S scores is 0.486. The Integration and Specialization Scores for Deisseroth are displayed in Figure 34.

Figure 34. Integration and Specialization Scores (Deisseroth)

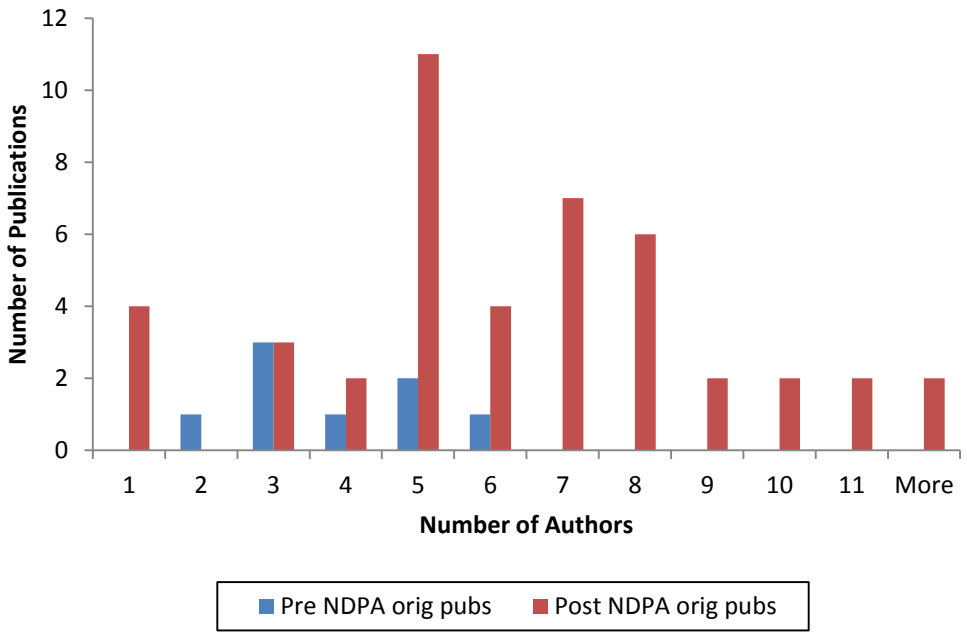
	Full Career (2474 cited references)	Pre-NDPA (405 cited references)	Post-NDPA (1574 cited references)
Integration	0.471	0.431	0.490
Specialization	0.642	0.797	0.630

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, Deisseroth is a "Disciplinarian" over all three time periods. His S score seems to be higher than the S scores over his full career and the post-NDPA period, but this may be due to the small sample size of publications during the pre-NDPA time period.

d. Collaboration

The median number of total authors for Deisseroth's total publication set was five. The pre-NDPA median was 3.5 while the post-NDPA median was six. A comparison of the pre- and post-NDPA distributions of the total number of authors may be seen in Figure 35.



Source: Web of Science

Figure 35. Distribution of Number of Authors in Original Publication Set (Deisseroth)

The number of unique authors in a researcher's publishing network is another metric that captures collaboration patterns. Deisseroth has published with approximately 201 unique individuals throughout his full career. In the pre-NDPA period, he collaborated with 18 unique individuals, and in the post-NDPA period, he collaborated with 158 researchers. Over his 10 NDPA-attributed publications, Deisseroth published with 28 unique researchers.

H. Pehr Harbury (2005)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers believed that Harbury had an innovative approach to synthesize organic compounds in a manner directed by attached oligonucleotides. His proposal could develop new technology to expand screening and small molecule development methods. The panel was "uniformly enthusiastic" about the potential for Harbury's research to result in a high impact breakthrough that could benefit both basic and applied research.

3. Nature of Project Risks and Outcomes

Both the Pioneer and the three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 65 and Table 66).

a. Typology of Project Risks

Table 65. Characterization of Unique Project Risk (Harbury)

Please indicate which of the following risks are applicable to the NDPA-funded project	Harbury	Expert 1	Expert 2	Expert 3
Conceptual risk	x		x	
Technical risk	x	x	x	
Experience risk	x			x
Multidisciplinary risk	x	x	x	
None of these risks				

Source: Pioneer interview, Expert review

At least two of three experts believed Harbury's research contained technical and multidisciplinary risks. Harbury himself believed that his research incorporated conceptual, technical, experience, and multidisciplinary risks.

Harbury remarked that his side project, nanocrystal DNA, was a conceptual risk because it suggested that DNA behaved in a way that had never before been observed. He noted that it was difficult to get these results published and his lab had to produce more evidence to deflect criticism for his work. The field had been embedded in the thinking that DNA may flow continuously for the past fifteen years, so no one wanted to believed that the molecules were either kinked or not bent.

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Harbury's research:

> "The approach of 'chemical evolution' combined the notion of coupling a selective advantage with replication and propagation…with non-biological molecules. It's an "out of the box" idea that demanded a combination of challenging organic chemistry and molecular biology."
>
> "The research is pretty routine and uninspiring; however the PI might not have an expertise in molecular force-fields and simulations."
>
> "Chemistry, molecular biology, engineering—each difficult things, [were] all included in the work."

Experts remarked that Harbury's research (i.e., "chemical evolution") incorporated knowledge from multiple fields (i.e., "organic chemistry, molecular biology, engineering"). One expert did not find his research to be creative, but acknowledged that experience risks may be involved (i.e., "no expertise in molecular force fields and simulations").

b. Typology of Potential Outcomes

Table 66. Characterization of Potential Pioneering Outcomes (Harbury)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Harbury	Expert 1	Expert 2	Expert 3
New Idea	x		x	
New Phenomenon	x			
New Methodology	x		x	
New Technology	x			
New Framework				
None of these outcomes		x		x

Source: Pioneer interview, Expert review

Two of three experts believed that Harbury's research displayed none of the described outcomes. Harbury himself thought his research could result in the formulation of a new idea, the discovery of new phenomena, the development of new methodology, and the invention of new technology.

Harbury remarked in his interview that another potential measure of what is pioneering could be the acknowledgement of a technology development project. The purpose of his project was to create a technology that may promote other scientific breakthroughs, but he noted that many groups of scientists consider that work to be "engineering" rather than "science."

Below is a selection of comments from experts that justify their evaluations of the potential pioneering outcomes of Harbury's research:

> "This is a very routine research with minimal impact on any field."
>
> "The 2007 JACS paper could make drug discovery more open to molecules not normally considered to be decent drug candidates."
>
> "Unfortunately, the realization of this idea has been very limited."

Two of the three experts found Harbury's research to be routine with limited impact. One expert thought his research could have positive implications for drug discovery.

c. Assessing Whether the Research Was Pioneering

Experts were also asked to rate whether they thought Harbury's research was pioneering. Two experts moderately agreed that Harbury's research was pioneering and one expert strongly disagreed. Below is a selection of comments from experts that justify their ratings.

> "This research has been routine with modest and inconsequential achievements."
>
> "The principle of chemical evolution has been described by Harbury prior to the granting of the NDPA. However, reducing this principle into practice is not so simple, as the subsequent years have shown."
>
> "Harbury was not first, but he may be the best experimentalist trying this platform."

Experts had mixed comments about the outcomes of Harbury's research. Two experts indicate that Harbury's research has had minimal success, while the remaining expert disapproved of Harbury for not giving credit to other researchers.

4. Value of the NDPA Program

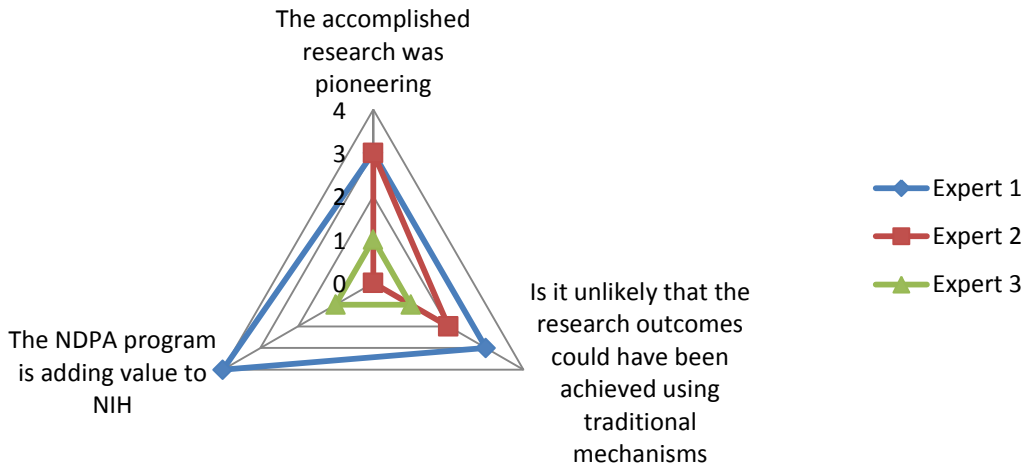
a. Pioneer Perspective

Harbury most appreciated the extended time period of the NDPA. He believes that "high-risk research [does not] cost any more than low-risk research," but that it does take a longer period of time to get results that are publishable. He thinks that the NDPA program could be improved if there are smaller amounts per year for a longer period of

time so that the award sum remains the same. Harbury says that he would have found funds somewhere else for his proposal had he not been funded through the NDPA.

b. Assessments of Value—Expert Perspective

Experts were asked to rate whether Harbury's results were a unique output of the Pioneer Award and whether the Pioneer Award is adding value to NIH (Figure 36).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 36. Experts' Opinions of the NDPA (Harbury)

One expert moderately agreed, one moderately disagreed, and one strongly disagreed that it is unlikely that Harbury's research outcomes could have been achieved through traditional mechanisms. One expert strongly agreed and one strongly disagreed that that the NDPA is adding value to NIH. One expert failed to respond, citing lack of knowledge with the Pioneer Award program.

Below is a selection of comments from experts about the value of the NDPA program:

> "Harbury is a highly original researcher with has multiple foci. The award yield little along the avenues of chemical evolution, but resulted in other interesting works (e.g. the DNA structural insights). These would not have been possible by the conventional routes."

> "The selection of the recipients of the NDPA program is highly political with ''bias'' toward mediocre individuals."

Experts who reviewed Harbury were in vast disagreement about the success and value of the NDPA program.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Harbury received the Pioneer Award in 2005, the pre-NDPA range refers to activity between 2001 and 2005, while the post-NDPA range refers to activity between 2006 and 2010.

a. Productivity

Harbury published a total of 32 original articles over the 23 years of his research career, giving him an average of 1.39 original publications per year (Table 67). In the pre-NDPA period, Harbury published 11 articles for a rate of 2.2 articles per year. In the post-NDPA period, Harbury published 9 articles for a rate of 1.8 articles per year.

Table 67. Summary of Publication Activity (Harbury)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of publications	11	9	5	32
Number of years	5	5	N/A	23
Publication rate	2.2	1.8	N/A	1.391304

Note: The publication rates shown are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science

Harbury published fewer original works during the post-NDPA period as compared to the pre-NDPA period. Of the nine post-NDPA publications he had, five were attributed to NDPA funding. During his interview, Harbury explained that he had performed NDPA-related research that had not yet been published. The publications attributed to NDPA funding are listed in Table 68.

Table 68. Publications Attributed to NDPA Funding (Harbury)

Title	Journal	Year Published
A Molecular Ruler for Measuring Quantitative Distance Distributions	PLOS One	2008
Design of protein-ligand binding based on the molecular-mechanics energy model	Journal of Molecular Biology	2008
Expedient Synthesis of a Modular Phosphate Affinity Reagent	Bioconjugate Chemistry	2010
Remeasuring the double helix	Science	2008
Synthetic ligands discovered by in vitro selection	Journal of the American Chemical Society	2007

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, Harbury's 29 original publications excluding reviews had been cited a total of 2,325 times. In the post-NDPA period, Harbury published 8 publications that had received a total of 97 citations. Five of the eight publications were attributed to NDPA funding, and they received a total of 58 citations.

Total number of citations and age-weighted citation rate do not display surprising results.

The statistics on the citations of this publication set are shown in Table 69.

Table 69. Summary of Citation Analyses (Harbury)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (29 pubs)	2,325	13.51	17
Pre-NDPA (10 pubs)	348	6.62	N/A
Post-NDPA (8 pubs)	97	5.26	N/A
Attributed to NDPA Funding (5 pub)	58	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Harbury published 11 articles in eight different sources in the pre-NDPA time period. He published 9 articles in nine different sources in the post-NDPA time period. Detailed data on Harbury's most published-in journals for the pre- and post-NDPA time periods are displayed in Table 70 and Table 71.

Table 70. Most Published-in Journals in the Pre-NDPA Period, 2001-2005 (Harbury)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
3	PLOS Biology	0.154645	99.05
2	Journal of Molecular Biology	0.233732	99.43
1	FASEB Journal	0.129982	98.74
1	Journal of Biological Chemistry	1.32919	99.96
1	Nature	1.76345	100
1	Nature Methods	0.061496	96.78
1	Nature Structural Biology	0.14844	98.7
1	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99

Source: Eigenfactor.org, Journal names came from Web of Science

Table 71. Most Published-in Journals in the Post-NDPA Period, 2006-2010 (Harbury)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
1	Abstracts of Papers of The American Chemical Society	N/A	N/A
1	Annual Review of Biochemistry	0.068524	97.32
1	Bioconjugate Chemistry	N/A	N/A
1	Current Opinion in Structural Biology	0.050685	95.85
1	Journal of Molecular Biology	0.233732	99.43
1	Journal of The American Chemical Society	0.951762	99.94
1	PLOS One	N/A	N/A
1	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
1	Science	1.58309	99.98

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 10 of Harbury's 11 publications, 90.91% were in journals at or above the 98th percentile (Table 72). In the post-NDPA period, four of nine publications, 44.44% were in journals of the same caliber. Harbury's single NDPA-attributed publication did not have an *Eigenfactor* score.

Table 72. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Harbury)

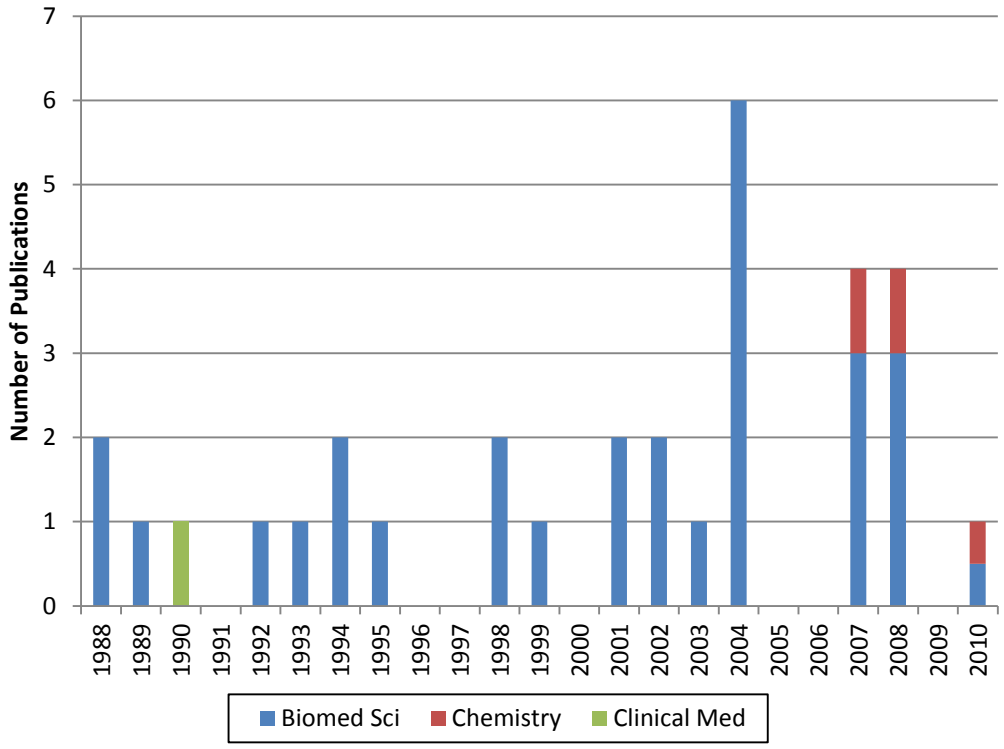
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (11 pubs)	10	90.91%
Post-NDPA (9 pubs)	4	44.44%
Attributed to NDPA Funding (5 pub)	3	60.00%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data is from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Harbury's 32 publications over the duration of his career can be categorized into a total of three different macro-disciplines. He published in one macro-discipline in his 11 pre-NDPA publications and two macro-disciplines in his 9 post-NDPA publications. The distribution of Harbury's publications into macro-disciplines for the full length of his career is displayed in Figure 37.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 37. Distribution of Publications into Macro-disciplines over Time (Harbury)

Harbury has remained in Biomedical Science throughout his career with his development of DNA-based technologies and his NDPA proposal for drug development using chemical evolution.

2) Body of Knowledge Cited

Harbury cited eleven different macro-disciplines in the 1,098 references of his 32 career publications. He cited nine macro-disciplines in the 340 references of his 11 pre-NDPA publications and seven macro-disciplines in the 345 references of his 9 post-NDPA publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The Integration and Specialization scores for Harbury are displayed in Table 73.

Table 73. Integration and Specialization Scores (Harbury)

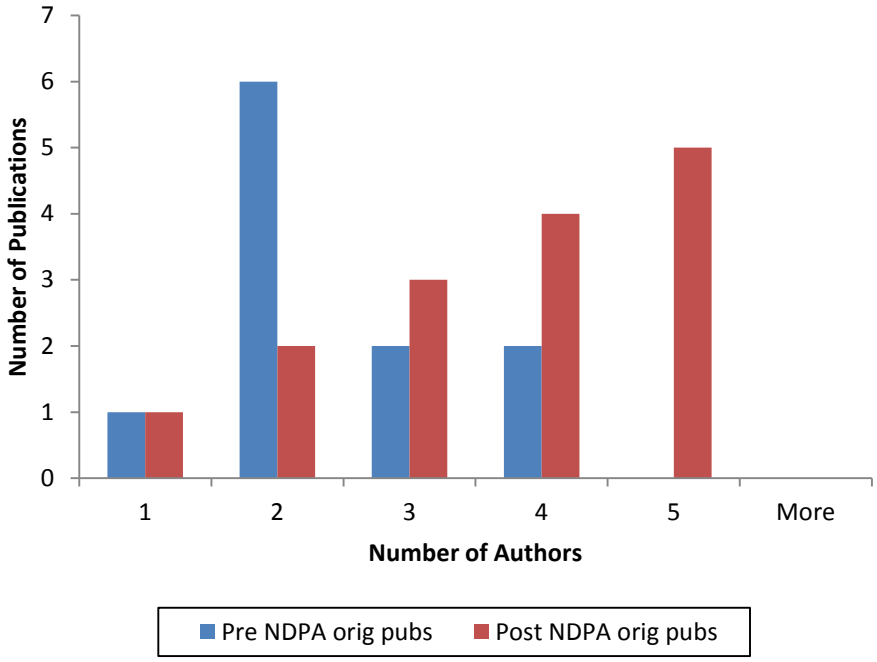
	Full Career (1098 cited references)	Pre-NDPA (340 cited references)	Post-NDPA (345 cited references)
Integration	0.339	0.329	0.414
Specialization	0.740	0.867	0.652

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, Harbury is a "Disciplinarian" for all three time periods measured. He draws from a set of sources that have little diversity and he publishes in similar fields.

d. Collaboration

The median number of total authors in Harbury's publication set was three. In the pre-NDPA period this median was two, and in the post-NDPA period it was three. A comparison of the total pre- and post-NDPA distributions of the total number of authors can be seen in Figure 38.



Source: Web of Science

Figure 38. Distribution of Number of Authors in Original Publication Set (Harbury)

The number of unique authors in a researcher's publishing network is another metric that captures co-authorship patterns. Harbury has published with approximately 45 unique individual throughout his full career. In the pre-NDPA period, he published with 13 researchers, and in the post-NDPA period, he published with 14 researchers. He published with 10 other people in his five NDPA-attributed publications.

I. Homme Hellinga (2004)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The panel of reviewers thought Hellinga had a strong background in "computer science, biochemistry, genetics… and computational chemistry." They believed that his proposal had the potential to produce a high impact breakthrough. Although they were not convinced that his ideas were unique, the panel of reviewers was "quite enthusiastic" about Hellinga's vision, intellect and creative past.

3. Nature of Project Risks and Outcomes

The Pioneers and three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 74 and Table 75).

a. Typology of Project Risks

Table 74. Characterization of Unique Project Risk (Hellinga)

Please indicate which of the following risks are applicable to the NDPA-funded project	Hellinga	Expert 1	Expert 2	Expert 3
Conceptual Risk	x		x	
Technical Risk	x	x	x	x
Experience Risk	x			
Multidisciplinary Risk	x	x		x
None of these risks				

Source: Pioneer interview, Expert review

At least two of three experts agreed that Hellinga's proposal incorporated technical and multidisciplinary risks. Hellinga himself thought his proposal incorporated conceptual, technical, experience, and multidisciplinary risks.

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Hellinga's research:

> "At the time of Hellinga's application, computational design of proteins with desired functions was a widely recognized goal, but few realizations of this idea had been achieved. Hellinga had promising results to suggest that he might be able to change this."

> "His plan to integrate computational design with a framework for high-throughput characterization was novel and required new techniques, although I wouldn't necessarily classify these as 'extraordinarily' difficult."

> "Hellinga's ideas with regard to large-scale, automated characterization of designs were novel and ahead of their time…the approach became a central element of his program, unfortunately lacking the state-of-the-art design component. This approach is now being embraced by others (but might well have been in any case)."

> "The initial proposal from Professor Hellinga's lab proposed a number of novel computational approaches to grafting functional binding sites into naïve scaffolds that would allow systematic engineering of novel enzymatic functions into proteins."

The experts thought Hellinga's proposal to use computational approaches for protein design to be a novel idea that required new technology.

b. Typology of Potential Outcomes

Table 75. Characterization of Potential Pioneering Outcomes (Hellinga)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Hellinga	Expert 1	Expert 2	Expert 3
New Idea				
New Phenomenon				
New Methodology	x	x	x	
New Technology	x			
New Framework				
None of these outcomes				x

Source: Pioneer interview, Expert review

Two of three experts believed Hellinga's research resulted in the development of a new methodology. Hellinga agreed with this assessment and added that his research may result in the invention of new technology.

Below is a selection of comments from the experts that justify their evaluations of the potential pioneering outcomes of Hellinga's research:

> "Although the outcomes of the Hellinga NDPA award were overall very disappointing, he did establish some new automated techniques for making and characterizing designed proteins that may prove useful to the field."

> "In sum, these seem solid and to be fair I must assume reproducible. However, these are not what I would call high impact and pioneering papers in the field. These make useful but somewhat incremental advances that are typical for most research papers."

> "The research initiative was largely unsuccessful."

The experts thought that Hellinga was unsuccessful in producing the results that his application suggested were possible. They also thought his research represented incremental, rather than substantial, advances in the field of protein design.

c. Assessing Whether the Research Was Pioneering

In addition to characterizing the associated risks, and identifying the potential outcomes of the research, experts were also asked to assess whether the accomplished work was pioneering. All three experts strongly disagreed that Hellinga's research accomplishments through the Pioneer Award were pioneering. Below is a selection of comments from experts about why Hellinga's research was or was not pioneering:

> "The retraction of two papers describing his most significant design work prior to the NDPA award, and significant questions about additional papers that have not been retracted, leave the community in doubt of all of his major claims…the utility of his methods remains unproven."

> "I think the key papers cited are solid, but rather average in their overall impact to the field…The key papers presented here are fine pieces of work and some may use this technology, but they do not push us closer to the bold goals set-forth in the original proposal."

The retraction of two papers led the experts to question seriously the validity of Hellinga's non-retracted publications. They also thought his results fell short of the goals set in his original proposal.

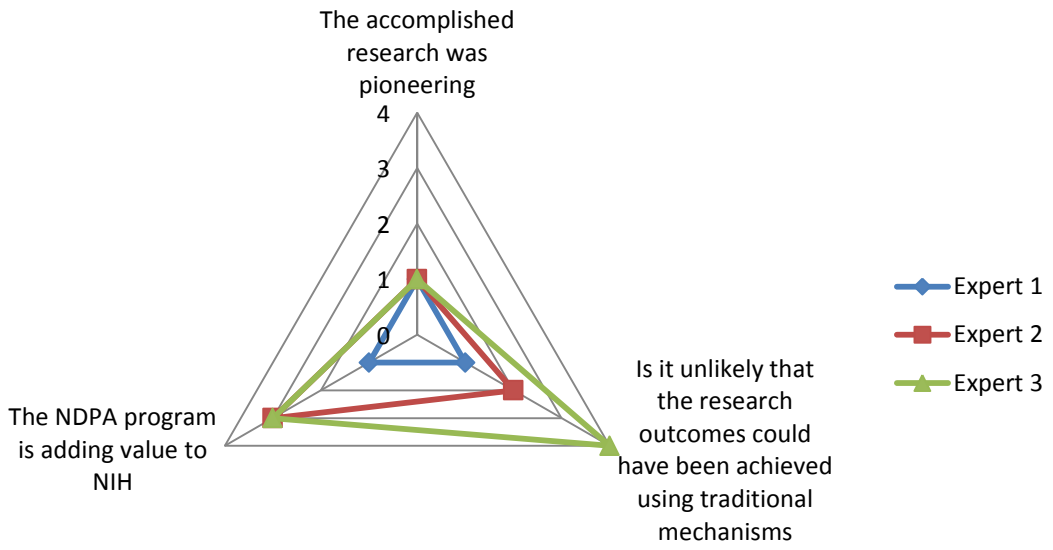
4. Value of the NDPA Program

a. Pioneer Perspective

Hellinga found the flexibility of the Pioneer Award to be useful in the course of his research because he "had the freedom to pursue [a] general line of engineering inquiry." He had not developed specific aims for his project until he had begun the research. The five year time length was also important because "difficult work" has a delay in output. It was relieving to have five years "without anybody overtly watching over [your] shoulders." If he had not been funded through the Pioneer Award, Hellinga explained that he would have attempted to get funding from other sources such as the Department of Defense. He did, however, note that his idea of the "evolution of protein expressions" may not have been pursued because his lab had been thinking of "studying disease at the…biophysical level" at the time of the award's receipt.

b. Expert Perspective

Experts were asked to rate whether Hellinga's results were a unique output of the Pioneer Award, and whether the Pioneer Award is adding value to NIH (Figure 39).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 39. Experts' Opinions of the NDPA (Hellinga)

One expert strongly agreed, one moderately disagreed, and one strongly disagreed that it is unlikely that the research outcomes could have been achieved using traditional mechanisms. The expert that strongly agreed explained that Pioneer Award likely contributed to the highly public nature of Hellinga's retractions and failures. Two experts moderately agreed and one strongly disagreed that the NDPA is adding value to NIH. Below is a selection of comments from experts about the value of the NDPA program:

> "In this case, and at least one other that I know about anecdotally, the funds allocated to these Pioneer Awards would have been much better spent via the traditional R01 mechanisms. On the whole, the body of traditional R01 research is outstanding and in my opinion deserves much deeper funding of this pool."

> "Unfortunately, many of these grand proposals have not actually delivered on what was promised. Some good science can come out, but it really seems to be a crap shoot."

> "The two cases I know have not been impressive, but the overall selection list and process seem to me to be sound."

Two of the three experts thought the NDPA was adding value to NIH. On the other hand, one expert stated that the funds would have been better distributed under the R01 mechanism.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Hellinga received the Pioneer Award in 2004, the pre-NDPA range refers to activity between 1999 and 2004, while the post-NDPA range refers to activity between 2005 and 2010.

a. Productivity

Hellinga has published a total of 70 original articles over the 26 years of his research career giving him an average of 2.69 publications per year (Table 76). In the pre-NDPA period, Hellinga published 27 articles for an average of 4.5 publications per year. In the post-NDPA period, Hellinga published 16 articles for an average of 2.67 publications per year.

Table 76. Summary of Publication Activity (Hellinga)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of publications	27	16	8	70
Number of years	6	6	N/A	26
Publication rate	4.5	2.666667	N/A	2.692308

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Hellinga published fewer original articles in the post-NDPA period as compared to the pre-NDPA period. Of the 16 articles he published in the period after receiving the award, eight were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 77.

Table 77. Publications Attributed to NDPA Funding (Hellinga)

Title	Journal	Year Published
Binding and signaling of surface-immobilized reagentless fluorescent biosensors derived from periplasmic binding proteins	Protein Science	2006
Identification of cognate ligands for the Escherichia coli phnD protein product and engineering of a reagentless fluorescent biosensor for phosphonates	Protein Science	2006
Ligand-induced conformational changes in a thermophilic ribose-binding protein	Bmc Structural Biology	2008
Picomole-scale characterization of protein stability and function by quantitative cysteine reactivity	Proceedings of the National Academy of Sciences of the United States of America	2010
Structural Adaptations that Modulate Monosaccharide, Disaccharide, and Trisaccharide Specificities in Periplasmic Maltose-Binding Proteins	Journal of Molecular Biology	2009
Structural Analysis of a Periplasmic Binding Protein in the Tripartite ATP-independent Transporter Family Reveals a Tetrameric Assembly That May Have a Role in Ligand Transport	Journal of Biological Chemistry	2008
Structural Analysis of Semi-specific Oligosaccharide Recognition by a Cellulose-binding Protein of Thermotoga maritima Reveals Adaptations for Functional Diversification of the Oligopeptide Periplasmic Binding Protein Fold	Journal of Biological Chemistry	2009
The backbone structure of the thermophilic Thermoanaerobacter tengcongensis ribose binding protein is essentially identical to its mesophilic E-coli homolog	Bmc Structural Biology	2008

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, Hellinga's 66 original publications excluding reviews had been cited a total of 2,649 times. In the post-NDPA period, Hellinga published 16 publications that had received a total of 147 citations by August 2010. Eight of the 16 were attributed to NDPA funding and they received a total of 34 citations.

The age-weighted citation rate of Hellinga's post-NDPA publication set seems quite a bit lower than his pre-NDPA publication set. The decrease in citation counts may be related to the damage his reputation suffered after retracting two papers during the NDPA period.

The statistics on Hellinga's publication set are shown in Table 78.

Table 78. Summary of Citation Analyses (Hellinga)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (66 pubs)	2,649	15.74	31
Pre-NDPA (25 pubs)	1,216	11.62	N/A
Post-NDPA (16 pubs)	147	5.81	N/A
Attributed to NDPA Funding (8 pubs)	34	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Hellinga published 27 publications in sixteen different sources in the pre-NDPA time period and 16 publication sin seven different sources in the post-NDPA time period. Detailed data on Hellinga's most published-in journals are shown below for the pre- and post-NDPA time periods, respectively (Table 79 and Table 80).

Table 79. Most Published-in Journals in the Pre-NDPA Period, 1999-2004 (Hellinga)

Number of Publications	Source	2008 Eigenfactor score	Eigenfactor Percentile
7	Protein Science	0.052031	95.97
5	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
2	Proteins-Structure Function and Genetics	0.068317	97.29
1	Abstracts of Papers of The American Chemical Society	N/A	N/A
1	Biochemistry	0.251045	99.49
1	Bioconjugate Chemistry	N/A	N/A
1	Biophysical Journal	0.187695	99.28
1	Current Opinion in Structural Biology	0.050685	95.85
1	Faseb Journal	0.129982	98.74
1	Journal of Inorganic Biochemistry	0.024174	90.32
1	Journal of Molecular Biology	0.233732	99.43
1	Journal of The American Chemical Society	0.951762	99.94
1	Nature	1.76345	100
1	Nature Materials	0.185541	99.25
1	Nature Structural Biology	0.14844	98.7
1	Science	1.58309	99.98

Source: Eigenfactor.org, Journal names came from Web of Science

Table 80. Most Published-in Journals in the Post-NDPA Period, 2005-2010 (Hellinga)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
6	Protein Science	0.052031	95.97
2	BMC Structural Biology	0.003666	56.64
2	Journal of Biological Chemistry	1.32919	99.96
2	Journal of Molecular Biology	0.233732	99.43
2	Journal of The American Chemical Society	0.951762	99.94

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 14 of Hellinga's 27 publications, 51.85%, were in journals at or above the 98th percentile (Table 81). In the post-NDPA period, 7 of 16 publications, 43.75% were in journals of the same caliber. Four of eight NDPA-attributed publications, 50.00%, had *Eigenfactor* values above the 98th percentile.

Table 81. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Hellinga)

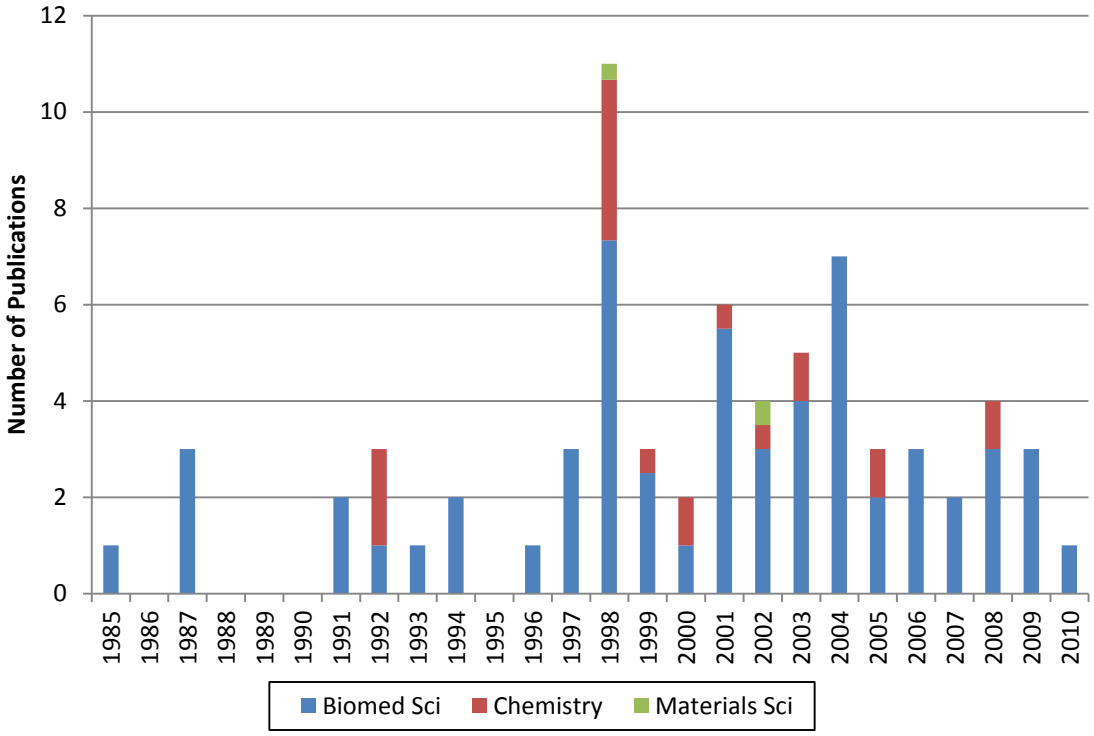
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (27 pubs)	14	51.85%
Post-NDPA (16 pubs)	7	43.75%
Attributed to NDPA Funding (8 pubs)	4	50.00%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores. Source: Publication data is from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Hellinga's 70 publications over the duration of his career can be categorized into a total of three different macro-disciplines. He published in three macro-disciplines over his 27 pre-NDPA publications. He published in two macro-disciplines over his 16 post-NDPA publications. The distribution of Hellinga's macro-disciplines for the full length of his career is shown in Figure 40.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 40**. Distribution of Publications into Macro-disciplines over Time (Hellinga)**

Hellinga published primarily in Biomedical Science and Chemistry throughout the course of his career with his work in protein design and drug development. The NDPA does not appear to have changed the types of journals in which he publishes.

2) Body of Knowledge Cited

Hellinga cited fourteen different macro-disciplines in the 2,846 references of his 70 career publications. This included thirteen macro-disciplines in the 873 references of his 27 pre-NDPA publications and thirteen macro-disciplines in the 841 references of his 16 career publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The I and S scores for Hellinga are shown in Table 82.

Table 82. Integration and Specialization Scores (Hellinga)

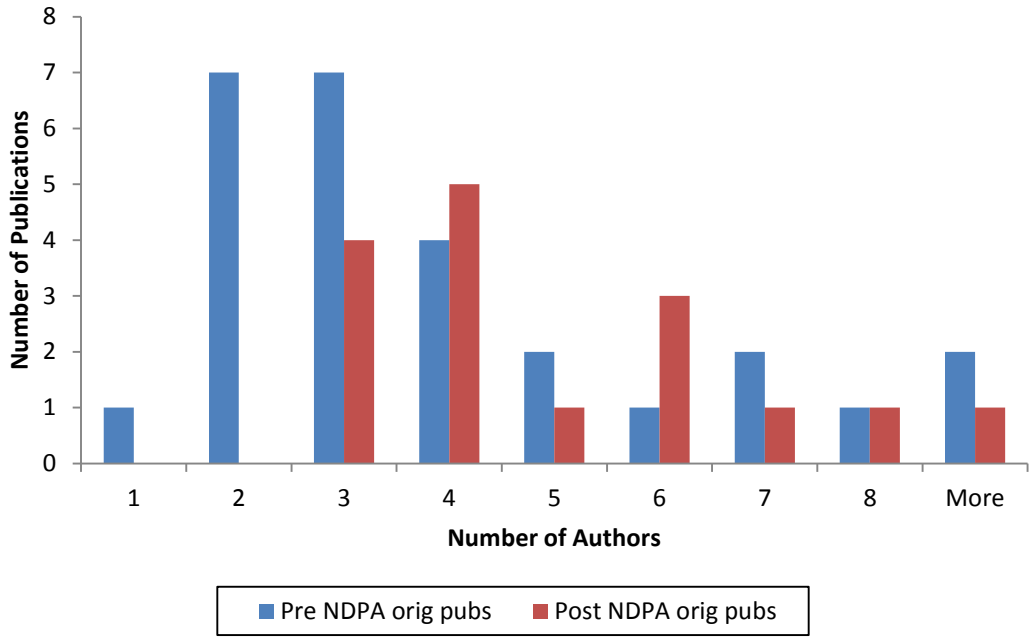
	Full Career (2846 cited references)	Pre-NDPA (873 cited references)	Post-NDPA (841 cited references)
Integration	0.353	0.369	0.373
Specialization	0.684	0.626	0.830

Source: Publication data are from Web of Science, scores were calculated using VantagePoint

Compared to the other Pioneers, Hellinga is a "Disciplinarian" for all three time periods. His S score appears to have increased in the post-NDPA time period. [comment]

d. Collaboration

The median total number of authors in Hellinga's publication set was three. In the pre-NDPA period, the median was three, while in the post-NDPA period, the median was four. A comparison of the pre- and post-NDPA author distributions for total number of authors may be seen in Figure 41.



Source: Web of Science

Figure 41. Distribution of Number of Authors in Original Publication Set (Hellinga)

The number of unique authors in a researcher's publishing network is another metric that captures co-authorship patterns. Hellinga has published with approximately 91 unique researchers throughout the duration of his career. In the pre-NDPA period, he published with 45 people, and in the post-NDPA period, he published with 46 people. Over his eight NDPA-attributed publications, Hellinga published with 12 unique authors.

J. Erich Jarvis (2005)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers believed that Jarvis possessed a bold vision and novel hypothesis "regarding the evolution of vocal learning mechanisms in birds and humans." They also noted his desire to develop technology that would be used to "modify avian non-vocal learners to enable them to develop primitive vocal learning skills." The committee wrote that it was "very enthusiastic" about Jarvis as a candidate based on these qualities and his "command of broad areas of neurobiology."

3. Nature of Project Risks and Outcomes

Both the Pioneer and the three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 83 and Table 84).

a. Typology of Project Risks

Table 83. Characterization of Unique Project Risk (Jarvis)

Please indicate which of the following risks are applicable to the NDPA-funded project	Jarvis	Expert 1	Expert 2	Expert 3
Conceptual Risk	x	x	x	
Technical Risk	x	x	x	
Experience Risk	x	x		x
Multidisciplinary Risk	x	x	x	x
None of these risks				

Source: Pioneer interview, Expert review

At least two of three experts agreed that Jarvis's research incorporated conceptual, technical, experience, and multidisciplinary risks. Jarvis agreed with the whole of this assessment.

In his interview, Jarvis was able to comment on some of the spillover effects of the risks of his research. For instance, he stated that tackling his new hypothesis that "there are parallels between human and bird brains" requires the "[development] of those techniques [that have not been proven or are extraordinarily difficult]," He also commented that since his "proposed research required knowledge of fields beyond [his] previously demonstrated expertise…[he] brought in post-docs…[and]…grad students who have computational biology experience or protein chemistry experience."

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Jarvis's research:

> "Jarvis has moved beyond his earlier expertise in several crucial ways. For example, he has broadened his outlook beyond avian species,…performed high-throughput evolutionary genomic analyses, and…moved into stem-cell technologies."
>
> "Jarvis has consistently, through his career, pioneered novel techniques (e.g. the use of immediate early gene expression to understand song circuits) and the current work shows more of the combination of pushing techniques in new directions, based on broad, fascinating hypotheses."
>
> "His team developed bioinformatic methods for identifying candidate genes that may contribute to vocal learning using a novel comparative genomics approach…They attempted to induce vocal learning in a non-learning species through challenging transplantation experiments, and they are using iPSC technologies to develop transgenic birds."
>
> "Jarvis has pioneered a powerful approach to understanding the basis of vocal learning, one which…integrates empirical data from a diverse range

of fields—neurobiology, behavioral research, genetics/genomics—in an array of model systems."

Experts recognized that Jarvis's research was pioneering in that it combined multiple areas of study (i.e., neurobiology, evolutionary theory, genomics), and that he developed new techniques and applied old techniques in innovating ways in order to pursue his hypotheses (i.e., "transplantation of vocal learning to non-learning species", "fusion of neuroanatomical tracers with IEG activity").

b. Typology of Potential Outcomes

Table 84. Characterization of Potential Pioneering Outcomes (Jarvis)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Jarvis	Expert 1	Expert 2	Expert 3
New Idea	x	x	x	
New Phenomenon	x	x	x	x
New Methodology	x	x	x	
New Technology				
New Framework	x	x	x	
None of these outcomes				

Source: Pioneer interview, Expert review

At least two of three experts agreed that Jarvis's research could result in the formulation of a new idea, the discovery of a new empirical phenomenon, the invention of new technology, and the synthesis of a new framework. Jarvis agreed with the experts in terms of the nature of the potential outcomes of his research.

Jarvis provided insight into the ways in which the outcomes of his research are pioneering. For example, although he indicated that his proposed research could result in the development of a new methodology and enable empirical testing of theoretical problems, his process order is reversed from the way it is represented in the typology. He stated that "[his] proposed research, [the empirical testing,] would actually support the new theory that [he is] proposing." In other words, he developed the new theory first, and then proceeded to develop new methodologies, via his Pioneer project, to empirically support his theory.

Below is a selection of comments from experts that justify their evaluations of the potential pioneering outcomes of Jarvis's research:

> "Jarvis has advanced a new theoretical model to explain the evolutionary emergence of vocal learning."

> "His research has uncovered new empirical phenomena, including identification of hitherto unknown neuroanatomical and behavioral

> features underlying mouse vocalization, and discovery of a conserved mechanism of stem cell induction across metazoan species."
>
> "The technique used to identify these [direct cortico-motor] connections, fusing neuroanatomical tracers with IEG activity to delimit functional regions, is innovative and could prove useful on a wide variety of other species."
>
> "The figure of the song control system in this proposal is outdated…These apparently simple additions to the old circuit diagram make functional explanation and comparison of the song system with other systems such as the human speech control circuits a lot harder…to claim."
>
> "Jarvis's already-published "motor theory"…is a novel (and plausible) hypothesis about the mechanistic basis of vocal learning and its evolutionary history, and it brings together ideas from many different fields (evolution, psychology and neuroscience)."

The reviewers were impressed with the new empirical phenomena Jarvis discovered (i.e., "neuroanatomical and behavioral features underlying mouse vocalization"). One expert, however, found the song control system on which the proposal is based to be outdated, leading the expert to cast aspersions on Jarvis's comparisons across disparate vocal learners.

c. Assessing Whether the Research Was Pioneering

The experts were also asked to rate whether Jarvis's research was pioneering. Two experts strongly agreed and one strongly disagreed that Jarvis's research was pioneering. Below is a selection of comments from experts about why Jarvis's research was or was not pioneering:

> "Jarvis has that rare combination of empirical rigor and technical savvy, theoretical understanding and breadth, and creativity and thinking "out of the box", that makes for a truly great researcher. He has consistently pushed the envelope of neurobiology."
>
> "I don't know what was accomplished. As far as I know, he has not made any major discovery or pointed out any major differences."

The positive experts believe Jarvis's work is novel and field-changing, while the negative expert did not think Jarvis had produced any major results.

4. Value of the NDPA Program

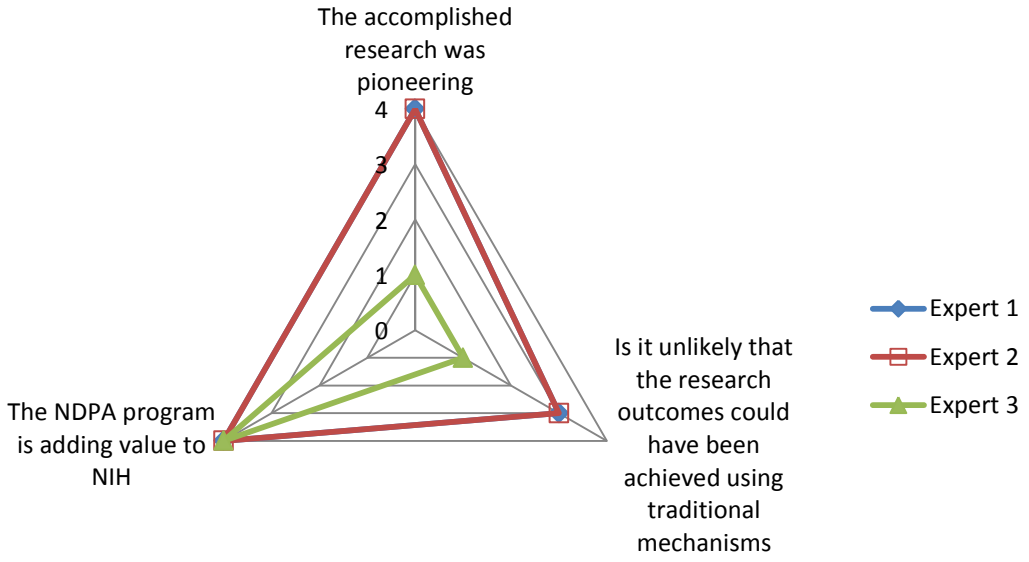
a. Pioneer Perspective

Jarvis characterized the value of the NDPA program in a few different ways. He stated his personal opinion that the NDPA's purpose is to allow researchers to take the long-term view and "push a field forward, open up a new field." He expressed the

NDPA's influence on his creative sensibilities by describing that "when [he] wrote [his] project…[he] was actually quite excited because [he] had never [before] had a chance to…express what [he]…would like to do…in a grant proposal." The act of writing it down "got [him] thinking a little bit more creatively." He also recognized that his NDPA research project would have been "dead on arrival" to a "regular NIH grant panel." The award also allowed Jarvis to pursue research on "ultrasonic vocalizations" in mice even though he had "never studied mice before." The flexibility of the award allowed him to follow the research where it lead him and produce unique findings. Jarvis also remarked that before becoming a Pioneer, his "personal focus was less in technology development...but now… [he thinks] it is very important, and…not something that [he] could have done that easily with the regular R01 grant." Jarvis additionally highlighted the freedom he was given in how the funds were used, saying that there was less "bureaucracy" and he "didn't have to worry about [justifying switching money]…from equipment to salary to supplies." Jarvis noted that he would have continued pursuing the ideas from his Pioneer Award "at a slower rate" if he had not gotten the funds.

b. Expert Perspective

Experts were asked to rate the value of the NDPA program in terms of the research it is funding and in terms of what it brings to the NIH portfolio (Figure 42).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 42. Experts' Opinions of the NDPA (Jarvis)

Two experts moderately agreed and one strongly disagreed that it is unlikely that the research outcomes could have been achieved using traditional mechanisms. All three experts strongly agreed that the NDPA is adding value to NIH.

Below is a selection of comments from experts about the value of the NDPA program:

> "Whether it is NIH or NSF, grants are very hard to get. So, if there is another mechanism for getting grants, people will go there. If the goal is to somehow, discover very unique researchers, then the program should support people who really deserve it."

> "The research Jarvis has performed…is too "pie in the sky" and risky, and lacking in short-term clinical relevance, to be a candidate for more typical sources of NIH funding."

> "The NDPA program, at least with regard to the work that I reviewed, fulfills an essential function in pushing forward the most creative science."

Two of the experts believe that the value of the NDPA is in its funding of creative and risky science. One believes that the NDPA's value comes from the fact that it is an additional funding mechanism in a world where grants are difficult to obtain.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Jarvis received the Pioneer Award in 2005, the pre-NDPA range refers to activity between 2001 and 2005 while the post-NDPA range refers to activity between 2006 and 2010.

a. Productivity

Jarvis has published a total of 59 original articles over the 25 years of his research career; this gives him an average of 2.36 original publications per year (Table 85). Pre-NDPA, Jarvis published 14 original publications for a rate of 2.8 original publications per year. Post-NDPA, he published 19 original publications for a rate of 3.8 original publications per year.

Table 85. Summary of Publication Activity (Jarvis)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of publications	14	19	8	59
Number of years	5	5	N/A	25
Publication rate	2.8	3.8	N/A	2.36

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Jarvis published more original works in the post-NDPA period than in the pre-NDPA period. Of the 19 articles he published after receiving the award, eight were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 86.

Table 86. Publications Attributed to NDPA Funding (Jarvis)

Title	Journal	Year Published
A molecular neuroethological approach for identifying and characterizing a cascade of behaviorally regulated genes	Proceedings of the National Academy of Sciences of the United States of America	2006
Assessing visual requirements for social context-dependent activation of the songbird song system	Proceedings of the Royal Society B-Biological Sciences	2009
Comparative genomics based on massive parallel transcriptome sequencing reveals patterns of substitution and selection across 10 bird species	Molecular Ecology	2010
Molecular Mapping of Movement-Associated Areas in the Avian Brain: A Motor Theory for Vocal Learning Origin	PLOS One	2008
Role of the midbrain dopaminergic system in modulation of vocal brain activation by social context	European Journal of Neuroscience	2007
Social context-dependent singing-regulated dopamine	Journal of Neuroscience	2006
The genome of a songbird	Nature	2010
The pallial basal ganglia pathway modulates the behaviorally driven gene expression of the motor pathway	European Journal of Neuroscience	2007

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, Jarvis's 52 original publications excluding reviews had been cited a total of 2,404 times. In the post-NDPA period, Jarvis published 17 publications that had received a total of 189 citations by August 2010. Eight publications were attributed to NDPA funding, and they received a total of 142 citations.

Total number of citations and age-weighted citation rate do not demonstrate surprising results. The statistics of the citations from this publication set are shown in Table 87.

Table 87. Summary of Citation Analyses (Jarvis)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (52 pubs)	2,404	16.43	23
Pre-NDPA (10 pubs)	1,049	11.41	N/A
Post-NDPA (17 pubs)	189	7.13	N/A
Attributed to NDPA Funding (8 pubs)	142	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Jarvis published 14 publications in eleven different sources in the pre-NDPA time period and 19 publications in fourteen different sources in the post-NDPA time period. Detailed information on Jarvis's most published in journals for the pre- and post-NDPA time periods can be found in Table 88 and Table 89, respectively.

Table 88. Most Published-in Journals in the Pre-NDPA Period, 2001-2005 (Jarvis)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
2	Behavioral Neurobiology of Birdsong	N/A	N/A
2	Journal of Comparative Neurology	0.06616	97.06
2	Journal of Neuroscience	0.52179	99.87
1	Bioinformatics	0.18214	99.23
1	Genome Research	0.12534	98.66
1	Integrative and Comparative Biology	0.01281	82.97
1	Journal of Comparative Physiology A-Neuroethology Sensory Neural And Behavioral Physiology	0.01051	79.63
1	Nature	1.76345	100
1	Nature Reviews Neuroscience	0.11399	98.43
1	PLOS Biology	0.15465	99.05
1	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99

Source: Eigenfactor.org, Journal names came from Web of Science

Table 89. Most Published-in Journals in the Post-NDPA Period, 2006-2010 (Jarvis)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
5	European Journal of Neuroscience	0.11552	98.47
2	Journal of Comparative Neurology	0.06616	97.06
1	Auk	0.00982	78.3
1	Journal of Neuroscience	0.52179	99.87
1	Journal of Ornithology	0.00077	19.55
1	Molecular Ecology	0.06926	97.38
1	Nature	1.76345	100
1	Nephrology	0.00384	57.82
1	Neuroscience Research	0.01428	84.67
1	PLOS Computational Biology	0.03063	92.35
1	PLOS One	N/A	N/A
1	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
1	Proceedings of The Royal Society B-Biological Sciences	0.10044	98.17
1	Zoological Science	0.00665	71.06

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 8 of Jarvis's 14 publications, 57.14%, were in journals at or above the 98th percentile (Table 90). In the post-NDPA period, 9 of Jarvis's 19 publications, 47.37% were in journals of the same caliber. Six of Jarvis's eight NDPA-attributed publications had *Eigenfactor* values above the 98th percentile.

Table 90. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Jarvis)

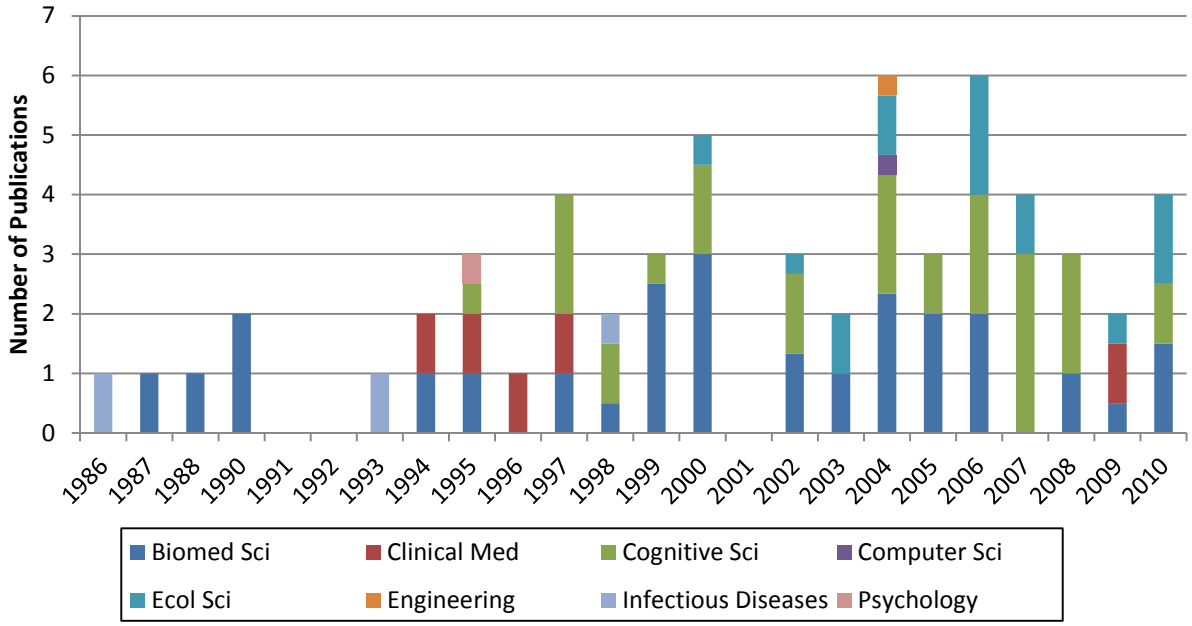
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (14 pubs)	8	57.14%
Post-NDPA (19 pubs)	9	47.37%
Attributed to NDPA Funding (8 pubs)	6	75.00%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data is from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Jarvis's 59 publications over the duration of his career can be categorized into a total of eight different macro-disciplines. He published in five disparate macro-disciplines in the pre-NDPA period with 14 publications, and four in the post-NDPA period with 19 publications. The distributions of Jarvis's publications into macro-disciplines for the full length of his career are displayed in Figure 43.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 43. Distribution of Publications into Macro-disciplines over Time (Jarvis)

Jarvis began his career primarily in Biomedical Science and Infectious Diseases, performing genetic manipulations on bacteria. In the decade leading up to his receipt of the NDPA, however, he began to enter Cognitive Science and Ecological Science in his research related to gene regulation in the brains of songbirds and the subsequent singing behaviors of these birds.

2) Body of Knowledge Cited

Jarvis cited fifteen different macro-disciplines in the 3,406 references of his 59 career publications. This included 13 macro-disciplines in the 1,329 references of his 14 pre-NDPA publications and 13 macro-disciplines in the 1,056 references of his 19 post-NDPA publications.

3) Integration and Specialization Scores

For the publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The scores for Jarvis are displayed in Table 91.

Table 91. Integration and Specialization Scores (Jarvis)

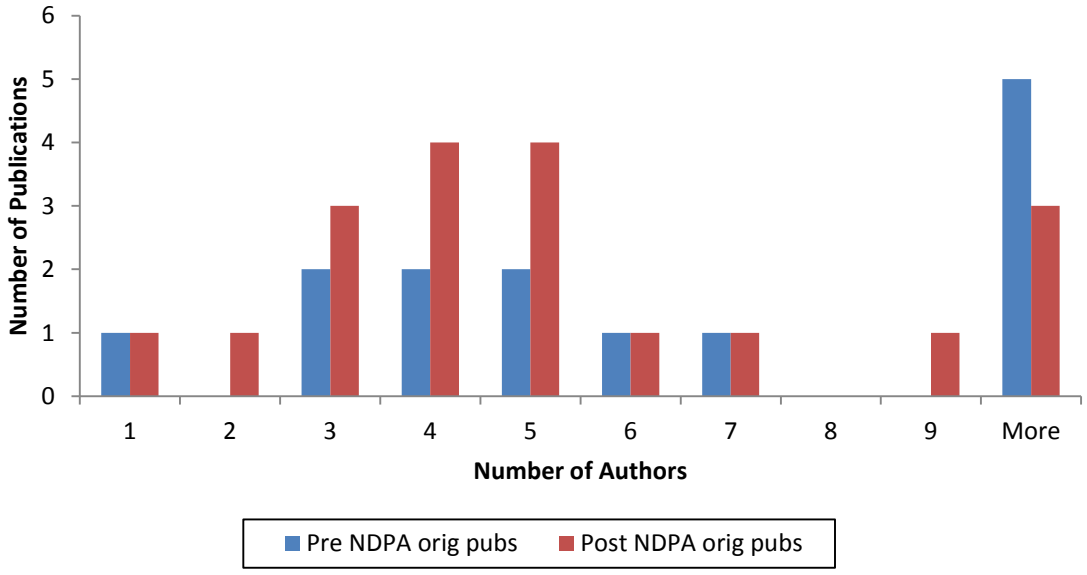
	Full Career (3406 cited references)	Pre-NDPA (1329 cited references)	Post-NDPA (1056 cited references)
Integration	0.540	0.505	0.532
Specialization	0.471	0.499	0.475

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, Jarvis generally appears to be a "Grazer" over his full career and during the post-NDPA period.[22] During the pre-NDPA period, he publishes and cites as a "Disciplinarian."

d. Collaboration

The median number of total authors in Jarvis's publication set was five. In the pre-NDPA period, this median was 5.5. In the post-NDPA period it was 5. A comparison of the pre- and post-NDPA distributions of the total number of authors can be seen in Figure 44.



Source: Web of Science

Figure 44. Distribution of Number of Authors in Original Publication Set (Jarvis)

[22] Porter et al. (2007) Measuring researcher interdisciplinarity.

The number of unique authors in a researcher's publishing network is another metric that captures co-authorship patterns. Jarvis has published with approximately 349 unique researchers for the duration of his full career. In the pre-NDPA period, he collaborated with 195 researchers, and in the post-NDPA period, he published with 131 researchers. Over his eight NDPA-attributed publications, Jarvis published with 112 unique researchers.

K. Joseph (Mike) McCune (2004)

1. Research Summary

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%) 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.

2. NDPA Reviewer Panel Opinions

The panel of reviewers was impressed with McCune's creative past and his risky and controversial proposal to develop a vaccine for AIDS. They believed his proposal had "scientific depth" and tackled an important problem. The panel thought McCune's work, if successful, could have wide applications for international health and "other diseases related to immune dysregulation."

3. Nature of Project Risks and Outcomes

The Pioneers and three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 92 and Table 93).

a. Typology of Project Risks

Table 92. Characterization of Unique Project Risk (McCune)

Please indicate which of the following risks are applicable to the NDPA-funded project	McCune	Expert 1	Expert 2	Expert 3
Conceptual Risk	x	x	x	x
Technical Risk	x			
Experience Risk	x		x	
Multidisciplinary Risk	x	x		
None of these risks				

Source: Pioneer interview, Expert review

All three experts agreed that McCune's project had a conceptual risk. McCune himself believed that his research incorporated conceptual, technical, experience, and multidisciplinary risks.

In his interview, McCune explained that his work was at odds with the prevailing wisdom on treating HIV/AIDS; he suggested that "a strong adaptive immune response might not be the way to treat a vaccine." His research also required the use of unproven techniques in order to study the fetal immune system and perform comparative work on non-human primates. His lab needed to collaborate with and hire researchers in "primatology, neonatology, pediatric gastroenterology" in order to bring in knowledge of the fields beyond his previous expertise.

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of McCune's research:

> "For many years the search for an AIDS vaccine has been made difficult…the idea that ALL immune responses to HIV are good…Dr. McCune and others proposed the…almost "heretical" idea that immune responses to HIV may in fact be bad, and that reducing the HIV-associated hyper immune activation and inflammation may be crucial to prevent AIDS and possibly protect from HIV transmission."

> "The areas beyond the previous knowledge of the PI include the catabolism of tryptophan and its role in Th17/Treg imbalance and the predisposition of the fetus to tolerance of maternal non-inherited antigens."

Experts thought McCune presented a conceptual risk in his idea that HIV infections were dependent upon high levels of immune activation. He expanded into new fields in his proposal by studying tryptophan and the fetal immune system.

b. Typology of Potential Outcomes

Table 93. Characterization of Potential Pioneering Outcomes (McCune)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	McCune	Expert 1	Expert 2	Expert 3
New Idea	x	x	x	x
New Phenomenon	x	x		
New Methodology	x		x	
New Technology				
New Framework	x	x	x	
None of these outcomes				

Source: Pioneer interview, Expert review

At least two of three experts agreed that McCune's research could result in the formulation of a new idea and the synthesis of a new framework. McCune believed his research could result in the formulation of a new idea, the discovery of a new phenomenon, the development of a new methodology, and the synthesis of a new framework.

Through his research, McCune made observations about the primate immune system that would have never been made if he had studied the mouse fetal immune system, "the dominant model for studying immunology." To "study small numbers of fetal hematopoietic stem cells," McCune's lab used new methodologies such as "high speed multiparameter flow cytometry."

Below is a selection of comments from the experts that justify their evaluations of the potential pioneering outcomes of McCune's research:

> "The main outcome of McCune recent research is the generation of a large number of very convincing experimental results…These important concepts may provide the theoretical basis for novel, immune-based interventions to treat and/or prevent HIV infection in humans."
>
> "Potential therapies may now be directed at restoring Th17 function at early stages of infection, perhaps leading to a whole new approach to AIDS vaccine development."
>
> "This research changes the paradigm of HIV pathogenesis, and perhaps pathogenesis of other latent viral infections."

Experts thought McCune's results could lead to a paradigm shift in how to treat HIV/AIDS and similar immune-based infections.

c. Assessing Whether the Research Was Pioneering

In addition to characterizing the associated risks and identifying the potential outcomes of the research, experts were also asked to assess whether the accomplished work was pioneering. Two experts strongly agreed and one moderately agreed that McCune's research was pioneering. Below is a selection of comments from experts about why McCune's research was pioneering:

> "Many of the experiments on discovering CD4 T cell subsets preceded this research, but the originality was in the application of that research to search for an active way that HIV causes immunodeficiency rather than the passive loss of helper T cells in general."
>
> "I think this investigator did not take anything for granted, but pursued an approach antagonistic to the mainstream views in his field, with success."
>
> "This research was pioneering in that it tested new, risky, and paradigm-shifting ideas using cutting edge experimental approaches thus resulting in major advances in the field of HIV/AIDS pathogenesis."

The experts thought McCune's results made major progress in the field of HIV/AIDS pathogenesis and treatment.

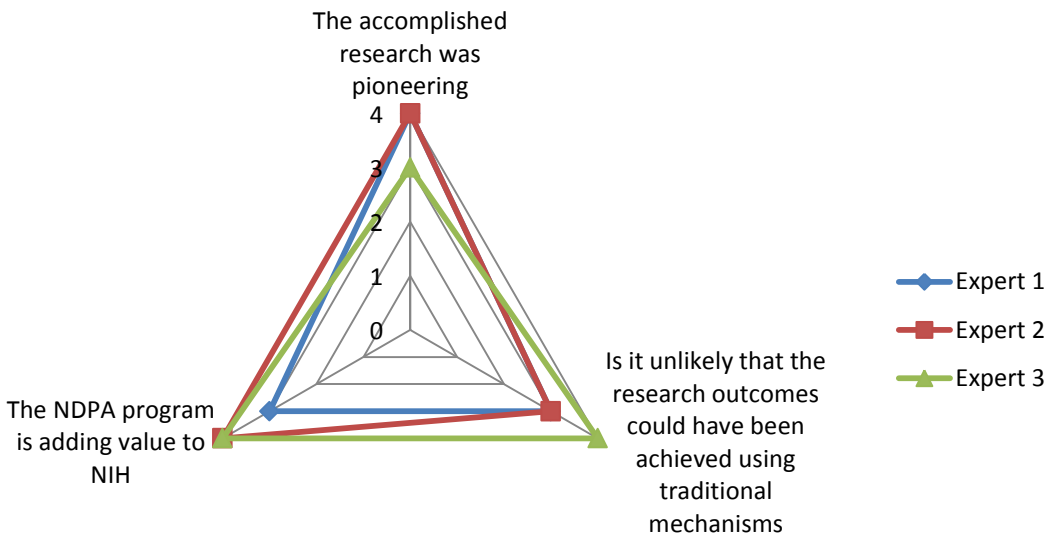
4. Value of the NDPA Program

a. Pioneer Perspective

McCune found the flexibility and amount of funds to be extremely useful for his NDPA project. These qualities allowed him to perform observational, rather than "hypothesis-driven," research, and try new experiments that ultimately failed or yielded little "interpretable data." He also explained that the Pioneer Award allowed him to begin "non-human primate work." Before this project, he had no preliminary data, connections, facilities, or students on that type of research. Funding primate work is often difficult because experiments take a long time, "data points are few and far between," and it is expensive. He explained that the money has "allowed [him] to sustain a culture of multidisciplinary work in humans" which is "risky by nature." If he had not been funded by the Pioneer Award, McCune would have pursued the project more slowly, and perhaps through funding from the Gates Foundation.

b. Expert Perspective

Experts were asked to rate whether McCune's results were a unique output of the Pioneer Award, and whether the Pioneer Award as a whole is adding value to NIH (Figure 45).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 45. Experts' Opinions of the NDPA

One expert strongly agreed and two moderately agreed that it is unlikely that the research outcomes could have been achieved using traditional mechanisms. Two experts strongly agreed and one moderately agreed that the NDPA program is adding value to NIH. Below is a selection of comments from experts about the value of the NDPA program:

> "Given the current TRAGIC state of affairs in terms of paylines for R01s and R21s it's unclear to me whether or not this type of award should represent a key priority…Yes, the NDPA does add to the value of the NIH portfolio, but we must be carefully examining each award and make sure that it will not detract from the R01/R21 pools."

> "The persistence of NIH peer review to minimize track record as the dominant tool of judging grants contrasts with successful review groups such as HHMI, the UK MRC, etc. The Pioneer Award mechanism provides expert review, not peer review. It is a shame it is limited by its requirements [50% time commitment for ~ $500,000 research support per year] to early and mid-phase scientist applicants."

> "This is the kind of program that allows very smart people room to develop novel ideas [without] the pressure of the R01 renewal cycle…ideas that take longer to mature[for ex., a cell type not even known at the time of award], can be synthesized readily with existing knowledge and lead to brand new and surprising insights."

The experts were very supportive of the value of the NDPA program. One expert, while approving of the results of the Pioneer Award, was concerned that it was detracting from the existing R01/R21 funds and applicant pool. The two other experts thought the Pioneer Award was a good independent funding mechanism that alleviates pressures of the R01 renewal cycle, allows for the development of innovative projects, and promotes good science from highly qualified researchers through its review system.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since McCune received the Pioneer Award in 2004, the pre-NDPA range refers to activity between 1999 and 2004 while the post-NDPA range refers to activity between 2005 and 2010.

a. Productivity

McCune has published a total of 130 original articles over the 24 years of his research career giving him an average of 5.42 publications per year (Table 94). In the pre-NDPA period, he published 40 articles for a rate of 6.67 publications per year. In the post-NDPA period, he published 32 articles for a rate of 5.33 articles per year.

Table 94. Summary of Publication Activity (McCune)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of publications	40	32	17	130
Number of years	6	6	N/A	24
Publication rate	6.666667	5.333333	N/A	5.416667

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

McCune published fewer works in the post-NDPA period than in the pre-NDPA period. In his interview, McCune noted that it was difficult to begin publishing in the non-human primate field because the publishing etiquette was different than what he was used to.

Of the 32 articles McCune published in the period after receiving the award, 17 were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 95.

Table 95. Publications Attributed to NDPA Funding (McCune)

Title	Journal	Year Published
Antiviral antibodies are necessary for control of simian immunodeficiency virus replication	Journal of Virology	2007
Central memory CD8(+) T cells appear to have a shorter lifespan and reduced abundance as a function of HIV disease progression	Journal of Immunology	2008
Correlating cellular and molecular signatures of mucosal immunity that distinguish HIV controllers from noncontrollers	Blood	2010
Critical Loss of the Balance between Th17 and T Regulatory Cell Populations in Pathogenic SIV Infection	PLOS Pathogens	2009
Cytomegalovirus-Specific T Cells Persist at Very High Levels during Long-Term Antiretroviral Treatment of HIV Disease	PLOS One	2010
Evidence for Persistent Low-Level Viremia in Individuals Who Control Human Immunodeficiency Virus in the Absence of Antiretroviral Therapy	Journal of Virology	2009
Growth hormone enhances thymic function in HIV-1-infected adults	Journal of Clinical Investigation	2008
HIV-induced changes in T cell signaling pathways	Journal of Immunology	2008
IFN-alpha-Induced Upregulation of CCR5 Leads to Expanded HIV Tropism In Vivo	PLOS Pathogens	2010
Loss of T cell responses following long-term cryopreservation	Journal of Immunological Methods	2007
Maternal Alloantigens Promote the Development of Tolerogenic Fetal Regulatory T Cells in Utero	Science	2008
Relationship between T cell activation and CD4(+) T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy	Journal of Infectious Diseases	2008
Suberoylanilide Hydroxamic Acid Reactivates HIV from Latently Infected Cells	Journal of Biological Chemistry	2009
Suppression of SIV-specific CD4(+) T cells by infant but not adult macaque regulatory T cells: implications for SIV disease progression	Journal of Experimental Medicine	2007
Tim-3 expression defines a novel population of dysfunctional T cells with highly elevated frequencies in progressive HIV-1 infection	Journal of Experimental Medicine	2008
Transcriptional Profiling in Pathogenic and Non-Pathogenic SIV Infections Reveals Significant Distinctions in Kinetics and Tissue Compartmentalization	PLOS Pathogens	2009
Tryptophan Catabolism by Indoleamine 2,3-Dioxygenase 1 Alters the Balance of T(H)17 to Regulatory T Cells in HIV Disease	Science Translational Medicine	2010

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, McCune's 121 original publications excluding reviews had been cited a total of 7,855 times. In the post-NDPA period, McCune published 32 publications that had received a total of 596 citations by August 2010. His 17 NDPA-attributed publications had received 315 citations by that time.

Total number of citations and age-weighted citation rate do not show surprising results over time.

The statistics on these publication sets are shown in Table 96.

Table 96. Summary of Citation Analyses (McCune)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (121 pubs)	7,855	26.34	43
Pre-NDPA (40 pubs)	3,057	17.53	N/A
Post-NDPA (32 pubs)	596	13.24	N/A
Attributed to NDPA Funding (17 pubs)	315	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTEr.

2) Journal Impact Factors

McCune published 40 articles in twenty-one different sources in the pre-NDPA period and 32 articles in twenty-one sources in the post-NDPA period. Detailed data on McCune's most published-in journals for the pre- and post-NDPA time periods respectively are shown in Table 97 and Table 98.

In the pre-NDPA period, 30 of McCune's 40 publications, 75%, were in journals at or above the 98th percentile (Table 99). In the post-NDPA period, 16 of McCune's 32 publications, 50%, were in journals of the same caliber. Eleven of 17 NDPA-attributed publications, 64.71% were in journals with *Eigenfactor* values above the 98th percentile.

Table 97. Most Published-in Journals in the Pre-NDPA Period, 1999-2004 (McCune)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
5	Journal of Immunology	0.475344	99.83
5	Journal of Infectious Diseases	0.120262	98.57
3	AIDS	0.078339	97.67
3	Journal of Experimental Medicine	0.272079	99.57
3	Journal of Immunological Methods	0.019682	88.2
3	Journal of Virology	0.250077	99.48
3	Nature Medicine	0.226874	99.39

Source: Eigenfactor.org, Journal names came from Web of Science

Table 98. Most Published-in Journals in the Post-NDPA Period, 2005-2010 (McCune)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
5	Journal of Virology	0.250077	99.48
3	Journal of Immunology	0.475344	99.83
3	PLOS Pathogens	0.030031	92.24
2	AIDS Research and Human Retroviruses	0.013442	93.75
2	JAIDS-Journal of Acquired Immune Deficiency Syndromes	0.047185	95.44
2	Journal of Experimental Medicine	0.272079	99.57
2	Journal of Infectious Diseases	0.120262	98.57

Source: Eigenfactor.org, Journal names came from Web of Science

Table 99. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (McCune)

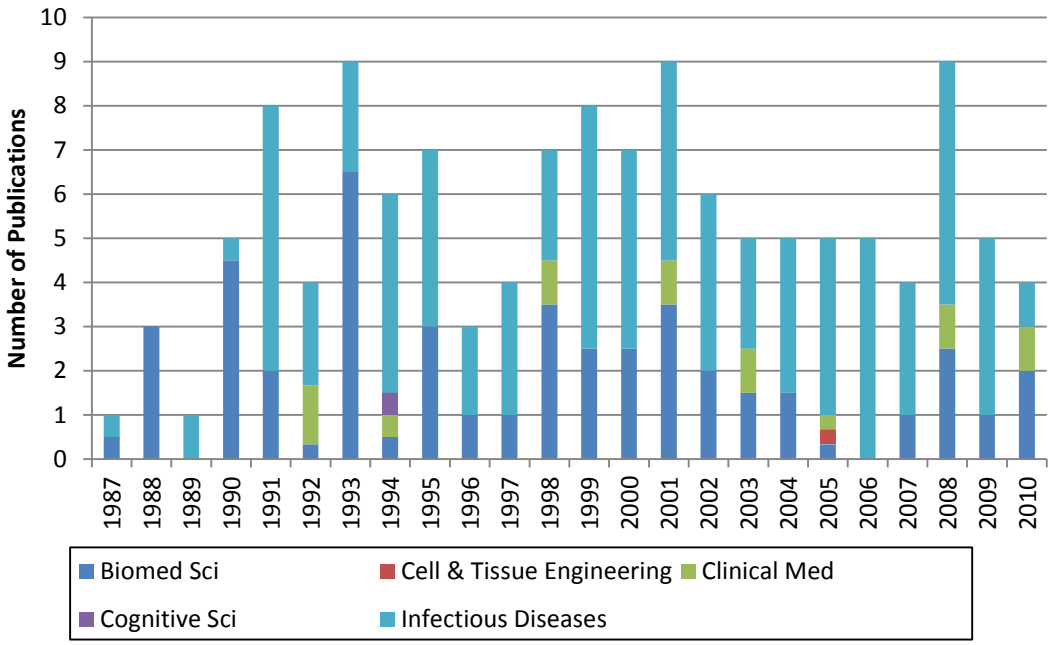
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (40 pubs)	30	75.00%
Post-NDPA (32 pubs)	16	50.00%
Attributed to NDPA Funding (17 pubs)	5	64.71%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data is from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

McCune's 130 publications over the duration of his career can be categorized into a total of five disparate macro-disciplines. He published in three macro-disciplines over his 40 pre-NDPA articles and four macro-disciplines over his 32 post-NDPA articles. The distribution of McCune's publications into macro-disciplines over the full length of his career may be seen in Figure 46.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 46. Distribution of Publications into Macro-disciplines over Time (McCune)

McCune has published consistently in Biomedical Science and Infectious Diseases throughout the course of his career with his work on HIV pathogenesis. The Pioneer

Award led him to study HIV in primate models, but there was little perceived change in the macro-disciplines of the journals in which he published.

2) Body of Knowledge Cited

McCune cited fifteen different macro-disciplines in the 4,621 cited references of his 130 career publications. This included thirteen macro-disciplines in the 1,565 cited references of his 40 pre-NDPA publications and eleven macro-disciplines in the 1,456 cited references of his 32 post-NDPA publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The Integration and Specialization scores for McCune are shown in Table 100.

Table 100. Integration and Specialization Scores (McCune)

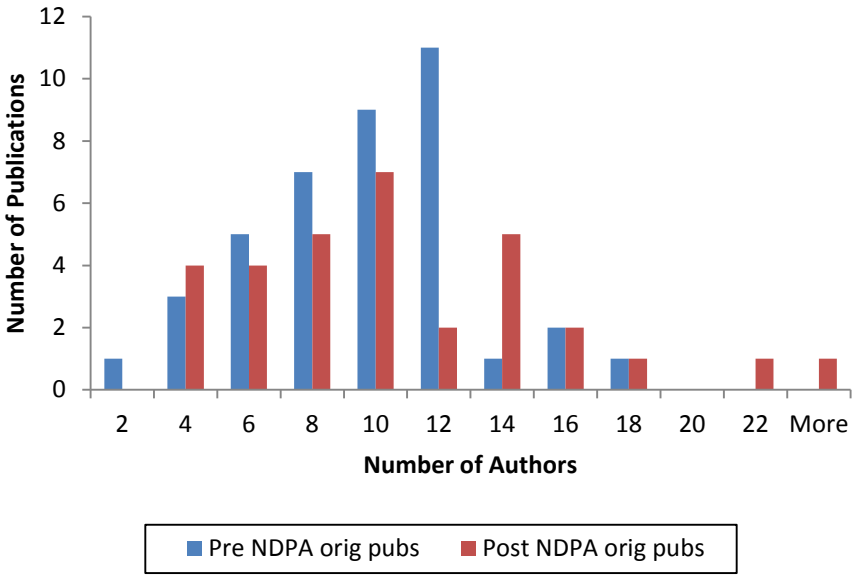
	Full Career (4621 cited references)	Pre-NDPA (1565 cited references)	Post-NDPA 1456 cited references)
Integration	0.470	0.471	0.491
Specialization	0.578	0.608	0.583

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, McCune appears to be a "Disciplinarian" over all three time periods measured.

d. Collaboration

The median number of total authors in McCune's publication set was 7.5. In the pre-NDPA period, this median was 9, and in the post-NDPA period, it was 9.5. A comparison of the pre- and post-NDPA collaboration patterns may be seen below (Figure 47).



Source: Web of Science

Figure 47. Distribution of Number of Authors in Original Publication Set (McCune)

The number of unique authors in a researcher's publishing network is another metric that captures co-authorship patterns. McCune has published with 383 unique individuals throughout the duration of his full career. He published with 172 individuals over his pre-NDPA publications, and 163 individuals over his post-NDPA publications. Over his 17 NDPA-attributed publications, McCune published with 110 other researchers. During his interview, McCune explained that he had to initiate collaborations and hire new researchers in fields such as primatology, neonatology, pediatric gastroenterology, and more in order to perform his NDPA-proposed research.

L. Steven McKnight (2004)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The panel of reviewers acknowledged the success of McKnight's previous achievements in both academia and industry in biochemistry and biotechnology. The panel was interested in funding his lab's newest line of inquiry, "the genetic and metabolic regulation of circadian rhythms" in yeast. This research was noted to have potential implications for cell cycle regulators in mammalian cells. His research has the potential to provide "a major new paradigm for understanding cellular and organismal biology."

3. Nature of Project Risks and Outcomes

The Pioneers and three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 101 and Table 102).

a. Typology of Project Risks

Table 101. Characterization of Unique Project Risk (McKnight)

Please indicate which of the following risks are applicable to the NDPA-funded project	McKnight	Expert 1	Expert 2	Expert 3
Conceptual Risk		x		
Technical Risk	x			
Experience Risk	x	x	x	x
Multidisciplinary Risk	x		x	
None of these risks				

Source: Pioneer interview, Expert review

All three of the experts believed that McKnight's NDPA proposal incorporated an experience risk. McKnight himself believed there were technical, experience, and multidisciplinary risks.

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of McKnight's research:

> "The McKnight group had not (previously) used continuous, steady-state cultures of yeast to obtain and study metabolically synchronous cultures."

"By the nature of the work and its outcomes, new avenues of investigation beyond the investigator's expertise ensued."

The experts thought McKnight's proposal extended into areas beyond his previous research specialty.

b. Typology of Potential Outcomes

Table 102. Characterization of Potential Pioneering Outcomes (McKnight)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	McKnight	Expert 1	Expert 2	Expert 3
New Idea	x	x	x	x
New Phenomenon	x	x		x
New Methodology	x		x	
New Technology				
New Framework	x	x		x
None of these outcomes				

Source: Pioneer interview, Expert review

At least two of three experts thought McKnight's work could result in the formulation of a new idea, the discovery of a new empirical phenomenon, and the synthesis of a new framework. McKnight thought his research could result in those outcomes in addition to the development of a new methodology.

Below is a selection of comments from the experts that justify their evaluations of the potential pioneering outcomes of McKnight's research:

> "I am a fan of their recent paper describing the dependence of mouse embryonic stem cells on specific metabolic pathways to sustain their ultra-fast rates of cell proliferation. I think this paper will eventually have a major impact. Even though humans don't have the particular enzyme responsible for this (explaining why some investigators may not consider this paper too important), in my opinion it is of the outmost significance to decipher the metabolic cues that limit mammalian cell proliferation. This paper set the stage for such future analyses in animal cells."

> "That clusters of genes in various metabolic pathways were expressed during different phases of growth permits computer modeling to predict cellular metabolism under various growth conditions…Along these lines, one might envisage novel methodology (e.g., convenient analytical kits) to monitor gene expression and/or critical metabolites to monitor health."

> "They also provided transcriptomic and metabolomic data sets that underlie metabolic oscillations. These were not new or pioneering, since other groups at the same time or even earlier described similar data sets.

> However, the McKnight data sets are more "user-friendly" to the community."

The experts thought McKnight's Pioneer project resulted in the observation of new phenomena related to mouse cell proliferation and had the potential to develop a new methodology to monitor health via the computer monitoring of gene expression, metabolites, or both.

c. Assessing Whether the Research Was Pioneering

In addition to characterizing the associated risks and identifying the potential outcomes of the research, experts were also asked to assess whether the accomplished work was pioneering. Two experts strongly agreed and one moderately agreed that McKnight's accomplished research was pioneering. Below is a selection of comments from experts justifying their assessments:

> "McKnight was not the only or the first person to study this problem using the techniques they used…However, their work pushed the field substantially. Perhaps a better way to think about it is: where would the field be without their contributions? In my opinion…it would still be in the 'obscure' zone."

> "This is not the only lab that performed global analyses of gene expression and metabolites. However…[the] data sets derived from this pioneering work has broad implications and will direct the work of many investigators for several years to come."

Despite the fact that he was neither the first nor only person to study this problem using the techniques he employed, all three experts found McKnight's research to be pioneering. Nevertheless, they agreed that his work pushed the field forward substantially and will have broader implications for this field in the future.

4. Value of the NDPA Program

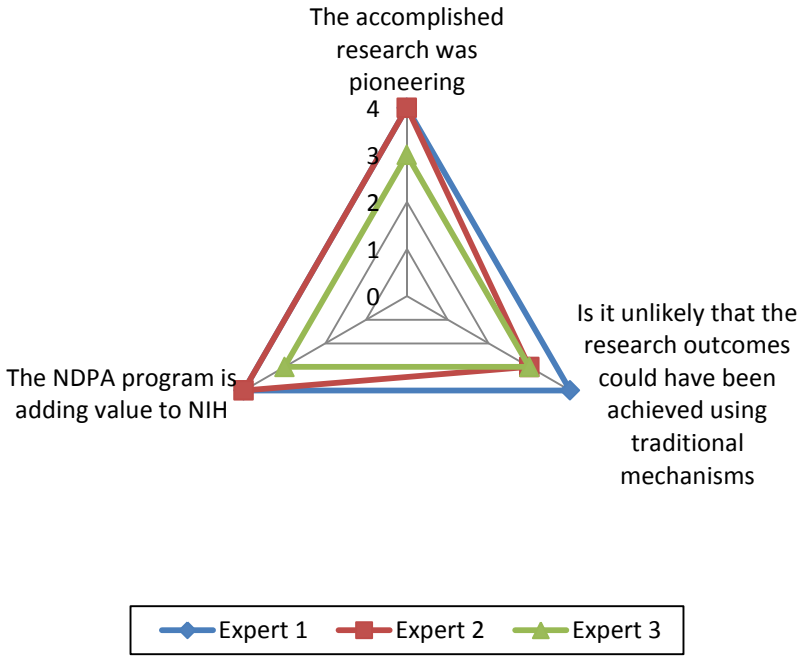
a. Pioneer Perspective

In his interview, McKnight explained that the Pioneer Award resources allowed him to "undertake two unbelievably risky projects." He believed that others would not have attempted his project because there was a lot of risk and work involved without any promises of success. The award allowed him to perform the screen and gather the groundwork data that supported his second (of two) projects supported by the NDPA. He was also able to purchase a mass spectrometer with NDPA funding. If he had not gotten the NDPA funds, McKnight would have still tried to pursue the idea although progress would have been less efficient and effective. He explained that he "couldn't have done

the neurogenesis screening" and "probably wouldn't have moved into stem cell work" because of a lack of resources to complete the first half of his project.

b. Expert Perspective

Experts were asked to rate whether McKnight's results were a unique output of the Pioneer Award, and whether the Pioneer Award is adding value to NIH (Figure 48).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 48. Experts' Opinions of the NDPA (McKnight)

One expert strongly agreed and two moderately agreed that it is unlikely that the research outcomes could have been achieved using traditional mechanisms. Two experts strongly agreed and one moderately agreed that the Pioneer Award is adding value to NIH.

Below is a selection of comments from experts about the value of the NDPA program:

> "The NDPA program gave an established, "star" scientist like McKnight extra freedom to tackle an important problem and bring a given field to prominence. I don't think that this could have been done through traditional funding mechanisms."

> "The unrestricted funding allowed Dr. Knight to expand the global analysis of gene expression and metabolites in yeast and stem cells and take chances that new and useful information would be obtained. With the

traditional NIH grants, he would have been under more pressure to perform work that would give predicted results."

"[The] people chosen to receive these awards always seem to be productive in making exciting discoveries. In this case, there is probably a high likelihood that the work would have been done with funds obtained through the usual channels."

Two experts had unreservedly good opinions of the NDPA, particularly in the case of McKnight's research. One expert remarked, however, that while it is good that talented researchers should have more freedom to pursue different new avenues, the researchers chosen could have probably obtained their results through the standard funding channels because they have always been exceptional.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since McKnight received the Pioneer Award in 2004, the pre-NDPA range refers to activity between 1999 and 2004 while the post-NDPA range refers to activity between 2005 and 2010.

a. Productivity

McKnight has published a total of 97 original articles over the 31 years of his research career, giving him an average of 3.13 articles per year (Table 103). In both the pre- and post-NDPA periods, he published 13 articles for an average rate of 2.17 articles per year.

Table 103. Summary of Publication Activity (McKnight)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of publications	13	13	3	97
Number of years	6	6	N/A	31
Publication rate	2.166667	2.166667	N/A	3.129032

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

McKnight published the same number of articles before and after receiving the award. In his interview, McKnight remarked that there was no difference in his rate of publication in the post-NDPA period. He also stated that he generally publishes very little because he wants to be proud of all his work.

Of the 13 post-NDPA articles, 3 were attributed to NDPA funding. McKnight noted that most of his published work since 2006 was related to the NDPA, so the publications attributed to NDPA funding do not reflect the full effect of the Pioneer Award on his research. The publications attributed to NDPA funding are listed in Table 104.

Table 104. Publications Attributed to NDPA Funding (McKnight)

Title	Journal	Year Published
Dependence of Mouse Embryonic Stem Cells on Threonine Catabolism	Science	2009
Discovery of a Proneurogenic, Neuroprotective Chemical	Cell	2010
Evidence of carbon monoxide-mediated phase advancement of the yeast metabolic cycle	Proceedings of the National Academy of Sciences of the United States of America	2009

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, McKnight's 86 original publications excluding reviews had been cited a total of 20,881 times. In the post-NDPA period, McKnight published 13 publications that had received a total of 362 citations by August 2010. Three of those 13 publications were attributed to NDPA funding and they received a total of 11 citations.

Total number of citations and age-weighted citation rate do not show surprising trends over time. It is expected that the number of citations and age-weighted citation rate would be lower for the post-NDPA period. The statistics of McKnight's publication set are shown in Table 105.

Table 105. Summary of Citation Analyses (McKnight)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (86 pubs)	20,881	33084	53
Pre-NDPA (11 pubs)	2,005	14.42	N/A
Post-NDPA (13 pubs)	362	8.74	N/A
Attributed to NDPA Funding (3 pbus)	11	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

McKnight published 13 publications in six different sources in the pre-NDPA time period and 13 publications in five different sources in the post-NDPA time period. Detailed data on McKnight's most published-in journals for the pre- and post-NDPA time periods respectively are shown in Table 106 and Table 107.

Table 106. Most Published-in Journals in the Pre-NDPA Period, 1999-2004 (McKnight)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
6	Science	1.58309	99.98
2	Cell	0.671695	99.89
2	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
1	Annual Review of Biochemistry	0.0685238	97.32
1	FASEB Journal	0.129982	98.74
1	Journal of Inorganic Biochemistry	0.0241742	90.32

Source: Eigenfactor.org, Journal names came from Web of Science

Table 107. Most Published-in Journals in the Post-NDPA Period, 2005-2010 (McKnight)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
7	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
3	Science	1.58309	99.98
1	Cell	0.671695	99.89
1	Cell Cycle	0.0633633	96.89
1	Schizophrenia Bulletin	0.0179353	87.21

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre- and post-NDPA period, 11 of McKnight's 13 publications, 84.62%, were in journals at or above the 98th percentile (Table 108). All three of McKnight's NDPA-attributed publications were published in journals of similar caliber.

Table 108. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (McKnight)

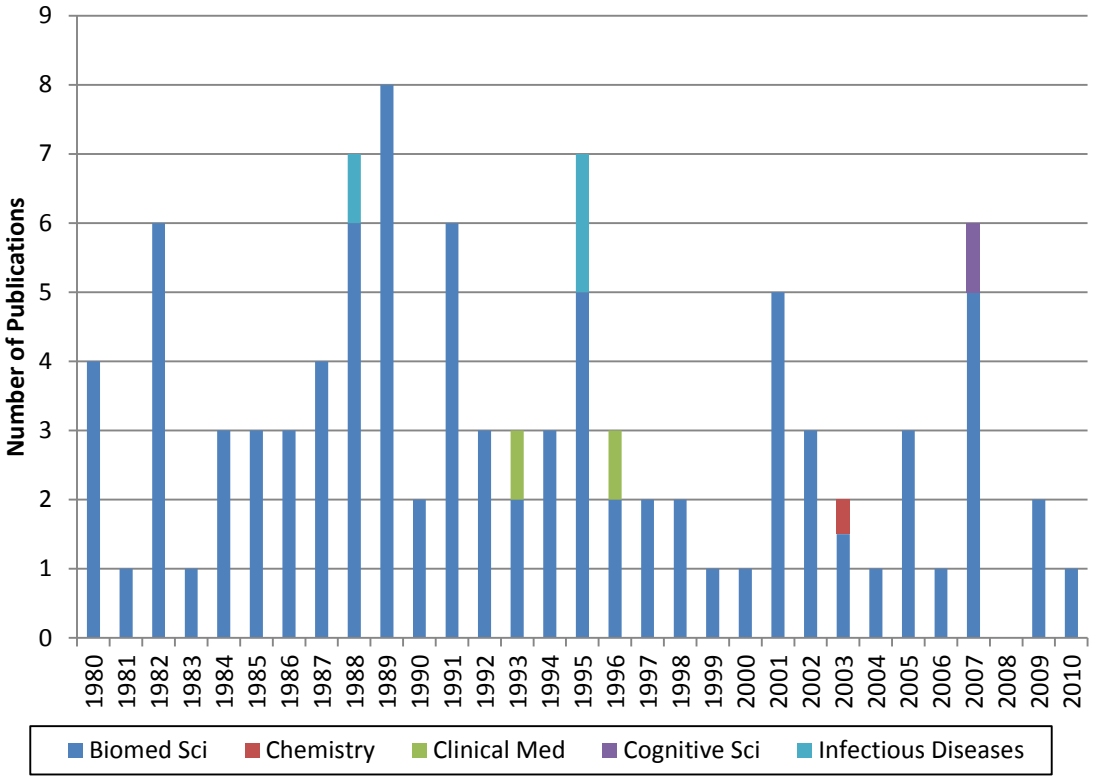
Publication Set	Numbers of Publications	Percentage of Publications
Pre-NDPA (13 pubs)	11	84.62%
Post-NDPA (13 pubs)	11	84.62%
Attributed to NDPA Funding (3 pubs)	3	100.00%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data are from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

McKnight's 97 publications over the duration of his career can be categorized into a total of five different macro-disciplines. He published in two macro-disciplines over 13 pre- and post-NDPA publications. The distribution of McKnight's publications into macro-disciplines over the full length of his career is shown in Figure 49.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 49. Distribution of Publications into Macro-disciplines over Time (McKnight)

McKnight published throughout his career primarily in Biomedical Science with his previous work on leucine zippers and his more recent work in cell cycle regulation.

2) Body of Knowledge Cited

McKnight cited thirteen different macro-disciplines in the 3,776 cited references of his 97 career publications. This included eleven macro-disciplines in the 479 cited references of his 13 pre-NDPA publications and twelve macro-disciplines in the 443 cited references of his 12 post-NDPA publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The Integration and Specialization scores for McKnight are displayed in Table 109.

Table 109. Integration and Specialization Scores (McKnight)

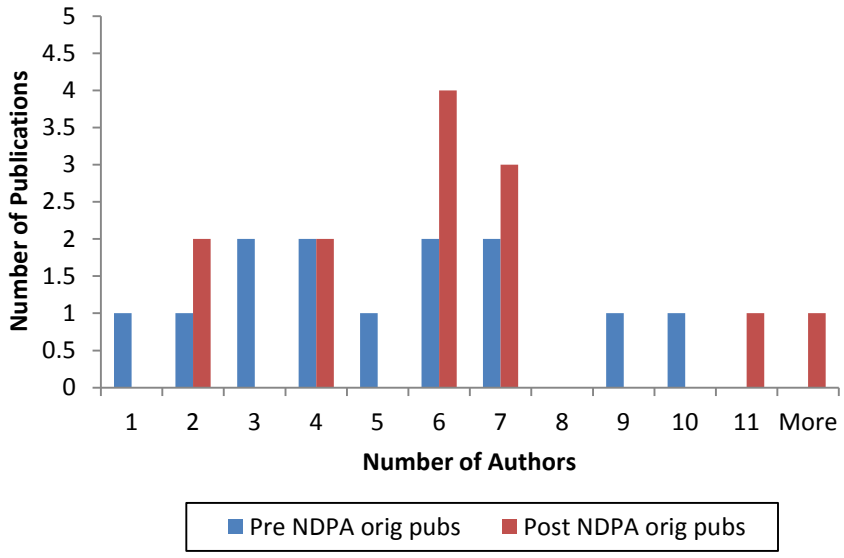
	Full Career (3776 cited references)	Pre-NDPA (479 cited references)	Post-NDPA (443 cited references)
Integration	0.305	0.464	0.494
Specialization	0.818	0.836	0.956

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, McKnight generally appears to be a "Disciplinarian" for the three time periods measured.

d. Collaboration

The median number of total authors in McKnight's publication set was three. In the pre-NDPA period the median was five, and in the post-NDPA period the median was six. A comparison of the pre- and post-NDPA distributions of the total number of authors can be seen in Figure 50.



Source: Web of Science

Figure 50. Distribution of Number of Authors in Original Publication Set (McKnight)

The number of unique authors in a researcher's publishing network is another metric that captures co-authorship patterns. McKnight has published with 184 unique authors throughout the duration of his career. In the pre-NDPA period he published with 29 researchers, and in the post-NDPA period, he published with 57 researchers. Over his three NDPA-attributed publications, McKnight published with 28 unique individuals.

M. Chad Mirkin (2004)

1. Research Summary

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 nano-viruses 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.

2. NDPA Reviewer Panel Opinions

The panel of reviewers believed Mirkin showed great potential because of his highly productive past, ability to "move into new areas," and the development of his diagnostic technology DPN. They were impressed with his "well-organized infrastructure and vast collaborative network."

3. Nature of Project Risks and Outcomes

The Pioneers and three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 110 and Table 111).

a. Typology of Project Risks

Table 110. Characterization of Unique Project Risk (Mirkin)

Please indicate which of the following risks are applicable to the NDPA-funded project	Mirkin	Expert 1	Expert 2	Expert 3
Conceptual Risk	x			x
Technical Risk	x	x		
Experience Risk	x	x		x
Multidisciplinary Risk	x			x
None of these risks			x	

Source: Pioneer interview, Expert review

Two of three experts agreed that Mirkin's NDPA proposal had an experience risk. Mirkin himself believed his proposal incorporated conceptual, technical, experience, and multidisciplinary risks.

In his interview, Mirkin explained that scientists had been convinced that "negatively charged entities will not enter cells," but his work proposed that the very negatively charged particle of DNA and gold could associate with proteins and be internalized by the cell. Mirkin's lab used new techniques to make an extracellular matrix to apply his dip pen technology. Mirkin also explained that his lab had moved into biology and medicine through collaborations with his institution's medical school and neuroscience department.

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Mirkin's research:

> "He has continued to make extremely clever innovations in these technologies to develop for example new diagnostic and biological tools (e.g., iterations on the nanobarcode concept and the 'nanoflares'), which require a broad appreciation of the physical chemistry, biology, and practical clinical issues."
>
> "The DPN techniques that have been developed were well on their way prior to this award."
>
> "The level of his science went up, and his direction moved more towards biomedicine."
>
> "Work on the oligo-nanoparticle conjugates is a good example of work that is challenging accepted wisdom- typically, cationic particles are thought to be taken up efficiently by cells and anionic particles are thought to be poorly taken up."

The experts were mixed about the risks of Mirkin's proposal. One expert noted that DPN had already been developed before he received the Pioneer Award. Other experts

stated that the NDPA allowed Mirkin to move into biomedicine, develop new nanotools, and challenge existing biological frameworks.

b. Typology of Potential Outcomes

Table 111. Characterization of Potential Pioneering Outcomes (Mirkin)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Mirkin	Expert 1	Expert 2	Expert 3
New Idea	x			
New Phenomenon	x	x		x
New Methodology	x	x		x
New Technology	x	x	x	x
New Framework		x		
None of these outcomes				

Source: Pioneer interview, Expert review

At least two of three experts agreed that Mirkin's research could result in the discovery of a new phenomenon, the development of a new methodology, and the invention of new technology. Mirkin believed his research could result in those same outcomes as well as the formulation of a new idea.

Mirkin explained that his technologies helped him to observe new phenomena "the chemical nuances of how things get into cells…how they bind to their targets inside the cell." His work developed "a whole new field in terms of nanostructured gene regulation agents and therapeutics."

Below is a selection of comments from the experts that justify their evaluations of the potential pioneering outcomes of Mirkin's research:

> "The appearance of several technologies he has developed in journals such as Nature Protocols is testament to the robustness of the approaches– in other words, a lot of these techniques really work well enough to be adapted and shared broadly to any lab."

> "His drive to commercialize these inventions means that these technologies that might remain esoteric chemist's toys can be accessed by a broader biomedical community."

Experts thought Mirkin greatly expanded the applicability of DPN through the Pioneer Award. They also noted that Mirkin's inventions were widely accessible to other research groups because they are being commercialized and published in important methods journals such as Nature Protocols.

c. Assessing Whether the Research Was Pioneering

In addition to characterizing the associated risks and identifying the potential outcomes of the research, experts were also asked to assess whether the accomplished work was pioneering. Two experts strongly agreed and one strongly disagreed that Mirkin's accomplished research was pioneering. Below is a selection of comments from experts about why Mirkin's research was or was not pioneering.

> "Mirkin is one of the leaders in the field, and has pioneered the way for others to follow with the techniques and methods he has developed. He has opened new insight in a number of areas."

> "From the publication list it does not appear that any significant biological questions were addressed with DPN. Thus, although DPN is certainly pioneering (and Mirkin is a pioneer), the use of DPN to address questions of biological significance was not advanced as a result of the award."

Experts were mixed about whether Mirkin's Pioneer-funded research produced pioneering results in the biomedical field, despite the fact that there was strong agreement that Mirkin himself was pioneering.

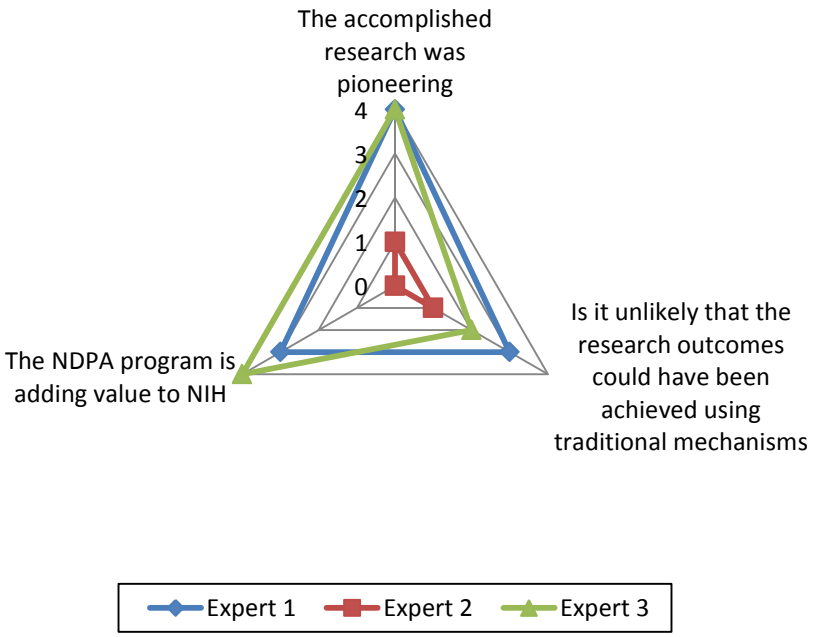
4. Value of the NDPA Program

a. Pioneer Perspective

Mirkin explained that before the Pioneer Award, his research had been focused on the physical sciences. The award made him and his lab think about how to use his nanotools to impact biology and medicine. The NDPA funds allowed him to tackle complex problems on a larger scale. He could "build a team of people…that involved folks coming from many different disparate disciplines" and follow a project that felt right intuitively but for which there was no concrete evidence. While other Pioneers remarked that the flexibility of the funds freed up time to be able to perform more research, Mirkin stated that the award was so large that he had to change his management plan in order to avoid "becoming an administrator." Mirkin stated that the results of his proposal probably would not have been achieved without the Pioneer Award.

b. Expert Perspective

Experts were asked to rate whether Mirkin's results were a unique output of the Pioneer Award, and whether the Pioneer Award is adding value to NIH (Figure 51).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 51. Experts' Opinions of the NDPA (Mirkin)

One expert moderately agreed, one moderately disagreed, and one strongly disagreed that it is unlikely that the research outcomes could have been achieved using traditional mechanisms. One expert strongly agreed and one moderately disagreed that the NDPA is adding value to NIH. One declined to respond on this question.

Below is a selection of comments from experts about the value of the NDPA program:

> "My opinion is that this program is not rewarding risk takers who are venturing into fields of study outside of their traditional areas of expertise. The program has been successful at selecting PI's with proven track records and well-funded research programs."
>
> "I strongly believe the NIH should have a mechanism to provide strong support to the most creative scientists…which is based on a track record of creativity and excellent science, and less about the fine details of individual research projects."
>
> "He was remarkably productive and moved the field visibly forward. This probably would not have happened at the same pace without the Pioneer Award, but I think it would have happened nonetheless."
>
> "The value is strongly dependent on awardees. Not all the awardees have had the same level of success that Mirkin has."

Experts were mixed about the value of the Pioneer Award in funding creative research in the context of Mirkin's research. One expert thought NIH was simply rewarding established researchers, while others thought that the NDPA was a good mechanism that supported creativity.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Mirkin received the Pioneer Award in 2004, the pre-NDPA range refers to activity between 1999 and 2004, while the post-NDPA range refers to activity between 2005 and 2010.

a. Productivity

Mirkin has published a total of 461 publications over the 25 years of his research career, which gives him a rate of 18.44 articles per year (Table 112). In the pre-NDPA period, he published 157 articles for a rate of 26.17 articles per year. In the post-NDPA period, he published 232 articles for a rate of 38.67 articles per year.

Table 112. Summary of Publication Activity (Mirkin)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	157	232	45	461
Number of Years	6	6	N/A	25
Publication Rate	26.16667	38.66667	N/A	18.44

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Mirkin published more original works in the post-NDPA period as compared to the pre-NDPA period. Before receiving the award, however, Mirkin was already an extremely productive researcher. His immense publishing power as compared to the other awardees is likely due to his establishment of multiple research companies. In his interview, Mirkin explained that they had a big increase in publication in the post-NDPA period because he was hiring more people and those people were adding to the production of publications.

Of the 232 articles he published in the period after receiving the award, 45 were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 113.

Table 113. Publications Attributed to NDPA Funding (Mirkin)

Title	Journal	Year Published
A Self-Correcting Inking Strategy for Cantilever Arrays Addressed by an Inkjet Printer and Used for Dip-Pen Nanolithography	Small	2008
Aptamer Nano-flares for Molecular Detection in Living Cells	Nano Letters	2009
Assembly and organization processes in DNA-directed colloidal crystallization	Proceedings of The National Academy of Sciences of The United States of America	2009
Asymmetric functionalization of gold nanoparticles with oligonucleotides	Journal of the American Chemical Society	2006
Carborane-Based Pincers: Synthesis and Structure of SeBSe and SBS Pd(II) Complexes	Journal of the American Chemical Society	2009
Complementary Electrical and Spectroscopic Detection Assays with On-Wire-Lithography-Based Nanostructures	Small	2009
Controlling the lattice parameters of gold nanoparticle FCC crystals with duplex DNA linkers	Nano Letters	2008
Core-Shell Triangular Bifrustums	Nano Letters	2009
Curvature-Induced Base Pair "Slipping" Effects in DNA-Nanoparticle Hybridization	Nano Letters	2009
Dip-pen nanolithography of high-melting-temperature molecules	Journal of Physical Chemistry B	2006
DNA-Gold Triangular Nanoprism Conjugates	Small	2008
Dynamic interconversion of amorphous microparticles and crystalline rods in salen-based homochiral infinite coordination polymers	Journal of the American Chemical Society	2007
Establishing the Design Rules for DNA-Mediated Colloidal Crystallization	Angewandte Chemie-International Edition	2010
Gene Regulation with Polyvalent siRNA-Nanoparticle Conjugates	Journal of the American Chemical Society	2009
Gold Nanoparticles for Biology and Medicine	Angewandte Chemie-International Edition	2010
Heteroligated Supramolecular Coordination Complexes Formed via the Halide-Induced Ligand Rearrangement Reaction	Accounts of Chemical Research	2008
In-Wire Conversion of a Metal Nanorod Segment into an Organic Semiconductor	Small	2009
Inversion of product selectivity in an enzyme-inspired metallosupramolecular tweezer catalyzed epoxidation reaction	Chemical Communications	2009
Iodide ions control seed-mediated growth of anisotropic gold nanoparticles	Nano Letters	2008
Maximizing DNA loading on a range of gold nanoparticle sizes	Analytical Chemistry	2006

Title	Journal	Year Published
Microarray detection of duplex and triplex DNA binders with DNA-modified gold nanoparticles	Analytical Chemistry	2007
Multiplexed Protein Arrays Enabled by Polymer Pen Lithography: Addressing the Inking Challenge	Angewandte Chemie-International Edition	2009
Nano-flares for mRNA Regulation and Detection	Acs Nano	2009
Nanoparticle-based bio-barcode assay redefines "undetectable' PSA and biochemical recurrence after radical prostatectomy	Proceedings of the National Academy of Sciences of the United States of America	2009
On-wire lithography: synthesis, encoding and biological applications	Nature Protocols	2009
PCR-like cascade reactions in the context of an allosteric enzyme mimic	Journal of the American Chemical Society	2008
Peptide antisense nanoparticles	Proceedings of the National Academy of Sciences of the United States of America	2008
Plasmonic Focusing in Rod-Sheath Heteronanostructure	Acs Nano	2009
Plasmonically Controlled Nucleic Acid Dehybridization with Gold Nanoprisms	Chemphyschem	2009
Polymer pen lithography	Science	2008
Polyvalent DNA Nanoparticle Conjugates Stabilize Nucleic Acids	Nano Letters	2009
Pyrene-appended fluorescent tweezers generated via the Weak-Link Approach and their halide recognition properties	Tetrahedron	2008
Redox-Activating Dip-Pen Nanolithography (RA-DPN	Journal of the American Chemical Society	2009
Regulating Immune Response Using Polyvalent Nucleic Acid-Gold Nanoparticle Conjugates	Molecular Pharmaceutics	2009
Reversible Ligand Pairing and Sorting Processes Leading to Heteroligated Palladium(II) Complexes with Hemilabile Ligands	Organometallics	2009
Supramolecular allosteric cofacial porphyrin complexes	Journal of the American Chemical Society	2006
Surface Plasmon-Mediated Energy Transfer in Heterogap Au-Ag Nanowires	Nano Letters	2008
Surprisingly Long-Range Surface-Enhanced Raman Scattering (SERS) on Au-Ni Multisegmented Nanowires	Angewandte Chemie-International Edition	2009
Templated Spherical High Density Lipoprotein Nanoparticles	Journal of the American Chemical Society	2009
The Role Radius of Curvature Plays in Thiolated Oligonucleotide Loading on Gold Nanoparticles	Acs Nano	2009
Three-Dimensional Hybridization" with polyvalent DNA-gold nanoparticle conjugates	Journal of the American Chemical Society	2008

Title	Journal	Year Published
Topographically Flat, Chemically Patterned PDMS Stamps Made by Dip-Pen Nanolithography	Angewandte Chemie-International Edition	2008
Triple-decker complexes formed via the weak link approach	Organometallics	2006
Troger's-Base-Derived Infinite Co-ordination Polymer Microparticles	Small	2009
Water-Soluble Macrocycles Synthesized via the Weak-Link Approach	Inorganic Chemistry	2009

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of Fall 2010, Mirkin's 439 original publications excluding reviews had been cited a total of 28,238 times. In the post-NDPA period, Mirkin published 221 publications that had received a total of 277 citations by August 2010. The 45 NDPA-attributed publications had received a total of 661 citations.

Total number of citations and age-weighted citation rate do not show surprising trends over time. It is expected that the number of citations and the age-weighted citation rate would be lower for the post-NDPA period.

The statistics on this publication set are shown in Table 114.

Table 114. Summary of Citation Analyses (Mirkin)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (439 pubs)	28,238	59.39	72
Pre-NDPA (154 pubs)	16,293	41.65	N/A
Post-NDPA (221 pubs)	5,803	36.85	N/A
Attributed to NDPA Funding (45 pubs)	661	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Mirkin published 156 publications in thirty-two different sources in the pre-NDPA period and 232 publications in forty-six different sources in the post-NDPA period. Detailed data on Mirkin's most published-in journals for the pre- and post-NDPA time periods respectively (Table 115 and Table 116).

Table 115. Most Published-in Journals in the Pre-NDPA Period, 1999-2004 (Mirkin)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
40	Abstracts of Papers of the American Chemical Society	N/A	N/A
26	Journal of the American Chemical Society	0.951762	99.94
14	Angewandte Chemie-International Edition	0.513861	99.85
11	Science	1.58309	99.98
9	Inorganic Chemistry	0.15184	99.03
8	Nano Letters	0.252897	99.51

Source: Eigenfactor.org, Journal names came from Web of Science

Table 116. Most Published-in Journals in the Post-NDPA Period, 2005-2010 (Mirkin)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
37	Journal of the American Chemical Society	0.951762	99.94
26	Small	0.036996	93.73
25	Angewandte Chemie-International Edition	0.513861	99.85
22	Abstracts of Papers of the American Chemical Society	N/A	N/A
21	Nano Letters	0.252897	99.51
9	Analytical Chemistry	0.198505	99.31
9	Inorganic Chemistry	0.15184	99.03

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 97 of Mirkin's 157 publications, 62.81% were in journals at or above the 98th percentile (Table 117). In the post-NDPA period, 147 of Mirkin's 232 publications, 63.36%, were published in journals of the same caliber. Of his 45

publications attributed to NDPA funding, 31 or 68.89% had *Eigenfactor* values at or above the 98th percentile.

Table 117. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Mirkin)

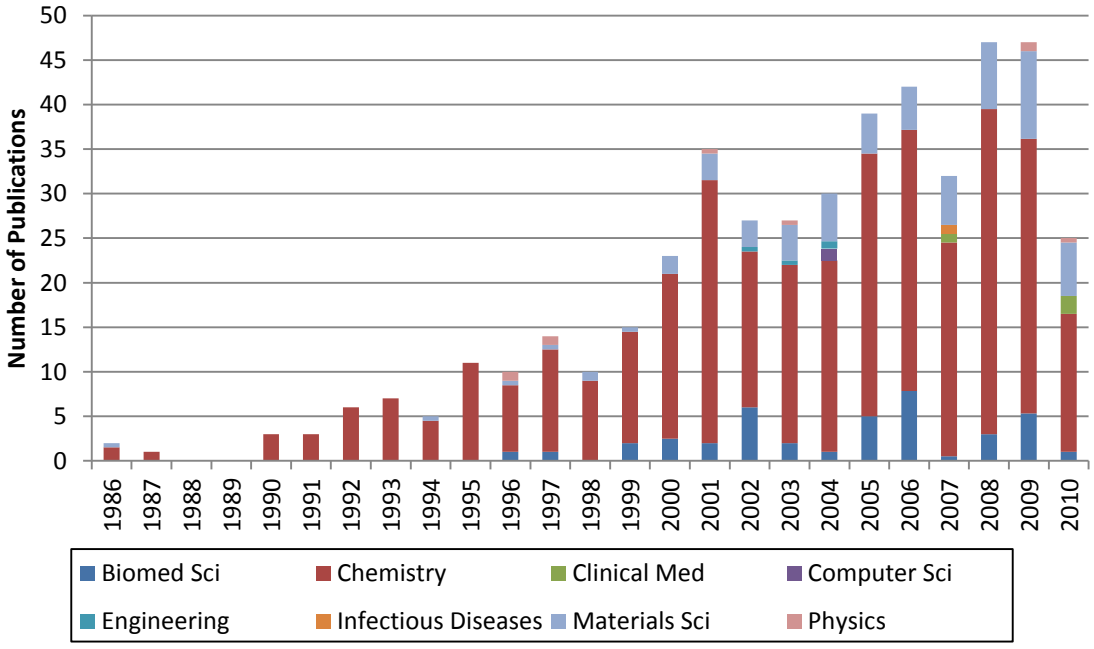
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (157 pubs)	97	62.81%
Post-NDPA (232 pubs)	147	63.36%
Attributed to NDPA Funding (45 pubs)	31	68.89%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data are from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Mirkin's 461 publications over the duration of his career can be categorized into a total of eight macro-disciplines. He published in six macro-disciplines over his 157 pre-NDPA publications and six macro-disciplines over his 232 post-NDPA publications. The distribution of Mirkin's career publications into macro-disciplines may be seen in Figure 52.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 52. Distribution of Publications into Macro-disciplines over Time (Mirkin)

Mirkin worked primarily in Chemistry for the duration of his career, but he also published consistently, albeit at lower rates, in Materials Science and Biomedical Science. Although Mirkin stated in his interview that he expanded greatly into biology and medicine after receiving the award, the number of Biomedical Science publications does not seem to have increased. It is possible that no publishing changes are perceived in this chart because multidisciplinary journals that Mirkin was publishing in before the award (i.e., Nature, Science) are categorized as Biomedical Science.

2) Body of Knowledge Cited

Mirkin cited seventeen different macro-disciplines in the 14,390 cited references of his 461 career publications. This included fifteen macro-disciplines in the 4,068 cited references of his 157 pre-NDPA publications and sixteen macro-disciplines in the 8,514 cited references of his 232 post-NDPA publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The Integration and Specialization scores for Mirkin's publications are shown in Table 118.

Table 118. Integration and Specialization Scores (Mirkin)

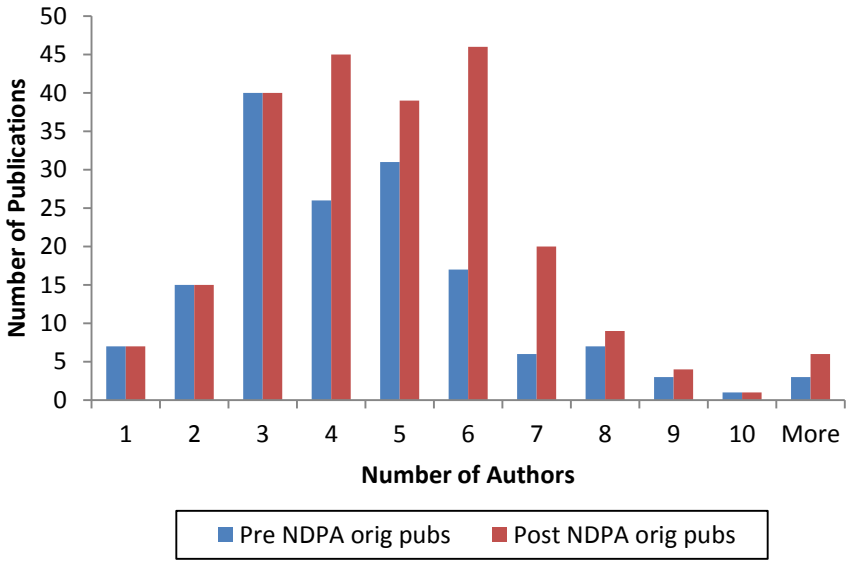
	Full Career (14390 cited references)	Pre-NDPA (4068 cited references)	Post-NDPA (8514 cited references)
Integration	0.516	0.472	0.531
Specialization	0.583	0.556	0.603

Source: Publication data are from Web of Science, scores were calculated using VantagePoint

Compared to the other Pioneers, Mirkin is near the mean in both I and S scores. He is just barely a "Disciplinarian" in all three measured periods.

d. Collaboration

The median number of total authors in Mirkin's publication set was four. In the pre-NDPA period this median was also four, but in the post-NDPA period it was five. A comparison of the pre- and post-NDPA distributions of the total number of authors may be seen in Figure 53.



Source: Web of Science

Figure 53. Distribution of Number of Authors in Original Publication Set (Mirkin)

The number of unique authors in a researcher's publishing network is another metric that captures co-authorship patterns. Mirkin has published with approximately 433 unique individuals throughout his full career. In the pre-NDPA period, he published with 138 researchers, and in the post-NDPA period, he published with 285 researchers. Over his 45 NPDA-attributed publications, Mirkin published with 85 individuals. In his interview, Mirkin explained that he began collaborations with virologists and researchers in the medical school and neuroscience departments due his shift into biology during the Pioneer Award.

N. Rob Phillips (2004)

1. Research Summary

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' *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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers was impressed with Phillips's history of unconventional scholarship and previous accomplishments in physical biology. While it was "unclear…whether he would succeed in generating important new data about molecular and cellular interactions," the panel thought Phillips was an "attractive fit" for the NDPA because of his "out of the box" thinking and newness to NIH.

3. Nature of Project Risks and Outcomes

The Pioneer and three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 119 and Table 120).

a. Typology of Project Risks

Table 119. Characterization of Unique Project Risk (Phillips)

Please indicate which of the following risks are applicable to the NDPA-funded project	Phillips	Expert 1	Expert 2	Expert 3
Conceptual Risk	x			
Technical Risk	x			x
Experience Risk	x	x		x
Multidisciplinary Risk	x	x	x	x
None of these risks				

Source: Pioneer interview, Expert review

At least two of three experts agreed that Phillips's NDPA proposal incorporated experience and multidisciplinary risks. Phillips himself stated that his proposal included conceptual, technical, experience, and multidisciplinary risks.

In his interview, Phillips stated that his NDPA project was more similar to the development of an approach to biology problems than a single project. He remarked that the extent of his technical risk included performing "12,000 PCR interactions at once on a little microfluidic chip." He also explained that his work attempts to apply physics principles to biological problems and biology principles to physics problems, thus rendering his work very multidisciplinary.

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Phillips's research:

> "Phillips moved from computational materials science to biophysics, applying coarse-grained mathematical models of elasticity to problems of membrane channel function, DNA looping, and the like."
>
> "Dr. Phillips developed a set of new analytical tools, relying on ideas in statistical physics, but also deeply rooted in the experimental biological details. This level of integration has not been pursued at this scale, both in the form of his book, and, for instance, in the description of membrane proteins interacting with membrane."
>
> "Phillips see both the details and the broader picture which allows him to extract physical ideas, quantifying them and make predictions, all without being paralyzed by a common problem in modeling biology… there is always an exception."

The experts were impressed with Phillips's synthesis of biological and physical ideas.

b. Typology of Potential Outcomes

Table 120. Characterization of Potential Pioneering Outcomes (Phillips)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Phillips	Expert 1	Expert 2	Expert 3
New Idea	x	x	x	x
New Phenomenon	x		x	x
New Methodology	x		x	x
New Technology	x			
New Framework	x	x	x	
None of these outcomes				

Source: Pioneer interview, Expert review

At least two of three experts agreed that Phillips's work had the potential to result in the formulation of new ideas, the discovery of new phenomena, the development of a new methodology, and the synthesis of a new framework. Phillips generally agreed with this assessment and added that his research could result in the invention of new technology.

Below is a selection of comments from the experts that justify their evaluations of the potential pioneering outcomes of Phillips's research:

> "Phillips's approach to transcription analysis will greatly enhance our understanding is likely to give us predictive tools."
>
> "To my knowledge, the description of membrane proteins interacting through the curvature-induced effects in the membrane and the effect of toxins on membrane proteins interacting through membrane shape is new and leads to an additional set of testable predictions."
>
> "Phillips developed a wide set of new theoretical ideas about quantifying biology and is applying them to a broad range of biological problems, gene packaging, membrane proteins interacting with the membrane and gene expression."

The experts thought Phillips observed new phenomena, particularly with regard to membrane proteins. They also believed his method of quantifying biology through physical principles was new.

c. Assessing Whether the Research Was Pioneering

In addition to characterizing the associated risks and identifying the potential outcomes of the research, experts were also asked to assess whether the accomplished work was pioneering. Two experts strongly agreed and one moderately agreed that Phillips's accomplished research was pioneering. Below is a selection of comments from experts justifying their assessment:

> "Through his book, his extensive collaborations, and his research, Dr. Phillips is opening a new area of research. We need people who can communicate between both physicists and biologists."
>
> "The level of quantification and precise mathematical description of the most basic biological processes has never been pushed as far. Phillips is pushing the envelope."

The experts were very positive about Phillips's ability to span both physics and biology and quantify biology in a meaningful way.

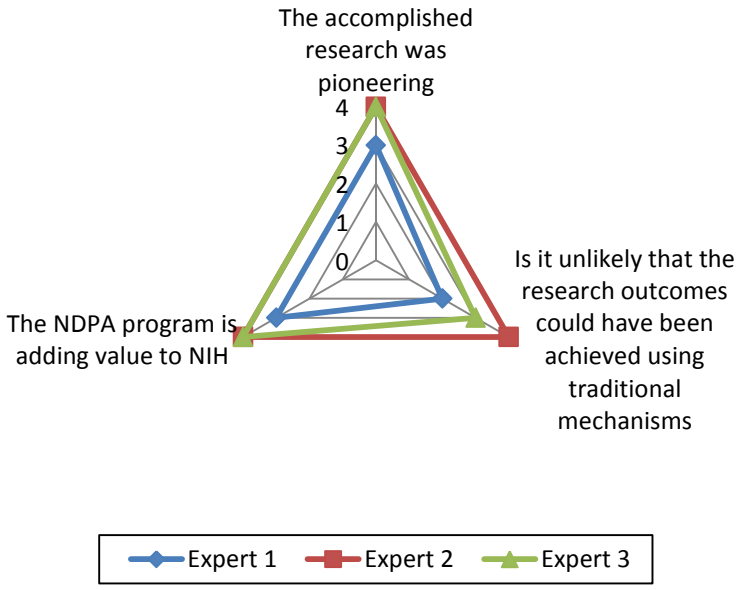
4. Value of the NDPA Program

a. Pioneer Perspective

Phillips found the NDPA valuable in that it allowed him to perform his research in peace for five years because he "[hated] the whole world of chasing after the next thing." He was also pleased the flexibility of the award allowed him to follow leads that he was excited about, improve the spaces in his lab, and hire new personnel. He also used some of the funds to get feedback on some of the work in his lab at his boot camp courses. Phillips remarked that the NDPA was "the greatest financial thing that happened to [him] in [his] career." He does not believe he would have been able to pursue his research proposal without having received this award.

b. Expert Perspective

Experts were asked to rate whether Phillips's results were a unique output of the Pioneer Award, and whether the Pioneer Award is adding value to NIH (Figure 54).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, 4 is strongly agree. Source: Expert review

Figure 54. Experts' Opinions of the NDPA (Phillips)

One expert strongly agreed, one moderately agreed, and one moderately disagreed that it is unlikely that the research outcomes could have been achieved using traditional mechanisms. Two experts strongly agreed and one moderately agreed that the NDPA program is adding value to NIH.

Below is a selection of comments from experts about the value of the NDPA program:

> "I think the main value is a program in which creative people are identified and given support without the requirement of detailed a priori research plans. As often said, if you knew enough to provide such details, you would not have to do the experiments. But with that attitude, it is very difficult to survive the pummeling of a study section."

> "We need to cultivate and tolerate some high risk/high reward research for truly innovative and risk taking endeavors. Such work doesn't happen on the scale of 1-2 years, but needs sufficient time to get developed, established and ultimately make its impact. The five year time scale is appropriate for this funding mechanism. This pioneering exploration can be both in the area of really hard experiments that explore new ideas and/or techniques, or the transformation of someone's research into a new area."

Experts generally held positive opinions of the NDPA's value to science and the NIH portfolio. They acknowledged that the flexibility of the budget and the five year period were critical aspects to the program's success.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Phillips received the Pioneer Award in 2004, the pre-NDPA range refers to activity between 1999 and 2004 while the post-NDPA range refers to activity between 2005 and 2010.

a. Productivity

Phillips has published a total of 76 original articles over the 21 years of his research career giving him an average of 3.62 articles per year (Table 121). In the pre-NDPA period, Phillips published 26 articles for a rate of 4.33 articles per year. In the post-NDPA period, Phillips published 34 articles for a rate of 5.67 articles per year.

Table 121. Summary of Publication Activity (Phillips)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	26	34	12	76
Number of Years	6	6	N/A	21
Publication Rate	4.333333	5.666667	N/A	3.619048

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Phillips published more articles in the post-NDPA period as compared to the pre-NDPA period. Of the 34 articles Phillips published in the period after receiving the award, 12 were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 122.

Table 122. Publications Attributed to NDPA Funding (Phillips)

Title	Journal	Year Published
A feeling for the numbers in biology	Proceedings of the National Academy of Sciences of the United States of America	2009
Biological consequences of tightly bent DNA: The other life of a macromolecular celebrity	Biopolymers	2007
Concentration and Length Dependence of DNA Looping in Transcriptional Regulation	Plos One	2009
Dynamics of DNA ejection from bacteriophage	Biophysical Journal	2006
Emerging roles for lipids in shaping membrane-protein function	Nature	2009
First-principles calculation of DNA looping in tethered particle experiments	Physical Biology	2009
Ion-Dependent Dynamics of DNA Ejections for Bacteriophage lambda	Biophysical Journal	2010
Measuring flux distributions for diffusion in the small-numbers limit	Journal of Physical Chemistry B	2007
Morphology and interaction between lipid domains	Proceedings of the National Academy of Sciences of the United States of America	2009
Reduced amino acid alphabets exhibit an improved sensitivity and selectivity in fold assignment	Bioinformatics	2009
The effect of genome length on ejection forces in bacteriophage lambda	Virology	2006
Trajectory Approach to Two-State Kinetics of Single Particles on Sculpted Energy Landscapes	Physical Review Letters	2009

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, Phillips's 68 original publications excluding reviews had been cited a total of 1,866 times. In the post-NDPA period, Phillips published 28 publications that had received a total of 484 citations by August

2010. The 12 NDPA-attributed publications had received a total of 149 citations by that time.

The age-weighted citation rate of Phillips's post-NDPA publication set is higher than that of his pre-NDPA publication set. It appears that his post-NDPA work has had a greater impact in terms of the citations it has received.

Statistics on this publication set are shown in Table 123.

Table 123. Summary of Citation Analyses (Phillips)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (68 pubs)	1,866	14.62	24
Pre-NDPA (25 pubs)	781	8.45	N/A
Post-NDPA (28 pubs)	484	9.89	N/A
Attributed to NDPA Funding (12 pubs)	149	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Phillips published 27 publications in thirteen different sources in the pre-NDPA time period and 33 publications in eighteen different sources in the post-NDPA time period. Detailed data on Phillips's most published-in journals for the pre- and post-NDPA time periods are shown in Table 124 and Table 125, respectively.

Table 124. Most Published-in Journals in the Pre-NDPA Period, 1999-2004 (Phillips)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
6	Biophysical Journal	0.187695	99.28
5	Modelling and Simulation in Materials Science and Engineering	0.007726	74.1
4	Journal of The Mechanics And Physics of Solids	0.02552	90.84
2	Physical Review Letters	1.2816	99.95
2	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99

Source: Eigenfactor.org, Journal names came from Web of Science

Table 125. Most Published-in Journals in the Post-NDPA Period, 2005-2010 (Phillips)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
9	Biophysical Journal	0.187695	99.28
4	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
3	Physical Review Letters	1.2816	99.95
2	Current Opinion in Genetics & Development	0.044997	95
2	Physical Review E	0.268875	99.55

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 11 of Phillips's 27 publications, 40.74%, were in journals at or above the 98th percentile (Table 126). In the post-NDPA period, 23 of his 33 publications, 69.70%, were published in journals of the same caliber. Eight of the 12 NDPA-attributed publications, 66.67%, had Eigenfactor values above the 98th percentile.

Table 126. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Phillips)

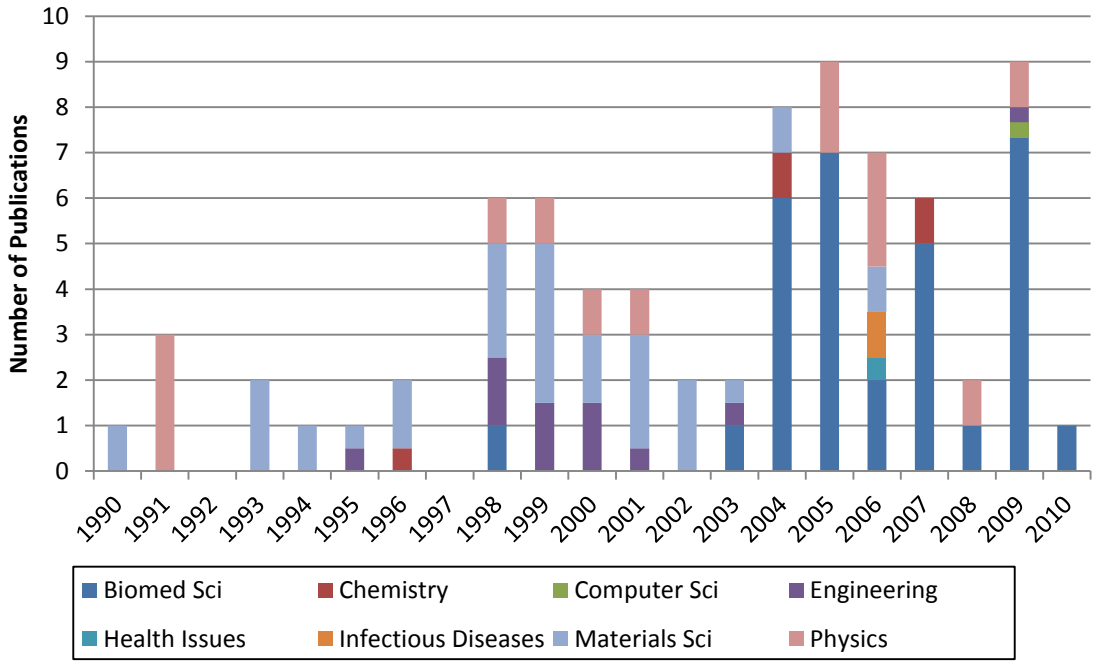
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (27 pubs)	11	40.74%
Post-NDPA (33 pubs)	23	69.70%
Attributed to NDPA Funding (12 pubs)	8	66.67%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data are from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Phillips's 76 publications over the duration of his career can be categorized into a total of eight different macro-disciplines. He published in five macro-disciplines in his 26 pre-NDPA publications and eight macro-disciplines in his 34 post-NDPA publications. The distribution of Phillips's publications into macro-disciplines for the full length of his career may be seen in Figure 55.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 55. Distribution of Publications into Macro-disciplines over Time (Phillips)

Phillips has had an eclectic publishing career. He began his career in the "hard sciences" with Physics, Materials Science, and Engineering. Shortly before receiving the NDPA, Phillips shifted his focus into Biomedical Science. From then on, he performed multidisciplinary work in both Physics and Biomedical Science, as corroborated by the nature of his NDPA proposal.

2) Body of Knowledge Cited

Phillips cited seventeen different macro-disciplines in the 2,544 cited references of his 76 career publications. This included twelve macro-disciplines in the 965 cited references of his 26 pre-NDPA publications and fifteen macro-disciplines in the 1,889 cited references of his 34 post-NDPA publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I scores is 0.572 and the mean S score is 0.486. The Integration and Specialization scores for Phillips are shown in the table in Table 127.

Table 127. Integration and Specialization Score (Phillips)

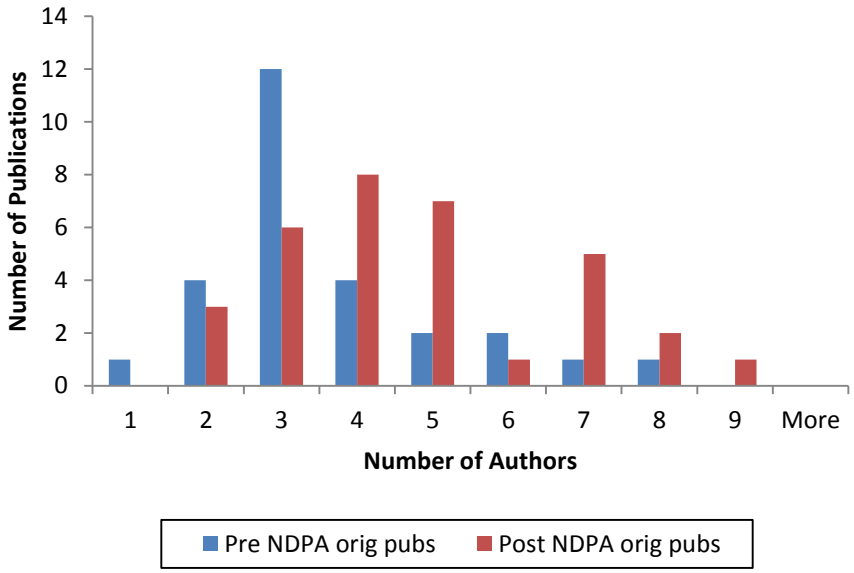
	Full Career (2544 cited references)	Pre-NDPA (607 cited references)	Post-NDPA (1424 cited references)
Integration	0.657	0.543	0.473
Specialization	0.377	0.546	0.435

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, Phillips appears to have altered his knowledge gathering and output practices over the course of his career. While he has been a "Renaissance Integrator" over the full course of his career, he was a "Disciplinarian" during the pre-NDPA period and a "Grazer" in the post-NDPA period. This volatility is likely due to his complete shift in research fields around the time he received the NDPA.

d. Collaboration

The median total number of authors in Phillips's publication set was four. In the pre-NDPA period the median was three, and in the post-NDPA period the median was four. A comparison of the pre- and post-NDPA distributions of the total number of authors can be seen in Figure 56.



Source: Web of Science

Figure 56. Distribution of Number of Authors in Original Publication Set (Phillips)

The number of unique authors in a researcher's publishing network is another metric that captures collaboration patterns. Phillips has published with approximately 91 researchers throughout his career. In the pre-NDPA period he published with 35 researchers, and in the post-NDPA period he published with 51 researchers. Over his 12 NDPA-attributed publications, Phillips published with 29 researchers.

O. Stephen Quake (2004)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers acknowledged that Quake's microfluidics technologies and physics and engineering approaches have great potential to solve biomedical problems. He was also relatively new to NIH. Quake was found to be "extremely talented and truly pioneering in technology development," and the reviewers expressed a hope that "a Pioneer Award would help anchor him in biology rather than have him drawn…to contemplate commercial applications of his technology."

3. Nature of Project Risks and Outcomes

The Pioneers and three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 128 and Table 129). Quake, however, was unable to be reached for an interview, so the following sections only incorporate opinions from the experts.

a. Typology of Project Risk

Table 128. Characterization of Unique Project Risk (Quake)

Please indicate which of the following risks are applicable to the NDPA-funded project	Expert 1	Expert 2	Expert 3
Conceptual Risk			
Technical Risk		x	x
Experience Risk	x	x	x
Multidisciplinary Risk	x		
None of these risks			

Source: Expert review

At least two of three experts agreed that Quake's NDPA proposal incorporated technical and experience risks. Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Quake's research:

> "Quake was certainly already an acknowledged expert in microfluidics, but was at the point of the award, continuing to expand his horizons in biology.

> Quake moved beyond the researcher's previous "engineering expertise of microfluidics."

Experts thought Quake moved beyond his expertise in engineering and physics into biology.

b. Typology of Potential Outcomes

Table 129. Characterization of Potential Pioneering Outcomes (Quake)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Expert 1	Expert 2	Expert 3
New Idea		x	x
New Phenomenon	x		
New Methodology	x		
New Technology		x	
New Framework			
None of these outcomes			

Source: Expert review

Two of three experts thought Quake's research could result in the formulation of a new idea. Below is a selection of comments from the experts that justify their evaluations of the potential pioneering outcomes of Quake's research:

> "Taking his already robust ideas about ways to automate biological experiments was primarily a method of accelerating an already-rapidly-growing process. The biological information derived from it could be transformational, but would have been achieved by others using other methods, perhaps at somewhat greater cost and a slower pace."

> Quake's research resulted in a new methodology for the assessment of "fetal health."

> Quake "[opened] up a new field—next [generation] sequencing."

Experts thought Quake automated biological experiments and applied his technologies to biomedical purposes, such as the assessment of fetal health.

c. Assessing Whether the Research Was Pioneering

In addition to characterizing the associated risks and identifying the potential outcomes of the research, experts were also asked to assess whether the accomplished work was pioneering. One expert strongly agreed, one moderately agree, and one moderately disagreed that Quake's accomplished research was pioneering. Below is a selection of comments from experts about why Quake's research was or was not pioneering:

> Quake "pioneered methodology" and displayed "amazing research capability as a bioengineer.

> "I would view a "pioneering" discovery to be something…that had no precedent, and which, once discovered, enabled discoveries in a wide range of fields. The development of a highly parallel microfluidic system is an enabler, but it is not pioneering, in my mind, because there was adequate prior precedent."
>
> "Quake is a true genius, and NIH did well to support this lab under this program. However, I think that the enabling technological work that Quake undertook to accomplish the biological goals had already been underway in his lab for some time."

Experts were mixed about whether Quake's NDPA-related research was pioneering because there was substantial precedent that prefaced Quake's discovery and the technological work in his lab had been underway for some time.

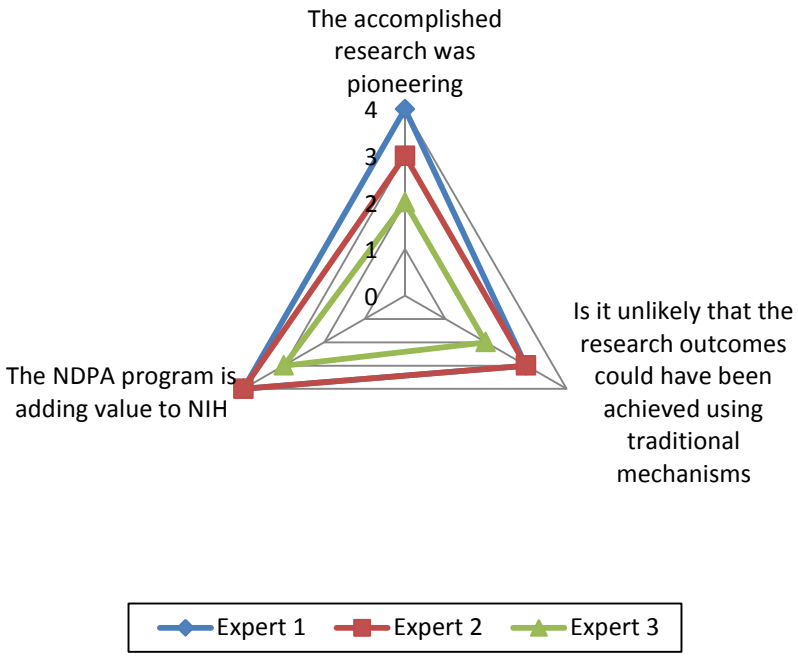
4. Value of the NDPA Program

a. Pioneer Perspective

STPI was unable to reach Quake for an interview.

b. Expert Perspective

Experts were asked to rate whether Quake's results were a unique output of the Pioneer Award, and whether the Pioneer Award is adding value to NIH (Figure 57).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 57. Experts' Opinions of the NDPA (Quake)

Two experts moderately agreed and one moderately disagreed that is unlikely that the research outcomes could have been achieved using traditional mechanisms. Two experts strongly agreed and one moderately agreed that the NDPA program is adding value to NIH. Below is a selection of comments from experts about the value of the NDPA program:

> "I agree strongly with the goals of the program—US researchers, the good ones, are, too often, slaves to the peer review process...Whether an individual genius will produce pioneering work on schedule, or use a windfall to further his existing agenda, depends on just how smart that genius is."
>
> "Like any venture investment, the risks are high, and so is the potential payoff. I say keep this going, even in hard times (and perhaps particularly in them)."
>
> "Someone as creative and productive as Quake should spend less time writing proposals and more time generating new knowledge. The NDPA allowed him to do that."

The experts had generally positive feelings about the value of the NDPA, saying that it frees up time for creative researchers. One expert, however, felt it was somewhat likely that the outcomes of Quake's proposal could have been achieved through traditional funding sources.

5. Descriptive Bibliometrics

Terms of comparison in these analyses include "pre-NDPA" and "post-NDPA." Since Quake received the Pioneer Award in 2004, the pre-NDPA range refers to activity between 1999 and 2004 while the post-NDPA range refers to activity between 2005 and 2010.

a. Productivity

Quake has published a total of 106 original articles over the 17 years of his research career for a rate of 6.24 articles per year (Table 130). In the pre-NDPA period, Quake published 48 original articles for a rate of 8 per year. In the post-NDPA period, he published 52 articles for a rate of 8.67 per year.

Table 130. Summary of Publication Activity (Quake)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	48	52	13	106
Number of Years	6	6	N/A	17
Publication Rate	8	8.666667	N/A	6.235294

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Quake published slightly more in the post-NDPA period. Of the 52 post-NDPA articles he published, 13 of them were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 131.

Table 131. Publications Attributed to NDPA Funding (Quake)

Title	Journal	Year Published
An in vitro microfluidic approach to generating protein-interaction networks	Nature Methods	2009
Automated microfluidic chromatin immunoprecipitation from 2,000 cells	Lab on a Chip	2009
Digital PCR provides sensitive and absolute calibration for high throughput sequencing	BMC Genomics	2009
Discovery of a hepatitis C target and its pharmacological inhibitors by microfluidic affinity analysis	Nature Biotechnology	2008
Experimental determination of the evolvability of a transcription factor	Proceedings of the National Academy of Sciences of the United States of America	2009
High-Throughput Sequencing of the Zebrafish Antibody Repertoire	Science	2009
Highly parallel measurements of interaction kinetic constants with a microfabricated optomechanical device	Applied Physics Letters	2009
Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood	Proceedings of the National Academy of Sciences of the United States of America	2008
Ostwald Ripening of Clusters during Protein Crystallization	Physical Review Letters	2010
Sensitivity of Noninvasive Prenatal Detection of Fetal Aneuploidy from Maternal Plasma Using Shotgun Sequencing Is Limited Only by Counting Statistics	PLOS One	2010
Single-molecule sequencing of an individual human genome	Nature Biotechnology	2009

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, Quake's 100 articles excluding reviews had been cited a total of 7,078 times. The statistics on Quake's publication sets are shown in Table 132.

Table 132. Summary of Citation Analyses (Quake)

Time Period	Number of Citations	Age-weighted citation rate (AWCR)	H-index
Full Career (100 pubs)	7,078	30.59	41
Pre-NDPA (45 pubs)	5,115	23.37	N/A
Post-NDPA (48 pubs)	1,415	18.85	N/A
Attributed to NDPA Funding (13 pubs)	265	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Quake published 48 publications in twenty-one different sources in the pre-NDPA time period and 51 publications in thirty-two different sources in the post-NDPA time period. Detailed data on Quake's most published-in journal for the pre- and post-NDPA time periods respectively are shown in Table 133 and Table 134.

Table 133. Most Published-in Journals in the Pre-NDPA Period, 1999-2004 (Quake)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
7	Physical Review Letters	1.2816	99.95
6	Abstracts of Papers of The American Chemical Society	N/A	N/A
5	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
4	Science	1.58309	99.98
3	Genome Research	0.125339	98.66
3	Nature Biotechnology	0.147052	98.94

Source: Eigenfactor.org, Journal names came from Web of Science

Table 134. Most Published-in Journals in the Post-NDPA Period, 2005-2010 (Quake)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
6	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
6	Science	1.58309	99.98
3	Analytical Chemistry	0.198505	99.31
3	Biophysical Journal	0.187695	99.28
3	Lab on a Chip	0.032581	92.76

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 34 of Quake's 48 publications, 70.83%, were in journals at or above the 98th percentile (Table 135). In the post-NDPA period, 32 of 52 publications, 62.75%, were in journals of the same caliber.

Table 135. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Quake)

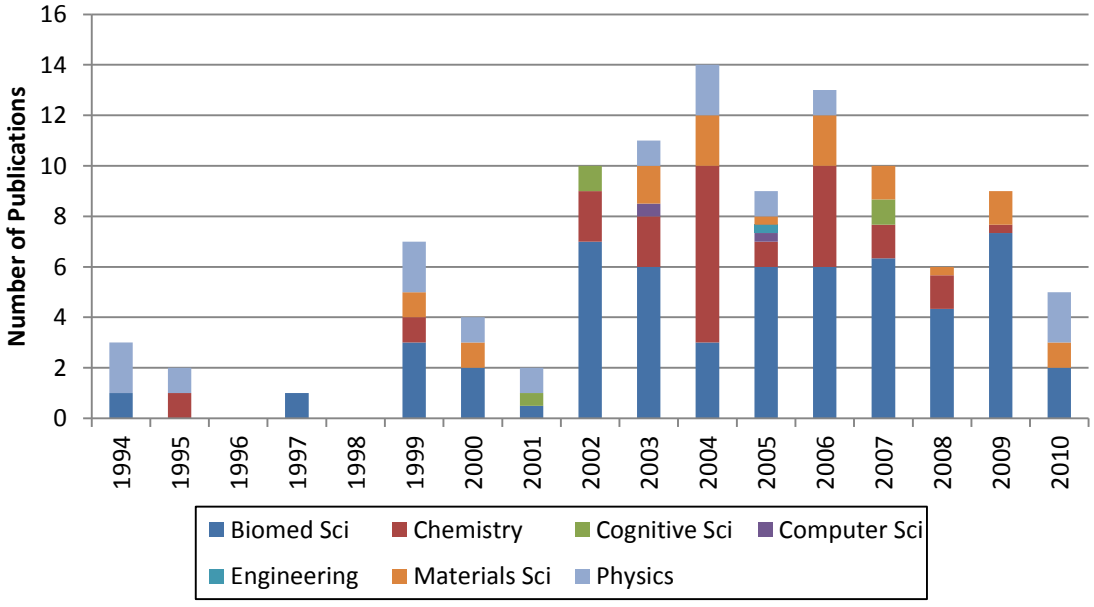
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (48 pubs)	34	70.83%
Post-NDPA (52 pubs)	32	62.75%
Attributed to NDPA Funding (13 pubs)	7	53.85%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data are from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Quake's 106 publications over the duration of his career can be categorized into a total of seven macro-disciplines. He published in six disparate macro-disciplines over his 48 pre-NDPA publications and seven disparate macro-disciplines over his 52 post-NDPA publications. The distribution of Quake's publications into macro-disciplines over the full length of his career is shown in Figure 58.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 58. Distribution of Publications into Macro-disciplines over Time (Quake)

Quake has published eclectically throughout his career but the majority of his publications fall into Biomedical Science and Chemistry. Despite his professed specialty in applied physics and engineering, particularly before the NDPA, the technologies he

developed seem to have biomedical applications; consequently, many of his publications were in Biomedical Science before he increased his focus in biology when he moved to Stanford.

2) Body of Knowledge Cited

Quake cited seventeen different macro-disciplines in the 2,968 references of his 106 career publications. This included fourteen macro-disciplines in the 965 references of his 48 pre-NDPA publications and sixteen macro-disciplines in the 1,889 references of his 52 post-NDPA publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The Integration and Specialization scores for Quake are shown in the table in Table 136.

Table 136. Integration and Specialization Scores (Quake)

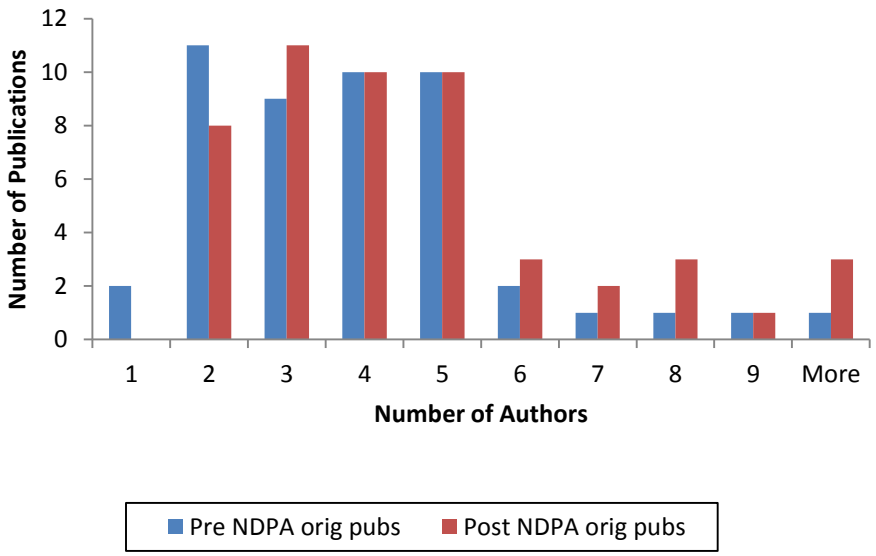
	Full Career (2968 cited references)	Pre-NDPA (965 cited references)	Post-NDPA (1889 cited references)
Integration	0.673	0.636	0.677
Specialization	0.385	0.377	0.412

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, Quake is a "Renaissance Integrator," a researcher who integrates information from many fields and consequently produces very interdisciplinary work. Given his background in microfluidics and his application of the technology to biomedicine, this interdisciplinarity seems accurate.

d. Collaboration

The median number of total authors in Quake's publication set was four for his full career, pre-NDPA time period, and post-NDPA time period. A comparison of the pre- and post-NDPA distributions of the total number of authors can be seen in Figure 59.



Source: Web of Science

Figure 59. Distribution of Number of Authors in Original Publication Set (Quake)

The number of unique authors in a researcher's publishing network is another metric that captures co-authorship patterns. Quake has published with approximately 210 unique individuals throughout his full career. In the pre-NDPA period, he collaborated with 72 authors, and in the post-NDPA period he collaborated with 152 authors. Over his 13 NDPA-attributed publications, he published with 35 authors.

P. Thomas Rando (2005)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers was impressed with Rando's approach to studying the environment of stem cells in the context of muscle cell injury response in aging animals. They believed that his work had potential for a high-impact breakthrough, but they were concerned about the suitability of his project for the NDPA. Ultimately, however, the panel felt that "alternative funding mechanisms are not likely to be successful."

3. Nature of Project Risks and Outcomes

The Pioneers and three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 137 and Table 138).

a. Typology of Project Risks

Table 137. Characterization of Unique Project Risk (Rando)

Please indicate which of the following risks are applicable to the NDPA-funded project	Rando	Expert 1	Expert 2	Expert 3
Conceptual Risk	x	x		x
Technical Risk				
Experience Risk	x			
Multidisciplinary Risk	x		x	x
None of these risks				

Source: Pioneer interview, Expert review

At least two of three experts agreed that Rando's NDPA proposal incorporated conceptual and multidisciplinary risks. Rando himself thought his proposal included conceptual, experience, and multidisciplinary risks.

In his interview, Rando stated that his proposal attempted to "understand aging in terms of…a reversible process" as opposed to "wear and tear," which was a controversial idea. As his research progressed, his lab needed to learn about epigenetics, a field he had neither worked on nor trained in.

Below is a selection of comments from experts that justify their evaluations of the pioneering risks of Rando's research:

> "The work of Dr. Rando utilized a previously developed, although not fully exploited, technique called parabiosis to address the question of

whether aging-related changes in circulating systemic factors were responsible for the changes in muscle stem cell behavior with age."

Rando "needed a broad perspective and view across area of research including stem cells, molecular and developmental biology, general gerontology, muscle physiology etc."

Rando's work studied whether "stem cells (are) involved in aging or is their dysfunction a consequence…most in the field would argue stem cell dysfunction is a consequence. (The) investigator questioned this view."

The experts believe Rando's proposal challenged existing perceptions on why aging occurs and brought multiple areas of research together to perform his study.

b. Typology of Potential Outcomes

Table 138. Characterization of Potential Pioneering Outcomes (Rando)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Rando	Expert 1	Expert 2	Expert 3
New Idea	x		x	x
New Phenomenon	x		x	x
New Methodology				x
New Technology				
New Framework	x			
None of these outcomes		x		

Source: Pioneer interview, Expert review

At least two of three experts agree that Rando's NDPA research could result in the formulation of a new idea and the discovery of a new phenomenon. Rando himself stated his research had the potential to result in the formulation of a new idea, the discovery a new phenomenon, and the synthesis of a new framework.

Rando indicated that he observed the reversibility of stem cell aging through his Pioneer-funded proposal, a phenomenon that has significant implications for regenerative medicine.

Below is a selection of comments from the experts that justify their evaluations of the potential pioneering outcomes of Rando's research:

"Rando's work has solidifed the notion that changes in systemic factors is a significant contributor to aging-related changes in stem cell behavior."

"His demonstration that the immortal strand hypothesis may be true for muscle stem cells was in direct conflict with recent data obtained for the hematopoietic system, and therefore, presented the stem cell community

with the possibility that different stem cells may have different mechanisms for preserving genomic integrity."

"The fundamental observation that was influential was already in press or published at the time of the award. In any case, I would not consider this observation (impact of the environment on stem cells) a fundamental advance. It contributed to an important shift in thinking, but these ideas were also coming from other directions as well."

While the experts agree that Rando made significant advances in the theory of the role of stem cells and the aging process, one expert thought that Rando's major discovery occurred before he received the Pioneer Award.

c. Assessing Whether the Research Was Pioneering

In addition to characterizing the associated risks and identifying the potential outcomes of the research, experts were also asked to assess whether the accomplished work was pioneering. Two experts strongly agreed and one moderately agreed that Rando's accomplished research was pioneering. Below is a selection of comments from experts about why Rando's research was or was not pioneering.

"I think Rando's work has been important and extremely well done. But has it broken fundamentally new ground? To a limited degree only, in my opinion."

"Rando's groundbreaking work set the scene for other stem cell researchers to begin characterizing the systemic, local, and cell autonomous changes that occur within a given stem cell system with age…Rando's work has continued to establish paradigms in the new field of stem cell aging."

All three experts believed that Rando's work was pioneering to an extent. One expert, however, determined that while his research was good science, the expert did not believe it had broken "fundamentally new" ground.

4. Value of the NDPA Program

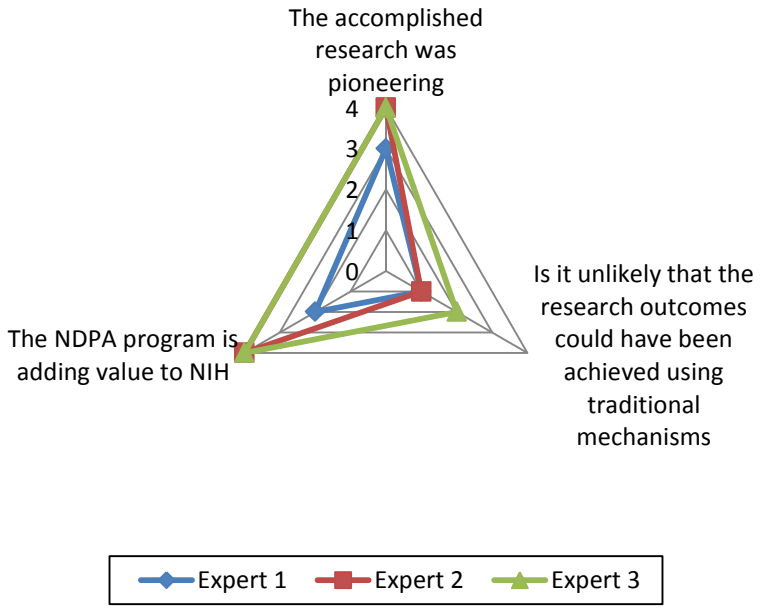
a. Pioneer Perspective

Rando explained in his interview that the NDPA allowed him to perform "a lot of screening projects" that are not normally funded at study sections because they are open-ended and unfocused. He underlined the importance of these types of experiments, saying that "carefully conceived unbiased screens…give you data for generating hypotheses." He also explained that he used the NDPA funds to perform "descriptive work," which is viewed pejoratively by reviewers. Rando believed the NDPA allowed his lab to "pursue lines of inquiries" with enhanced flexibility, and the money gave him the luxury of time. He was able to expand his lab, set a foundation, and focus on doing experiments that

were important rather than those which would allow you to publish frequently. If he had not gotten the NDPA funding, his lab would have attempted to pursue the project, but Rando is not certain they would have gotten very far.

b. Expert Perspective

Experts were asked to rate whether Rando's results were a unique output of the Pioneer Award, and whether the Pioneer Award is adding value to NIH (Figure 60).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 60. Experts' Opinions of the NDPA (Rando)

One expert moderately disagreed and two strongly disagreed that it is unlikely that the research outcomes could have been achieved using traditional mechanisms. Two experts strongly agreed and one moderately disagreed that the NDPA program is adding value to NIH.

Below is a selection of comments from experts about the value of the NDPA program:

> "Even though some of the research could have been accomplished using traditional NIH funding mechanisms overall it seems that given the controversial area…that funding would have been difficult to obtain."

> "These investigators have had the luxury to worry a little less about the next RO1 and oversee their high quality research more closely. This results in a greater frequency of high quality publications, the type of which would likely be published anyway (but less quickly). This increase in quality research adds value to the portfolio. But it does not add the KIND of value

that I believe the NDPA program set out to add—truly ground breaking research with novel ideas that are highly influential."

"To identify truly ground-breaking ideas and work, the review process probably needs to be as unconventional and creative as the people/ideas that you are seeking. A new approach should be considered to continue this otherwise very worthy goal."

The experts had mixed opinions about the value of the NDPA program. All three believed that Rando likely could have been funded by traditional mechanisms, and one expert did not think the NDPA had funded groundbreaking research as was originally intended.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Rando received the NDPA in 2005, the pre-NDPA range refers to activity between 2001 and 2005 while the post-NDPA range refers to activity between 2006 and 2010.

a. Productivity

Rando has published a total of 93 original articles over the 26 years of his research career for a rate of 3.58 publications per year (Table 139). In the pre-NDPA period, Rando published 41 publications for a rate of 8.2 per year. In the post-NDPA period, he published 19 publications for a rate of 3.8 per year.

Table 139. Summary of Publication Activity (Rando)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	41	19	3	93
Number of Years	5	5	N/A	26
Publication Rate	8.2	3.8	N/A	3.576923

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Rando published considerably more publications in the pre-NDPA time period than in the post-NDPA time period. In his interview, Rando indicated that the Pioneer Award gave him the sense that he had several years to take his time and do important research rather than focus on publishing. Rando also indicated that much of his NDPA-related

research is still being developed, and that it may be a couple more years before those results are published.

Of the 19 publications Rando published in the period after receiving the award, three were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 140.

Table 140. Publications Attributed to NDPA Funding (Rando)

Title	Journal	Year Published
BCL9 is an essential component of canonical Wnt signaling that mediates the differentiation of myogenic progenitors during muscle regeneration	Developmental Biology	2009
Focal Adhesion Kinase Signaling Regulates the Expression of Caveolin 3 and beta 1 Integrin, Genes Essential for Normal Myoblast Fusion	Molecular Biology of the Cell	2009
Preventing oxidative stress: a new role for XBP1	Cell Death And Differentiation	2009

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, Rando's 84 original publications excluding reviews had been cited a total of 3,434 times. In the post-NDPA period, Rando published 16 publications that had received a total of 546 citations by August 2010. The two NDPA-attributed publications had received 10 citations by that time.

Total number of citations and age-weighted citation rate do not show surprising results. It is expected that the number of citations and age-weighted citation rate would be lower in the post-NDPA period.

The statistics on this publication set are displayed in Table 141.

Table 141. Summary of Citation Analyses (Rando)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (84 pubs)	3,434	20.52	30
Pre-NDPA (37 pubs)	1,385	13.54	N/A
Post-NDPA (16 pubs)	546	11.69	N/A
Attributed to NDPA Funding (3 pubs)	18	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Rando published 41 publications in twenty-three different sources in the pre-NDPA time period and 19 publications in seventeen different sources in the post-NDPA time period. Detailed data on Rando's most published-in journals for the pre- and post-NDPA time periods, show in Table 142 and Table 143, respectively.

Table 142. Most Published-in Journals in the Pre-NDPA Period, 2001-2005 (Rando)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
10	Molecular Biology of The Cell	0.16188	99.11
4	Neuromuscular Disorders	0.00997	78.6
3	Journal of Cell Science	0.179164	99.21
3	Muscle & Nerve	0.018851	87.72
2	Human Molecular Genetics	0.134882	98.81
2	Molecular Therapy	0.042602	94.66

Source: Eigenfactor.org, Journal names came from Web of Science

Table 143. Most Published-in Journals in the Post-NDPA Period, 2006-2010 (Rando)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
2	Cell	0.671695	99.89
2	Developmental Biology	0.125557	98.68
1	Aging Cell	0.016721	86.44
1	Biochimica Et Biophysica Acta-Molecular Basis of Disease	0.016463	86.27
1	Cell Death And Differentiation	0.06284	96.84
1	Cell Stem Cell	N/A	N/A
1	Experimental Cell Research	0.066382	97.1
1	FASEB Journal	0.129982	98.74
1	Human Gene Therapy	0.01756	86.9
1	Molecular Biology of The Cell	0.16188	99.11
1	Nature	1.76345	100
1	Nature Clinical Practice Neurology	0.005697	67.61
1	Nucleic Acids Research	0.371094	99.76
1	PLOS Biology	0.154645	99.05
1	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
1	Science	1.58309	99.98
1	Stem Cell Reviews	0.00293	50.64

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 21 of Rando's 41 publications, 51.22%, were in journals at or above the 98th percentile (Table 144). In the post-NDPA period, 11 of Rando's 19 publications were in journals of the same caliber. Both of Rando's NDPA-attributed publications had *Eigenfactor* values above the 98th percentile.

Table 144. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Rando)

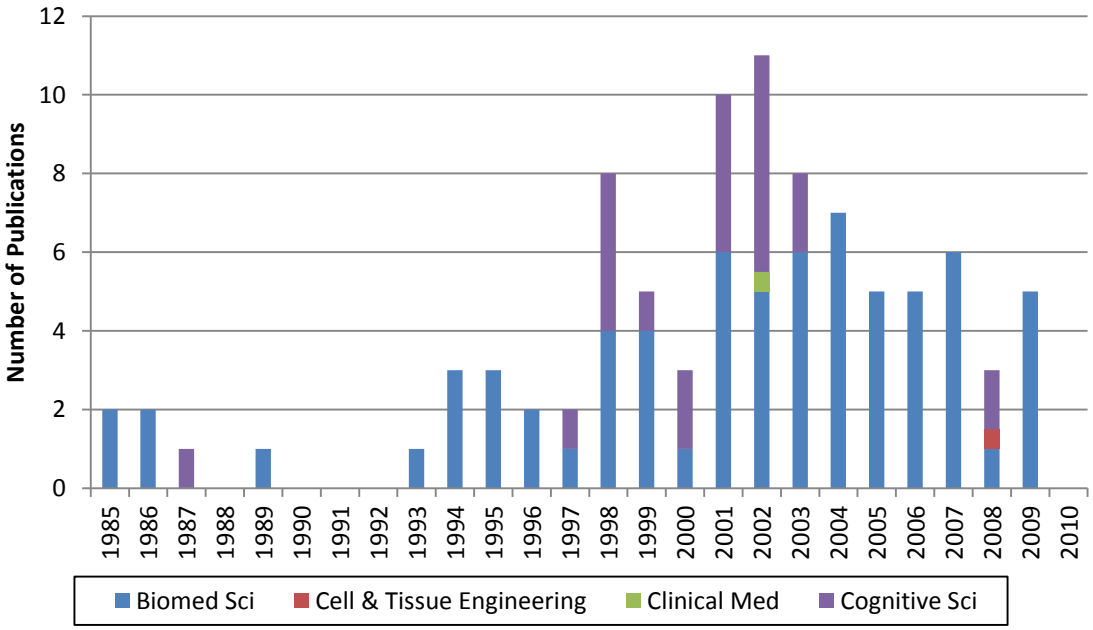
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (41 pubs)	21	51.22%
Post-NDPA (19 pubs)	11	57.89%
Attributed to NDPA Funding (3 pubs)	2	66.67%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data are from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Rando's 93 publications over the duration of his career can be categorized into a total of four different macro-disciplines. He published in three macro-disciplines in the pre-NDPA period with 41 publications as well as in the post-NDPA period with 19 publications. The distribution of Rando's publications into macro-disciplines for the full length of his career may be seen in Figure 61.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 61. Distribution of Publications into Macro-disciplines over Time (Rando)

Rando has published primarily in the Biomedical Science for the duration of his career with his work on stem cells.

2) Body of Knowledge Cited

Rando cited thirteen different macro-disciplines in the 3,506 references of his 93 career publications. This included eleven macro-disciplines in the 1,384 references of his 41 pre-NDPA publications and eleven macro-disciplines in the 1,044 references of his 19 post-NDPA publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The Integration and Specialization scores for Rando are shown in the table in Table 145.

Table 145. Integration and Specialization Scores (Rando)

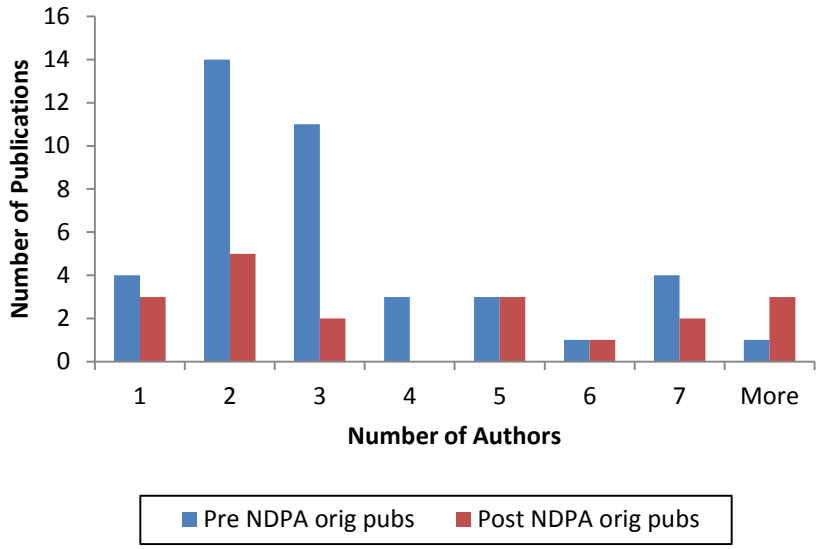
	Full Career (3506 cited references)	Pre-NDPA (1384 cited references)	Post-NDPA (1044 cited references)
Integration	0.423	0.394	0.394
Specialization	0.619	0.560	0.769

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, Rando is a strict "Disciplinarian" for the three time periods measured.

d. Collaboration

The median number of total authors in Rando's publication set was three over his full career, pre-NDPA period, and post-NDPA period. A comparison of the pre- and post-NDPA distributions of the total number of authors can be seen in Figure 62.



Source: Web of Science

Figure 62. Distribution of Number of Authors in Original Publication Set (Rando)

The number of unique authors in a researcher's publishing network is another metric that captures co-authorship patterns. Rando has published with approximately 117 researchers throughout his full career. In the pre-NDPA period, he published with 41 researchers. In the post-NDPA period, Rando published with 55 researchers despite having published significantly fewer papers. Over the three NDPA-attributed publications, Rando collaborated with 18 other individuals.

Q. Derek Smith (2005)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers noted Smith's previous accomplishments in developing a mathematical tool for influenza vaccine development. His eventual goal was to be able to "predict strain evolution." There was some concern about the lack of detail and the fact that the project was similar to his previous work, but the panel was impressed with the potential impact his research could have worldwide on human health.

3. Nature of Project Risks and Outcomes

The Pioneers and three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 146 and Table 147).

a. Typology of Project Risks

Table 146. Characterization of Unique Project Risk (Smith)

Please indicate which of the following risks are applicable to the NDPA-funded project	Smith	Expert 1	Expert 2	Expert 3
Conceptual Risk	x			
Technical Risk	x			
Experience Risk	x			
Multidisciplinary Risk	x		x	x
None of these risks		x		

Source: Pioneer interview, Expert review

At least two of three experts agreed that Smith's NDPA proposal incorporated multidisciplinary risk. Smith himself believed that his proposal included conceptual, technical, experience, and multidisciplinary risk.

In his interview, Smith said that his lab had to overcome five to ten "very tough technical issues" for his antigenic cartography technique. His projects in general have incorporated fields beyond his previous expertise in computer scientist. He explained that many people think he is a virologist or immunologist. His projects incorporate all of these ideas.

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Smith's research:

> "This NDPA application involved a unique combination of antigenic mapping (cartography), molecular phylogenetics, and fitness measures. Dr. Smith is only doing this sort of research, and he has provided fundamental new insights into the basic biology of influenza virus."
>
> "The contributions of this candidate have been to apply a technique that displays data from antigenic analyses. I suspect the idea is to provide a pictorial representation of the data which might be more readily understandable than the raw data…[For] the scientists…with whom the candidate collaborates, I doubt if it is relevant…I therefore consider the candidate's contributions…to be minimal."

The experts were mixed about the risks of Smith's research. Two experts thought he did great work combining information from different fields, but one expert thought the impact of his pictorial representations to have minimal relevance to scientists in his field.

b. Typology of Potential Outcomes

Table 147. Characterization of Potential Pioneering Outcomes (Smith)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Smith	Expert 1	Expert 2	Expert 3
New Idea	x		x	x
New Phenomenon	x		x	x
New Methodology	x		x	
New Technology	x			
New Framework	x		x	
None of these outcomes		x		

Source: Pioneer interview, Expert review

At least two of three experts agreed that Smith's research had the potential to result in the formulation of a new idea and the discovery of a new phenomenon. Smith himself

believed his research had the potential to result in the formulation of a new idea, the discovery of a new empirical phenomenon, the development of a new methodology, the invention of new technology, and the synthesis of a new framework.

Smith noted that cartography allowed him to quantify selection pressures on the virus based on immunity in the population, an observation that has changed the way epidemiological data is framed. His work has also provided new methodologies for measuring selection pressure, viral growth rates, and viral fitness. Furthermore, the antigenic, genetic, epidemiological, immunological, and virological data that his lab has gathered has been united into a "common cognitive framework."

Below is a selection of comments from the experts that justify their evaluations of the potential pioneering outcomes of Smith's research.

> "The research undertaken under this NDPA application produced (i) a new theory of the global spread of seasonal influenza virus…and (ii) new data on the antigenic diversity present in the H1N1/09 ('swine flu') virus. Both of these findings are central to improving influenza vaccines."
>
> "It may be that in studies of some infectious diseases other than influenza, the data handling procedures that the candidate prefers could be of use."

The experts thought his technology may have applications on other diseases. The use of cartography has also yielded new theories about the way seasonal influenza spreads throughout the world.

c. Assessing Whether the Research Was Pioneering

In addition to characterizing the associated risks and identifying the potential outcomes of the research, experts were also asked to assess whether the accomplished work was pioneering. One expert strongly agreed, one moderately agreed, and one moderately disagreed that Smith's accomplished research was pioneering. Below is a selection of comments from experts about why Smith's research was or was not pioneering:

> "It is now clear that this research program can be extended to a variety of other pathogens…he is the only person who has attempted to marry antigenic and phylogenetic data. This is clearly pioneering."
>
> "For research to be pioneering it would for me, have to have more value than the candidate has contributed."

Two experts believed the wide applicability and multidisciplinarity of Smith's work made him a pioneer. One expert did not think his research was having enough impact to be considered "pioneering."

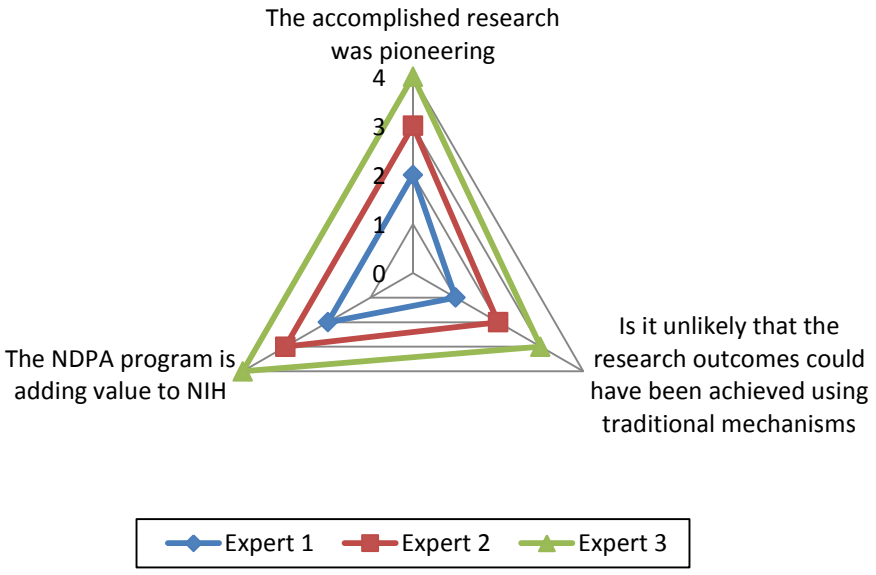
4. Value of the NDPA Program

a. Pioneer Perspective

Smith stressed the role of the NDPA in providing flexible funding to researchers. He was able to further establish his lab and accelerate the pace of his research with the funds. In this vein, he hired an administrator so that he could think more about scientific problems. He added that the Pioneer Award allowed his lab to prime its research to produce more high-impact results in the future. The award was also instrumental in his career advancement; he transitioned from a post-doctoral position to a full professorship. If he had not received the Pioneer Award, Smith would have tried to pursue the project at a smaller and more manageable scale.

b. Expert Perspective

Experts were asked to rate whether Smith's results were a unique output of the Pioneer Award and whether the Pioneer Award is adding value to NIH (Figure 63).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 63. Experts' Opinions of the NDPA (Smith)

One expert moderately agreed, one moderately disagreed, and one strongly disagreed that it is unlikely that the research outcomes could have been achieved using traditional mechanisms. One expert strongly agreed, one moderately agreed, and one moderately disagreed that the NDPA is adding value to NIH. Below is a selection of comments from experts about the value of the NDPA program:

"The NDPA allows more innovative ideas to be pursued than under the standard NIH grant awarding program, where large amounts of preliminary data are often required. The NDPA seems to allow high-risk research themes to be pursued, which is an essential aspect of scientific creativity."

"Smith's work seems pretty good but I'm not positive that it couldn't be done without the Pioneer or the effect of the other projects."

The experts were mixed about the value of the NDPA program. The one expert who did not believe the NDPA was adding value to NIH was only commenting on the NDPA in the context of his or her opinions of Smith's research, which they did not find pioneering.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Smith received the NDPA in 2005, the pre-NDPA range refers to activity between 2001 and 2005 while the post-NDPA range refers to activity between 2006 and 2010.

a. Productivity

Smith has published a total of 21 original articles over the 14 years of his research career for a rate of 1.5 publications per year (Table 148). In the pre-NDPA period, he published 6 articles for a rate of 1.2 per year. In the post-NDPA period, he published 12 articles for a rate of 2.4 per year.

Table 148. Summary of Publication Activity (Smith)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	6	12	8	21
Number of Years	5	5	N/A	14
Publication Rate	1.2	2.4	N/A	1.5

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Smith published more articles in the post-NDPA period than in the pre-NDPA period. Compared to most of the other awardees, Smith has not published very often over

the course of his career. He explained in his interview that he prefers to focus on publishing potentially transformative work rather than publishing in great quantity. Furthermore, since his research translates readily to public health and animal health applications, Smith does not find publishing to be as essential as other researchers might.

Of the 12 articles Smith published in the period after receiving the award, eight were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 149.

Table 149. Publications Attributed to NDPA Funding (Smith)

Title	Journal	Year Published
Antigenic and Genetic Characteristics of Swine-Origin 2009 A(H1N1) Influenza Viruses Circulating in Humans	Science	2009
Antigenic and genetic evolution of swine influenza A (H3N2) viruses in Europe	Journal of Virology	2007
Evaluation of serological trials submitted for annual re-licensure of influenza vaccines to regulatory authorities between 1992 and 2002	Vaccine	2009
Influenza vaccine strain selection and recent studies on the global migration of seasonal influenza viruses	Vaccine	2008
Quantifying the Impact of Immune Escape on Transmission Dynamics of Influenza	Science	2009
Reemergence of Enterovirus 71 in 2008 in Taiwan: Dynamics of Genetic and Antigenic Evolution from 1998 to 2008	Journal of Clinical Microbiology	2009
The global circulation of seasonal influenza A (H3N2) viruses	Science	2008
Use of Antigenic Cartography in Vaccine Seed Strain Selection	Avian Diseases	2010

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, Smith's 20 original publications excluding reviews had been cited a total of 1,235 times. In the post-NDPA period, Smith published 12 publications which had received 389 citations by August 2010. His five publications attributed to NDPA funding had received 238 citations by that time.

Smith's post-NDPA publication set has a higher age-weighted citation rate than the pre-NDPA publication set. In terms of citations, his collective publications after receiving the award have had a greater impact on the scientific community.

The statistics on this publication set are shown in Table 150.

Table 150. Summary of Citation Analyses (Smith)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (20 pubs)	1,235	16.95	13
Pre-NDPA (6 pubs)	749	10.80	N/A
Post-NDPA (12 pubs)	389	12.85	N/A
Attributed to NDPA Funding (8 pubs)	371	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Smith published six publications in six different sources in the pre-NDPA period and 12 publications in seven different sources in the post-NDPA period. Detailed data on Smith's most published-in journals for the pre- and post-NDPA time periods are shown in Table 151 and Table 152, respectively.

Table 151. Most Published-in Journals in the Pre-NDPA Period, 2001-2005 (Smith)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
1	JAMA-Journal of The American Medical Association	0.380982	99.77
1	Journal of General Virology	0.046143	95.24
1	Journal of Immunology	0.475344	99.83
1	Journal of Virology	0.250077	99.48
1	Science	1.58309	99.98
1	Vaccine	0.069251	97.36

Source: Eigenfactor.org, Journal names came from Web of Science

Table 152. Most Published-in Journals in the Post-NDPA Period, 2006-2010 (Smith)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
4	Vaccine	0.069251	97.36
3	Science	1.58309	99.98
1	Avian Diseases	0.006836	71.64
1	Influenza And Other Respiratory Viruses	N/A	N/A
1	Journal of Clinical Microbiology	0.121537	98.6
1	Journal of Virology	0.250077	99.48
1	Virus Research	0.018739	87.67

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, four of Smith's six publications, 66.67% were in journals at or above the 98th percentiles (Table 153). In the post-NDPA period, five of 12 publications, 41.67%, were in journals of the same caliber. All five of Smith's NDPA-attributed publications were also in journals with *Eigenfactor* values above the 98th percentile.

Table 153. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Smith)

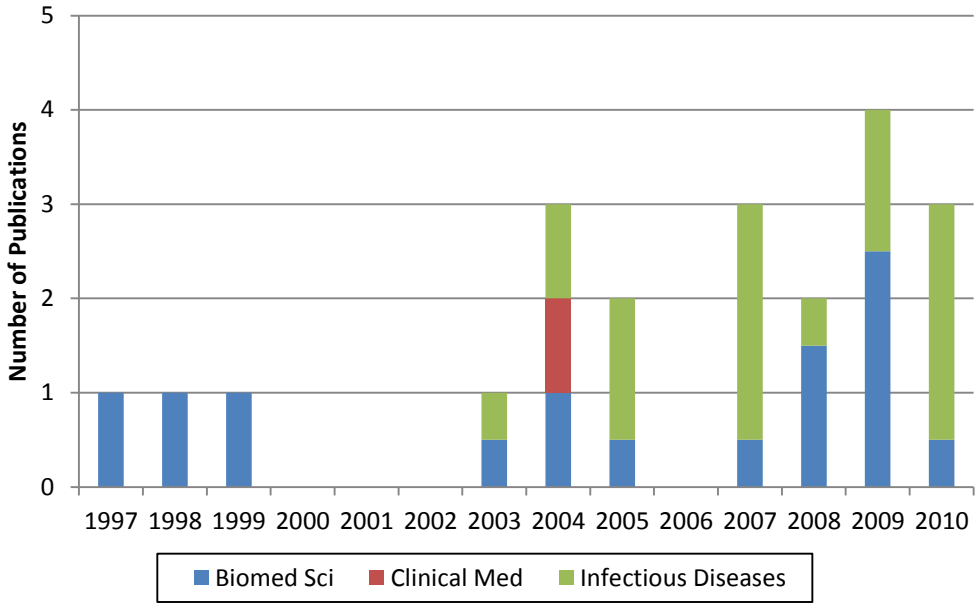
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (6 pubs)	4	66.67%
Post-NDPA (12 pubs)	5	41.67%
Attributed to NDPA Funding (8 pubs)	5	62.50%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data are from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Smith's 21 publications over the duration of his career can be categorized into a total of three different macro-disciplines. He published in three macro-disciplines over his six pre-NDPA publications. He published in two macro-disciplines in the post-NDPA period with twelve publications. The distribution of Smith's publications into macro-disciplines for the full length of his career may be seen in Figure 64.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 64. Distribution of Publications into Macro-disciplines over Time (Smith)

Smith's publications have been evenly split between Biomedical Science and Infectious Diseases with his work in influenza tracking and other public health issues.

2) Body of Knowledge Cited

Smith cited fourteen macro-disciplines in the 634 cited references of his 21 career publications. This included thirteen macro-disciplines in both the 210 cited references of his six pre-NDPA publications and 332 cited references of his twelve post-NDPA publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I scores is 0.572 and the mean S score is 0.486. The Integration and Specialization scores for Smith are shown in the table in Table 154.

Table 154. Integration and Specialization Scores (Smith)

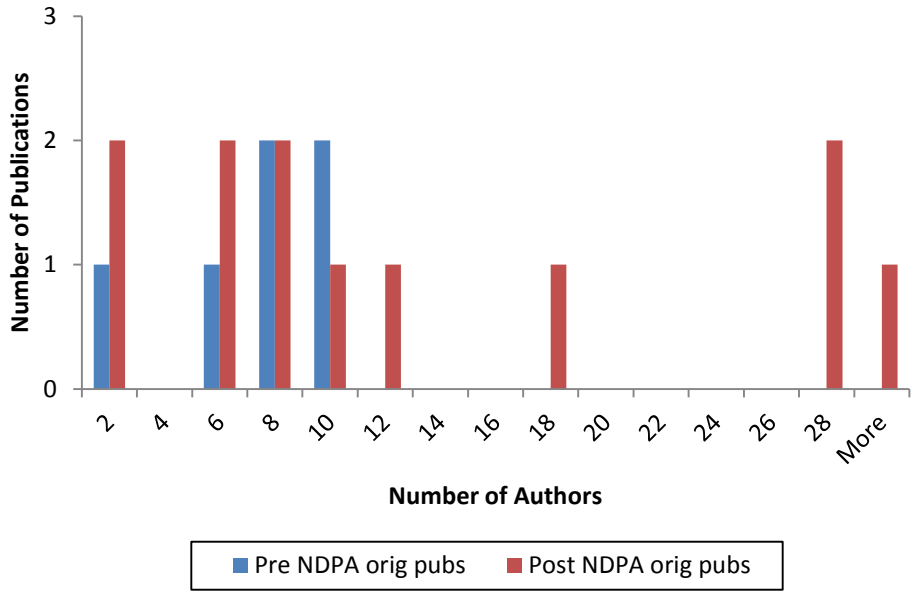
	Full Career (634 cited references)	Pre-NDPA (210 cited references)	Post-NDPA (332 cited references)
Integration	0.619	0.635	0.587
Specialization	0.602	0.595	0.661

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, Smith is a "Single Interdiscipline Specialist," a researcher who integrates many fields into a specialized research area output.

d. Collaboration

The median number of total authors in Smith's publication set was seven. In the pre-NDPA period, this median was seven. In the post-NDPA period, the median was nine. A comparison of the pre- and post-NDPA distributions of the total number of authors can be seen in Figure 65.



Source: Web of Science

Figure 65. Distribution of Number of Authors in Original Publication Set (Smith)

The number of unique authors in a researcher's publishing network is another metric that captures co-authorship patterns. Smith has published with 135 unique individuals throughout his full career. In the pre-NDPA period, he published with 24 individuals, and in the post-NDPA period, he published with 119 researchers. Over his eight NDPA-attributed publications, Smith published with 102 researchers. Smith published with a much wider range of individuals after receiving the award. Perhaps his wider collaboration network contributed to his higher citation rate in the post-NDPA period.

R. Giulio Tononi (2005)

1. Research Summary

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 M.D. in 1985, and a Ph.D. 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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers was impressed with the quality and importance of Tononi's research on the function of sleep. They were concerned however, that he may not be an appropriate candidate for the NDPA because his approaches are supported by preliminary data from his and other labs.

3. Nature of Project Risks and Outcomes

The Pioneers and three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 155 and Table 156).

a. Typology of Project Risks

Table 155. Characterization of Unique Project Risk (Tononi)

Please indicate which of the following risks are applicable to the NDPA-funded project	Tononi	Expert 1	Expert 2	Expert 3
Conceptual Risk	x	x	x	
Technical Risk	x	x	x	x
Experience Risk	x	x		x
Multidisciplinary Risk	x	x	x	x
None of these risks				

Source: Pioneer interview, Expert review

At least two of three experts thought Tononi's NDPA proposal incorporated conceptual, technical, experience, and multidisciplinary risks. Tononi agreed with this assessment of his proposal risks.

Tononi discussed the nature of his risks in his interview. He hypothesized that sleep restores the plasticity of the brain during the wake state, an idea that contradicted the

prevailing ideas of the neuroscience and sleep fields. He also began using techniques he had never used before such as in vivo microscopy. In general, his lab combines multiple fields of study, from biology to computer modeling to human work.

Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Tononi's work:

> "This has required numerous approaches which have included high density EEG, the use of Drosophila as a model for sleep, and the development of computer models."

The experts thought Tononi used a variety of approaches in his sleep research. They thought his hypothesis challenged previous conceptions of the purpose of sleep.

b. Typology of Potential Outcomes

Table 156. Characterization of Potential Pioneering Outcomes (Tononi)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Tononi	Expert 1	Expert 2	Expert 3
New Idea	x	x	x	x
New Phenomenon	x	x	x	x
New Methodology	x	x	x	x
New Technology			x	x
New Framework	x	x	x	x
None of these outcomes				

Source: Pioneer interview, Expert review

At least two of three experts agreed that Tononi's NDPA-related research could result in the formulation of a new idea, the discovery of a new empirical phenomenon, the development of a new methodology, the invention of a new technology, and the synthesis of a new framework. Tononi generally agreed with this assessment, but did not think that his research would result in the invention of new technology.

Tononi believes that his research has produced a new and unified theory of sleep function that will change the way it is considered and studied in the future.

Below is a selection of comments from experts that justify their evaluations of the potential pioneering outcomes of Tononi's research:

> "Tononi offered a novel theoretical perspective in his "synaptic homeostasis hypothesis," which posits sleep is a restorative process that maintains the brain's plasticity for new experiences, learning and memory in the wake state, and that this is accomplished by reducing the synaptic burden on neurons generated during wakefulness."

> "He has skillfully combined the use of animal models (rodent), basic experimentation in healthy humans, and predictions of computer models (which derive from and relate to his longstanding interests in consciousness)."
>
> "The findings emerging from Tononi's research program are highly relevant to information theory and artificial intelligence."
>
> "His group has developed novel techniques to determine changes in synaptic potentiation from wakefulness to sleep. These include studies in: gene expression…neurotransmitters, learning and memory involving numerous species including Drosophila, rodents, birds, and humans."

The experts were highly impressed with Tononi's use of animal and computer models, the vast range of his sleep research, and the implications it has on information theory, mental health, behavior, and artificial intelligence.

c. Assessing Whether the Research Was Pioneering

In addition to characterizing the associated risks and identifying the potential outcomes of the research, experts were also asked to assess whether the accomplished work was pioneering. All three experts strongly agreed that Tononi's accomplished research was pioneering. Below is a selection of comments from experts about why Tononi's research was or was not pioneering:

> "Tononi has done an outstanding job of applying technically demanding and conceptually enriching studies to address a question of fundamental relevance to the human condition."
>
> "Tononi et al. have also demonstrated how local electrical stimulation can generate synaptic potentiation and increase slow wave activity in a brain region during sleep. This opens up the possibility of a potential application for noninvasive therapy to enhance slow wave sleep benefits in those deficient in this neural state (e.g., elderly), and potentially reduce performance errors in those with limited sleep opportunities."
>
> "The discoveries made by this group are also applicable to the entire fascinating area of consciousness…This work helps explain why the final common effect of anesthetic agents is loss of consciousness."

All three experts strongly believed that Tononi's research was pioneering because of its paradigm-shifting results on sleep function and its applicability to multiple areas of science.

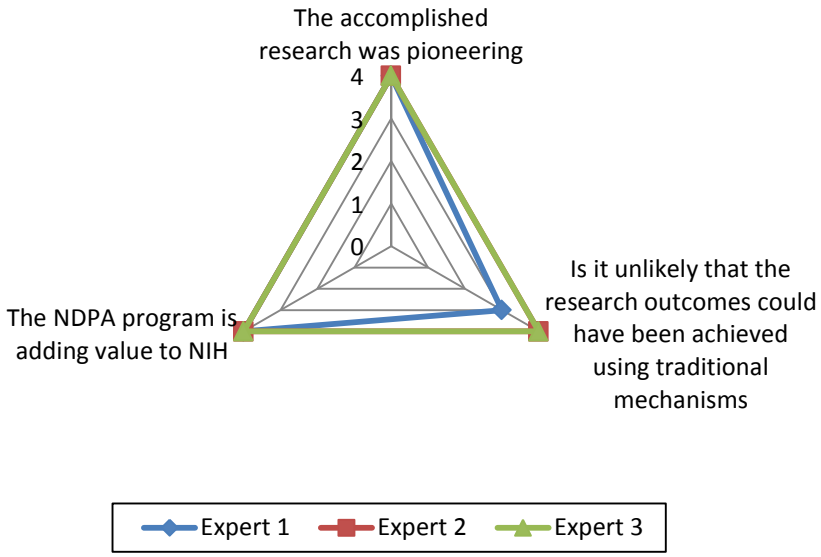
4. Value of the NDPA Program

a. Pioneer Perspective

Tononi appreciated the long-term aspect of the Pioneer Award funds because his lab did not have to worry about finding the answer in one or two years. The award also allowed him to try multiple techniques and approaches to test his hypothesis because of the large amount of money and the flexibility he had with it. The lessened bureaucracy saved him time and allowed him to divert intellectual and physical resources to solving the problems of the science rather than the grant. He was also able to purchase a two photon microscopy system to enhance his research methods. If he had not received the Pioneer Award, Tononi would have attempted to perform his NDPA project. He doubts, however, that he would have had as much success because he wouldn't have upgraded his lab to take his sleep research to "the fundamental level."

b. Expert Perspective

Experts were asked to rate whether Tononi's results were a unique output of the Pioneer Award, and whether the Pioneer Award is adding value to NIH (Figure 66).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 66. Experts' Opinions of the NDPA (Tononi)

Two experts strongly agreed and one moderately agreed that it is unlikely that the research outcomes could have been achieved using traditional mechanisms. Three experts strongly agreed that the NDPA program is adding value to NIH.

Below is a selection of comments from experts about the value of the NDPA program:

> "Given the inherently parochial and risk-avoidant nature of both study sections and funding programs, NIH needs NDPA-like initiatives to support scientific work on bold questions of biology and behavior."
>
> "I believe that a careful review of past and recent records at CSR will show that Tononi's NIH applications on consciousness…unfortunately often have not been assigned fundable scores…In my opinion, Tononi's outstanding success in the past five years has been significantly facilitated by the Pioneer Award program."
>
> "During the course of this award, Tononi and his group have made many very important discoveries which have made major contributions to the fields of both sleep and consciousness. The project has involved numerous researchers from disparate backgrounds."

All three experts thought Tononi's research has made great advances in sleep research. Furthermore, they also agreed that this project likely would not have been funded through traditional mechanisms, particularly when considering the scores of Tononi's previous NIH applications.

5. Descriptive Bibliometrics

Terms of comparison in these analyses include "pre-NDPA" and "post-NDPA." Since Tononi received the Pioneer Award in 2005, the pre-NDPA range refers to activity between 2001 and 2005 while the post-NDPA range refers to activity between 2006 and 2010.

a. Productivity

Tononi published a total of 198 original articles over the 23 years of his research career (Table 157). In the pre-NDPA period, Tononi published 58 articles for a rate of 11.6 per year. In the post-NDPA period, he published 87 articles for a rate of 17.4 per year.

Table 157. Summary of Publication Activity (Tononi)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	58	87	17	198
Number of Years	5	5	N/A	23
Publication Rate	11.6	17.4	N/A	8.608696

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Tononi published more articles in the post-NDPA period than in the pre-NDPA period. Interestingly, Tononi remarked in his interview that he did not think his publication rate had changed much after receiving the award. He also stated that the long-term aspect of the award gave him the freedom to consider whether what he was publishing was important.

Of the 87 post-NDPA articles he published, 17 were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 158.

Table 158. Publications Attributed to NDPA Funding (Tononi)

Title	Journal	Year Published
Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness	Proceedings of the National Academy of Sciences of the United States of America	2010
Consciousness and Anesthesia	Science	2008
Cortical Firing and Sleep Homeostasis	Neuron	2009
Cortical metabolic rates as measured by 2-deoxyglucose-uptake are increased after waking and decreased after sleep in mice	Brain Research Bulletin	2008
Dreaming and the brain: from phenomenology to neurophysiology	Trends in Cognitive Sciences	2010
Effects of Skilled Training on Sleep Slow Wave Activity and Cortical Gene Expression in the Rat	Sleep	2009
Homeostatic regulation of sleep in the white-crowned sparrow (Zonotrichia leucophrys gambelii)	BMC Neuroscience	2008
Increased Volatile Anesthetic Requirement in Short-sleeping Drosophila Mutants	Anesthesiology	2009
Integrated information in discrete dynamical systems: Motivation and theoretical framework	PLOS Computational Biology	2008
Is sleep essential	PLOS Biology	2008
Long-Term Homeostasis of Extracellular Glutamate in the Rat Cerebral Cortex across Sleep and Waking States	Journal of Neuroscience	2009
Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep	Nature Neuroscience	2008
Qualia: The Geometry of Integrated Information	PLOS Computational Biology	2009
Slow waves, synaptic plasticity and information processing: insights from transcranial magnetic stimulation and high-density EEG experiments	European Journal of Neuroscience	2009

TMS-Induced Cortical Potentiation during Wakefulness Locally Increases Slow Wave Activity during Sleep	PLOS One	2007
Triggering Slow Waves During NREM Sleep in the Rat by Intracortical Electrical Stimulation: Effects of Sleep/Wake History and Background Activity	Journal of Neurophysiology	2009
Widespread Changes in Synaptic Markers as a Function of Sleep and Wakefulness in Drosophila	Science	2009

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, Tononi's 177 original articles excluding reviews had been cited a total of 4,642 times. Tononi's 83 post-NDPA publications had been cited 807 times by August 2010. The 14 publications that had been attributed to the NDPA had 164 citations by that time.

The age-weighted citation rate of Tononi's post-NDPA publication set is higher than that of his pre-NDPA publication set. That indicates that Tononi's publications after receiving the award have had a greater impact on the scientific community than those he published in the pre-NDPA period.

The statistics on this publication set are shown in Table 159.

Table 159. Summary of Citation Analyses (Tononi)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (177 pubs)	4,642	28.86	37
Pre-NDPA (53 pubs)	1,567	14.78	N/A
Post-NDPA (83 pubs)	807	15.30	N/A
Attributed to NDPA Funding (17 pubs)	251	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Tononi published 48 publications in 22 different sources in the pre-NDPA period and 87 publications in 33 different sources in the post-NDPA period. Detailed data on Tononi's most published-in journals for the pre- and post-NDPA periods are shown in Table 160 and Table 161.

Table 160. Most Published-in Journals in the Pre-NDPA Period, 2001-2005 (Tononi)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
25	Sleep	0.02837	91.87
3	Archives Italiennes de Biologie	0.001029	24.56
3	Journal of Neuroscience	0.521789	99.87
3	Nature	1.76345	100
3	Neuropsychopharmacology	0.059698	96.62

Source: Eigenfactor.org, Journal names came from Web of Science

Table 161. Most Published-in Journals in the Post-NDPA Period, 2006-2010 (Tononi)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
33	Sleep	0.02837	91.87
6	Journal of Neuroscience	0.521789	99.87
5	Journal of Sleep Research	0.006154	69.27
4	Biological Psychiatry	0.113895	98.42
4	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 14 of Tononi's 58 publications, 24.14%, were in journals at or above the 98th percentile (Table 162). In the post-NDPA period, 27 of Tononi's 87 publications, 31.03%, were in journals of the same caliber. Nine of Tononi's NDPA-attributed publications were at or above the 98th percentile.

Table 162. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Tononi)

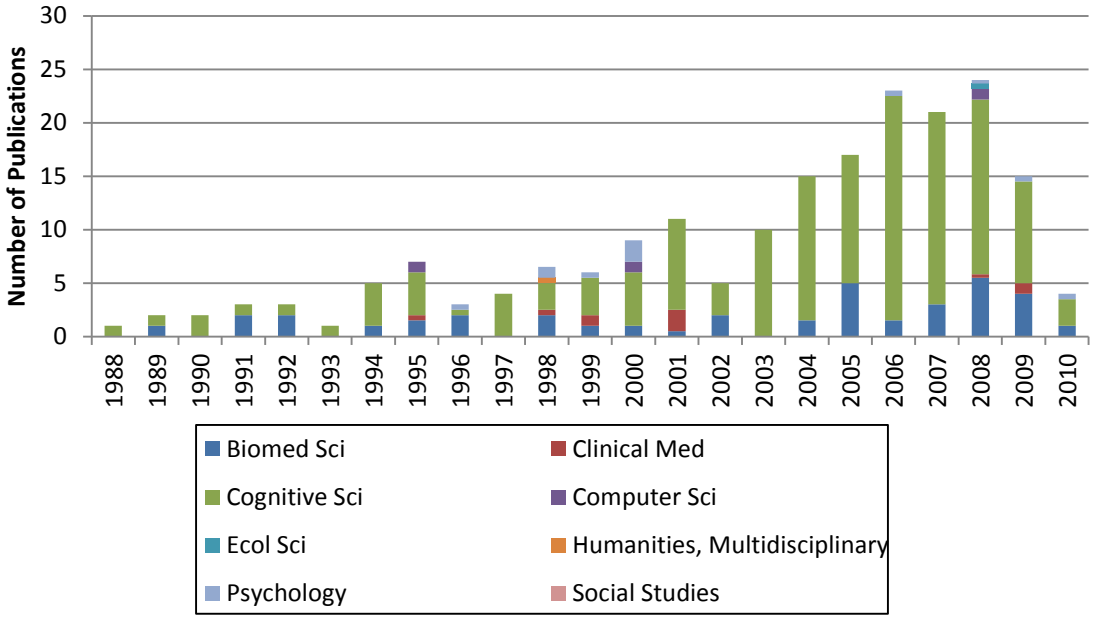
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (58 pubs)	14	24.14%
Post-NDPA (87 pubs)	27	31.03%
Attributed to NDPA Funding (17pubs)	8	52.94%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data are from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Tononi's 198 publications over the duration of his career can be categorized into seven different macro-disciplines. He published in three macro-disciplines over his 58 pre-NDPA publications and six macro-disciplines over his 87 post-NDPA publications. The distribution of Tononi's publications into macro-disciplines over time may be seen in Figure 67.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 67. Distribution of Publications into Macro-disciplines over Time (Tononi)

Tononi has spent the majority of his career publishing in Cognitive Science and, to a lesser extent, Biomedical Science with his studies in the function of sleep. Biomedical applications of his work include sleep disorders and the enhancement of sleep value.

2) Body of Knowledge Cited

Tononi cited seventeen different macro-disciplines over the 6,849 cited references of his 198 career publications. This included twelve macro-disciplines over the 1,542 cited references of his 58 pre-NDPA publications and seventeen macro-disciplines over the 2,696 cited references of his 87 post-NDPA publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I scores is 0.572 and the mean S score is 0.486. The Integration and Specialization scores for Tononi are shown in Table 163.

Table 163. Integration and Specialization Scores (Tononi)

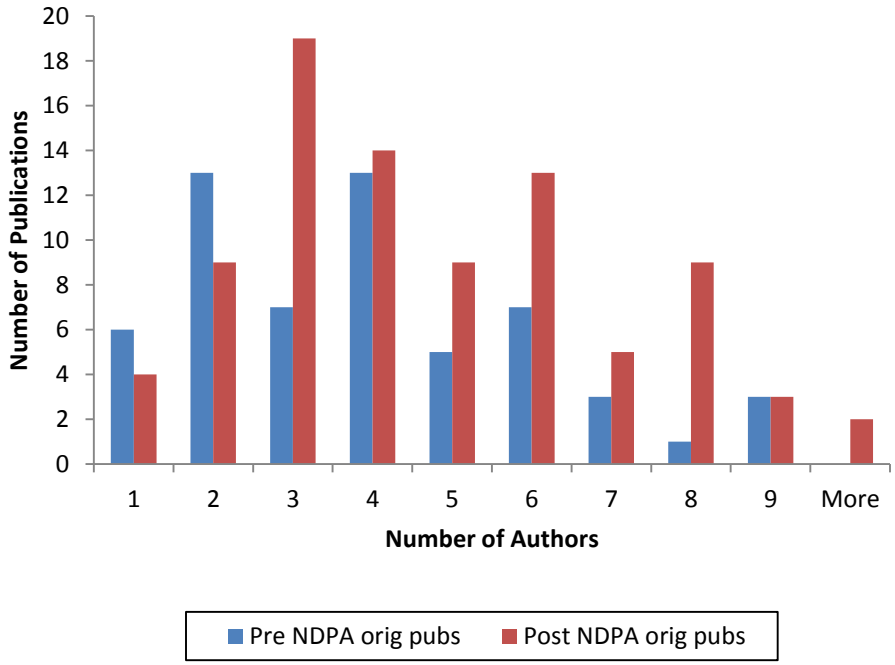
	Full Career (6849 cited references)	Pre-NDPA (1542 cited references)	Post-NDPA (2696 cited references)
Integration	0.501	0.491	0.509
Specialization	0.569	0.611	0.551

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, Tononi is a moderate "Disciplinarian." Although his research encompasses many different fields (i.e., Neuroscience, Cognitive Science, Psychology, Biology), these categories are closely related.

d. Collaboration

The median number of total authors in Tononi's publication set was four for his career, pre-NDPA period, and post-NDPA period. Time period comparisons for the number of authors in Tononi's publication set may be seen in Figure 68.



Source: Web of Science

Figure 68. Distribution of Number of Authors in Original Publication Set (Tononi)

The number of unique authors in a researcher's publishing network is another metric that captures collaboration patterns. Tononi has published with 135 unique researchers throughout his full career. In the pre-NDPA period, he collaborated with 51 researchers, and in the post-NDPA period, he collaborated with 82 researchers. Over his 17 NDPA-attributed publications, he published with 35 other people. Tononi explained in his interview that the NDPA enabled him to start collaborations or have his students trained in other labs without worrying about money.

S. Clare Waterman (2005)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The panel of reviewers thought Waterman had an energetic vision for imaging components of cell mobility via quantitative methods. They were impressed with her integrated approach, but were concerned about her "articulation" of the measurements and systems she was studying.

3. Nature of Project Risks and Outcomes

Because she relinquished the award, an expert review was not performed for Waterman's case study.

Waterman believed that her NDPA project incorporated technical, experience, and multidisciplinary risks. Her unproven techniques included the use of biological approaches for in vivo cell imaging combined with mathematical theories. Her combination of cell and molecular biology, particularly cytomechanics, and mathematics was a "relatively unique" combination of disciplines.

In terms of the nature of the outcomes of her NDPA project, Waterman stated that her research had the potential to result in new methodologies and new technologies. She noted that her research would not necessarily result in new theories because in biology, "every single experiment…is hypothesis-driven." She explained that "biologists don't [really] think about theories…most of [them] are mired in the details." Instead, she characterized her work as providing evidence for an existing and continually developing theory of cell migration.

4. Value of the NDPA Program—Pioneer Perspective

In her interview, Waterman also expressed her opinion on the value of the Pioneer Award. The large amount of money relieved her funding worries, an attribute which allows researchers to "be creative" and "follow [her] nose." The funding amount also allowed her to hire new and more people that wanted to work on new things. This hiring "changed the direction of [her] science" because the new hires "wanted to work on something new, something different." If she had not been funded by the Pioneer program

she would have pursued her project elsewhere. She had been working on a grant with a group of people as the "microscopist" and "cell biologist" at the time. Waterman explained that she would have applied "everywhere" for funding, and she imagines that a likely source would have been another non-GM NIH institute.

T. Nathan Wolfe (2005)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The panel of reviewers considered Wolfe's proposal to be an "intriguing vision for the potential power of developing an infrastructure for monitoring the emergence of viral diseases in the context of hunting populations in Africa." Overall, the panel was impressed with the "importance of the problem and its potential impact on worldwide human health." Nonetheless, the panel did not consider Wolfe to be appropriate for an NDPA due to their concerns that "despite the value of the data collection, Wolfe did not address specific research questions that would utilize the data." The views of the reviewer panel demonstrate how difficult it may be to convey a new idea without including specific aims.

3. Nature of Project Risks and Outcomes

Both the Pioneer and the three experts were asked to characterize in what ways the risks and outcomes of the Pioneer's research were pioneering (Table 164 and Table 165).

a. Typology of Project Risks

Table 164. Characterization of Unique Project Risk (Wolfe)

Please indicate which of the following risks are applicable to the NDPA-funded project	Wolfe	Expert 1	Expert 2	Expert 3
Conceptual Risk	x	x	x	x
Technical Risk	x	x		
Experience Risk	x			
Multidisciplinary Risk	x	x	x	x
None of these risks				

Source: Pioneer interview, Expert review

At least two of three experts thought Wolfe's work contained conceptual and multidisciplinary risks. Wolfe himself believed his work incorporated conceptual, technical, experience, and multidisciplinary risks. Below is a selection of comments from the expert reviewers which demonstrate how they interpreted the risks associated with Wolfe's Pioneer research:

> "The findings are challenging prevailing dogmas on the consequences of viruses, bacteria and parasites jumping species. The investigations have tracked the evolution of pathogens in animals and their counterparts in humans to assess how species specificity occurs. To fully unravel the relationship required crossing disciplinary barriers understanding history, human settlements, human behavior, genetics and epidemiology, amongst others."
>
> "The approach of looking for the origins of human infectious disease by going to the sources of contact between humans and primates is novel."
>
> "The novelty of the work, and Nathan Wolfe's main contribution, is in the sampling of wild or wild-born animals."
>
> "To some extent the research does involve a unique combination of perspectives and disciplines, in the sense that most molecular evolution research fails to give much consideration to the field aspects of the research, and "freezer sampling" is usually done rather than thoughtful sampling of relevant populations, resulting sometimes in skewed results and questionable interpretations."

The expert reviewers agreed that the research as proposed was risky because his proposal involved a unique combination of disciplines: biology, epidemiology, ecology, and anthropology. Wolfe's idea to sample wild animals, and bushmeat hunters looking for possible cross-species transmission, presented a unique and unprecedented perspective for identifying potential origins of human epidemics.

b. Typology of Potential Outcomes

Table 165. Characterization of potential pioneering outcomes (Wolfe)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Wolfe	Expert 1	Expert 2	Expert 3
New Idea	x	x	x	
New Phenomenon	x	x		x
New Methodology				
New Technology			x	
New Framework	x			
None of these outcomes				

Source: Pioneer interview, Expert review

At least two of three experts agreed that Wolfe's research had the potential to advance new ideas and observe new empirical phenomena. Wolfe thought his research had the potential to advance new ideas, discover new phenomena, and synthesize a new framework. Below is a selection of comments from expert reviewers which reflect how the reviewers identified the potential outcomes of Wolfe's research:

> "By supporting sample collection in very unusual and hard-to-reach populations of animals and humans, the NDPA has opened up the possibility of more relevant application of genomic evolutionary methods, even if the promise of this approach has yet to be fully realized."
>
> "New ideas have been formulated around the key steps for a parasite to move from animals to humans. These ideas are re-shaping some of our understanding of how pathogens can infect new species and then gain specificity to infect only the new species."
>
> "An interesting approach (not necessarily—an instrument) has been utilized and subsequently expanded to meet the research needs for monitoring new zoonoses."
>
> "By extending sampling for molecular and genomic evolutionary studies into little-sampled populations of animals and humans in remote areas, and by studying both humans and the animals that live in close proximity with them, Dr. Wolfe has been making new discoveries of viral pathogens and will probably continue to do so."
>
> "The research has resulted in the discovery of new viruses that could potentially be etiologies of the next human scourges."

Wolfe and the expert reviewers generally agreed that his research could result in the development of new theories or discovery of new phenomena. Primarily, the experts believe through his Pioneer research, Wolfe will continue to discover new viral

pathogens, and that his work will open up multiple applications for monitoring and understanding zoonotic diseases.

c. Assessing Whether the Research Was Pioneering

In addition to characterizing the associated risks and identifying the potential outcomes of the research, expert reviewers were also asked to assess whether the accomplished work was pioneering. Two experts moderately agreed that Wolfe's research accomplishments through the Pioneer Award were pioneering, citing the following reasons:

> "I moderately agreed that that the accomplished research in pioneering because the research has made at least one (and possibly, two) key contributions. It has, however, not resulted in a major paradigm shift. I believe this research has substantial potential, going forward, to have this kind of paradigm changing [effect]."

> "Dr. Wolfe occupies a unique niche that garners him much attention, and he has pioneered the exploration of the human-animal interface, identifying new pathogens and generating paradigm-shifting (if highly controversial and possibly flawed) new insights."

One reviewer declined to answer the question citing it was too early to determine:

> "I am not sure yet. New viruses have been found. Whether those are significant or not will not be known for quite some time."

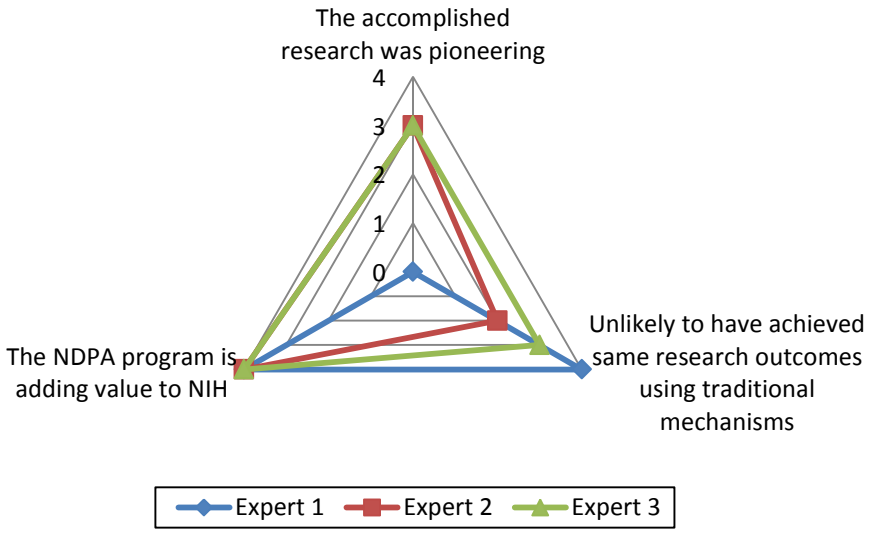
4. Value of the NDPA Program

a. Pioneer Perspective

Wolfe stated that the NDPA gave him the foundation to leave academia, and fully explore his work. Wolfe left a tenured faculty position during his third year of the NDPA, to start his own research institution where he could fully pursue his research career without constraints. Wolfe credited the NDPA with giving him "institutional flexibility and stability," and recommended that the NDPA model be adopted across NIH agencies, where each IC could fund a few researchers per year. As a researcher, Wolfe believes the Pioneer Award "lets you take a breath," and that his five years under the NDPA were "all about career trajectory." Wolfe commends the model for supporting individual investigators, and explained that "the NIH shouldn't feel it has to defend itself for funding people. Say 'OK,' the rest of the funding goes to projects, but this award is going to people."

b. Expert Perspective

Experts were asked to rate whether Wolfe's results were a unique output of the Pioneer Award, and whether the Pioneer Award is adding value to NIH (Figure 69).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 69. Experts' Opinions of the NDPA (Wolfe)

One expert strongly agreed, one moderately agreed, and one moderately disagreed that it is unlikely that Wolfe's research outcomes could have been achieved under traditional funding mechanisms. All three experts strongly agreed that the NDPA program is adding value to NIH. Below is a selection of comments from reviewers about the value of the NDPA program:

> "NIH study sections can indeed become fossilized and convention-bound, and having an alternative pathway for review and award, even if it results in work of varying quality, is highly valuable for the health of the whole biomedical research enterprise. The somewhat uneven quality of some of the NDPA-supported research is an expected and quite acceptable consequence of adding review and award process that tolerates higher-risk research."

> "NDPA has enabled these researchers to undertake some important research issues."

> "Despite my uncertainty about this particular case, supporting investigators like this adds a whole other dimension to the NIH portfolio. Work like this could not be supported through traditional mechanisms and is potentially of very high significance."

Experts had mixed opinions regarding whether the same work could have been achieved under traditional funding mechanisms, but all three of the experts agreed that the NDPA program added value to the NIH portfolio.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Wolfe received the NDPA in 2005, the pre-NDPA range refers to activity between 2001 and 2005 while the post-NDPA range refers to activity between 2006 and 2010.

a. Productivity

Wolfe published a total of 44 publications over the 18 years of his research career giving him a rate of 2.44 articles per year (Table 166). In the pre-NDPA period, Wolfe published 19 articles for a rate of 3.8 articles per year. In the post-NDPA period, Wolfe published 22 articles for a rate of 4.4 articles per year.

Table 166. Summary of Publication Activity (Wolfe)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	19	22	10	44
Number of Years	5	5	N/A	18
Publication Rate	3.8	4.4	N/A	2.44

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution in specific years.
Source: Web of Science, NIH RePORTER.

Wolfe published more original works in the post-NDPA period than in the pre-NDPA one. Of the 22 articles Wolfe published in the post-NDPA period, ten articles were attributed to NDPA funding. These publications are listed in Table 167.

Table 167. Publications Attributed to NDPA Funding (Wolfe)

Title	Journal	Year Published
Ancient origin and molecular features of the novel human T-lymphotropic virus type 3 revealed by complete genome analysis	Journal of Virology	2006
Ancient, independent evolution and distinct molecular features of the novel human T-lymphotropic virus type 4	Retrovirology	2009
Central African hunters exposed to simian immunodeficiency virus	Emerging Infectious Diseases	2005
Coinfection of Ugandan Red Colobus (Procolobus [Piliocolobus] rufomitratus tephrosceles) with Novel, Divergent Delta-, Lenti-, and Spumaretroviruses	Journal of Virology	2009
Emergence of a novel and highly divergent HTLV-3 in a primate hunter in Cameroon	Virology	2010
Exposure to wild primates among HIV-infected persons	Emerging Infectious Diseases	2007
Genetic characterization of the complete genome of a highly divergent simian T-lymphotropic virus (STLV) type 3 from a wild Cercopithecus mona monkey	Retrovirology	2009
Seroprevalence and distribution of Flaviviridae, Togaviridae, and Bunyaviridae arboviral infections in rural Cameroonian adults	American Journal of Tropical Medicine and Hygiene	2006
Simian T-Lymphotropic Virus Diversity among Nonhuman Primates, Cameroon	Emerging Infectious Diseases	2009
The Origin and Prevention of Pandemics	Clinical Infectious Diseases	2010

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of August 2010, Wolfe's 41 original publications excluding reviews were cited a total of 750 times. In the post-NDPA period, Wolfe published 20 publications that had received a total of 100 citations by August 2010. Five publications were attributed to NDPA funding and they had received 19 citations by that time. Details on this publication set are shown in Table 168.

Table 168. Summary of Citation Analyses (Wolfe)

Publication Set	Number of Citations	Age-weighted citation rate (AWCR)	H-index
Full Career (41 pubs)	750	10.77	15
Pre-NDPA (19 pubs)	577	9.10	N/A
Post-NDPA (20 pubs)	100	5.24	N/A
Attributed to NDPA Funding (10 pubs)	74	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Wolfe published 19 articles in eleven different sources in the pre-NDPA period and 22 articles in fourteen different sources in the post-NDPA period. Detailed data on Wolfe's most published-in journals for the pre- and post-NDPA time periods respectively are shown in Table 169 and Table 170.

Table 169. Most Published-in Journals in the Pre-NDPA Period, 2001-2005 (Wolfe)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
6	AIDS Research and Human Retroviruses	0.013442	93.75
3	Emerging Infectious Diseases	0.076733	97.63
2	Virology	0.065876	97.05
1	American Journal of Tropical Medicine and Hygiene	0.034157	93.14
1	Bulletin of the World Health Organization	0.021817	89.27
1	Environmental Health Perspectives	0.065295	97
1	JAIDS-Journal of Acquired Immune Deficiency Syndromes	0.047185	95.44
1	Journal of Molecular Evolution	0.019668	88.19
1	Journal of Wildlife Diseases	0.005831	68.1
1	Lancet	0.411772	99.78

Source: Eigenfactor.org, Journal names came from Web of Science

Table 170. Most Published-in Journals in the Post-NDPA Period, 2006-2010 (Wolfe)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
3	AIDS Research And Human Retroviruses	0.013442	93.75
3	Emerging Infectious Diseases	0.076733	97.63
2	American Journal of Tropical Medicine And Hygiene	0.034157	93.14
2	Journal of Virology	0.250077	99.48
2	Retrovirology	N/A	N/A
2	Virology	0.065876	97.05

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 2 of Wolfe's 19 publications, 10.53%, were in journals at or above the 98th percentile (Table 171). In the post-NDPA period, 4 of Wolfe's 22 publications, 18.18%, were in journals of the same caliber. Three of the ten NDPA-attributed publications had Eigenfactor values above the 98th percentile.

Table 171. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Wolfe)

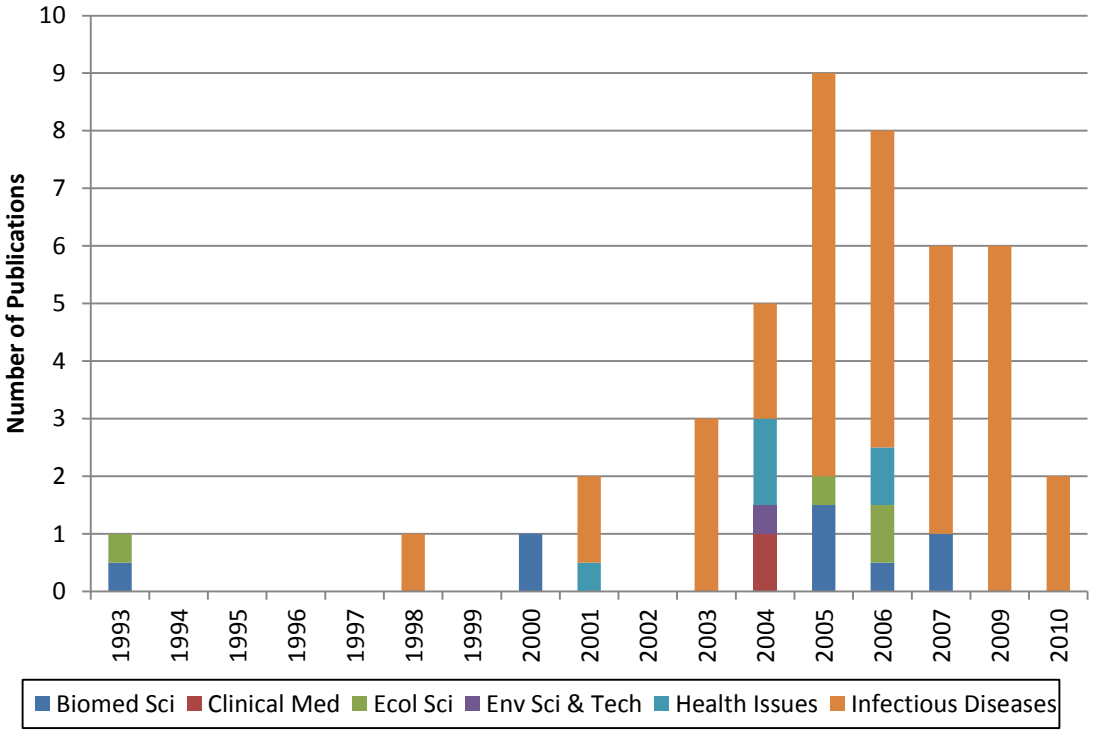
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (19 pubs)	2	10.53%
Post-NDPA (22 pubs)	4	18.18%
Attributed to NDPA Funding (10 pubs)	3	30.00%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data are from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Wolfe's 44 publications over the duration of his career can be categorized into a total of six macro-disciplines. He published in six macro-disciplines over his 19 pre-NDPA publications and in four macro-disciplines over his 22 post-NDPA publications. The distribution of Wolfe's publications into macro-disciplines for the full length of his career may be seen in Figure 70.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 70. Distribution of Publications into Macro-disciplines over Time (Wolfe)

Wolfe published primarily in Infectious Diseases throughout his career with his work in infectious disease tracking and emergence.

2) Body of Knowledge Cited

Wolfe cited fifteen disparate macro-disciplines over the 1,440 cited references of his 44 career publications. This included fourteen macro-disciplines over the 515 cited references of his 19 pre-NDPA publications and over the 788 cited references of his 22 post-NDPA publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I score is 0.572 and the mean S score is 0.486. The Integration and Specialization scores for Wolfe are shown in the table in Table 172.

Table 172. Integration and Specialization Scores (Wolfe)

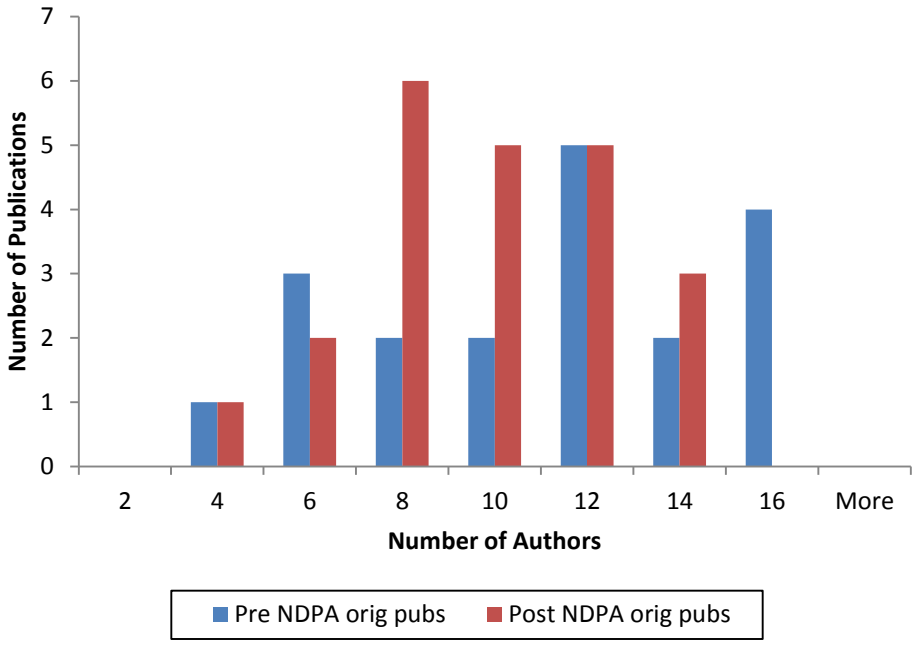
	Full Career (1440 cited references)	Pre-NDPA (515 cited references)	Post-NDPA (788 cited references)
Integration	0.627	0.644	0.571
Specialization	0.472	0.467	0.522

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, Wolfe is a "Renaissance Integrator" and "Single Interdiscipline Specialist" due to his high integration of different types of information.

d. Collaboration

The median number of total authors in Wolfe's publication set was 10. In the pre-NDPA period this median was 11, while in the post-NDPA period this median was 9.5. A comparison of the pre- and post-NDPA distributions of the total number of authors can be seen in Figure 71.



Source: Web of Science

Figure 71. Distribution of Number of Authors in Original Publication Set (Wolfe)

The number of unique authors in a researcher's publishing network is another metric that captures co-authorship patterns. Wolfe has published with approximately 147 unique individuals throughout his full career. In the pre-NDPA period, he published with 79

people, and in the post-NDPA period he co-authored with 87 people. Over his 10 NDPA-attributed publications, he published with 48 other people.

U. Xiaoliang (Sunney) Xie (2004)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The panel of reviewers noted Xie's history of pioneering work in molecular imaging of single cells. They believed that Xie's research was at a stage of tool development, collaborative testing, and then application. They believed his project required technical risks and a driving vision in order to be successful. They felt he had the potential to make important biomedical breakthroughs.

3. Nature of Project Risks and Outcomes

The Pioneers and three experts were asked to characterize in what ways the risks and outcomes of the awardee's research were pioneering (Table 173 and Table 174).

a. Typology of Project Risks

Table 173. Characterization of Unique Project Risk (Xie)

Please indicate which of the following risks are applicable to the NDPA-funded project	Expert 1	Expert 2	Expert 3
Conceptual Risk			
Technical Risk	x	x	x
Experience Risk	x	x	x
Multidisciplinary Risk	x	x	
None of these risks			

Source: Expert review

At least two of the three experts thought Xie's research contained technical, experience, and multidisciplinary risks. Xie did not comment on the nature of the risks of his research. Below is a selection of comments from the experts that justify their evaluations of the pioneering risks of Xie's research:

> "At the beginning of this project, bacterial imaging had not been a primary focus of the researcher's efforts, so the researcher added this skill during this project."

The experts thought Xie had used unproven technology, expanded his research into new areas such as bacterial imaging, and combined a number of different perspectives such as chemistry, biology, and physics.

b. Typology of Potential Outcomes

Table 174. Characterization of Potential Pioneering Outcomes (Xie)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Expert 1	Expert 2	Expert 3
New Idea	x		
New Phenomenon	x		x
New Methodology	x	x	x
New Technology	x	x	
New Framework			
None of these outcomes			

Source: Expert review

At least two of three experts believed Xie's research had the potential to discover new empirical phenomena, develop new methodology, and invent new technology. Below is a selection of comments from the experts that justify their evaluations of the potential pioneering outcomes of Xie's research:

> "His successes during the past few years are in showing dual mechanisms in single-molecule catalysis that could not have been found in bulk experiments; his ability to watch gene expression and protein production, one-molecule-at-a-time inside cells in real time, showing bursts of activity, and showing that the action of a single molecule can affect the phenotype of a cell; and his exquisite technology development, in single-molecule and CARS methods."

> "The research showed directly the appearance of the gamma distribution in copy number, an experimental validation of prior theoretical concepts."

The experts thought Xie pushed technology development in his field, approached his project from a number of different perspectives, and experimentally validated previous concepts.

c. Assessing Whether the Research Was Pioneering

In addition to characterizing the associated risks and identifying the potential outcomes of the research, experts were also asked to assess whether the accomplished work was pioneering. Two experts strongly agreed and one moderately agreed that Xie's research was pioneering. Below is a selection of comments from experts about why Xie's research was pioneering:

> "What sets his work apart from more traditional NIH-funded work are the real pioneering depth of technology development, and his ability to push far into physics (both in his experimental methodologies and in his pioneering theoretical modeling), well beyond what NIH would typically support."
>
> "The studies are very good, but not all are earth-shaking. First, one must ask why leakage expression in E. coli of the lac gene expression is so surprising… On the other hand, the direct imaging of TF binding in the 2007 paper is a very good advance, as is the quantification of phenotype switching of Choi et al."

One expert found Xie's technology development and theoretical modeling to be exciting and important. One expert, on the other hand, thought Xie overemphasized some of the implications of his research in order to publish in high-impact journals.

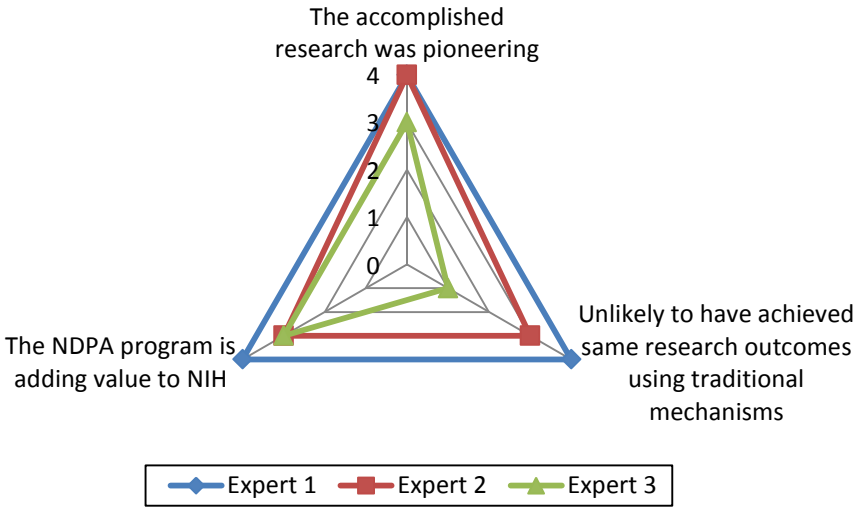
4. Value of the NDPA Program

a. Pioneer Perspective

In his interview, Xie said that his project probably would not have been funded under a normal study section because he had "no credibility in molecular biology." Xie appreciated the flexibility of the NDPA because there are difficulties in predicting how he is going to spend the next three years if he is conducting "cutting-edge research." In retrospect, the NDPA "changed the way [he pursues] scientific research." By working at the interface of multiple disciplines, he explained that you can "capitalize" on your strengths and apply knowledge from one field to another. If he had not received the NDPA, Xie would have still attempted to pursue his project, but it would not have been done so quickly.

b. Expert Perspective

Experts were asked to rate whether Xie's results were a unique aspect of the Pioneer Award, and whether the Pioneer Award is adding value to NIH (Figure 72).



Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly disagree. Source: Expert review

Figure 72. Experts' Opinions of the NDPA (Xie)

One expert strongly agreed, one moderately agreed, and one strongly disagreed that it is unlikely that the research outcomes could have been achieved under traditional funding mechanisms. One expert strongly agreed and two moderately agreed that NDPA is adding value to NIH. Below is a selection of comments from experts about the value of the NDPA program:

> "I think it's successful because the NDPA bets on investigators, not projects; because it is reviewed by arms-length reviewers, not direct competitors, as happens in most panel-based study section reviews; because it involves short proposals; because it aims at big blue-sky gambles; because it is not reviewed by scrutinizing preliminary results; and because it provides a longer-term larger more stable pot of funds for an investigator than a typical RO1."

> "On the whole, the NPDA is stimulating quality research. But this question has only a yes/no answer. The program also seems to be stimulating over-emphasis of research implications to the extent that the awardee feels it essential to publish only in Nature and Science."

Despite mixed opinions about the uniqueness of the outcomes produced by Xie as a result of the NDPA, the experts agreed that the NDPA is adding value to NIH because it focuses on investigators and not projects.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Xie received the Pioneer Award in 2004, the pre-NDPA range

refers to activity between 1999 and 2004 while the post-NDPA range refers to activity between 2005 and 2010.

a. Productivity

Xie has published a total of 136 original articles over the 18 years of his research career for a rate of 7.56 original publications per year (Table 175). In the pre-NDPA period, he published 54 articles for a rate of 9 per year. In the post-NDPA period, he published 58 articles for a rate of 9.67 per year.

Table 175. Summary of Publication Activity (Xie)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	54	58	8	136
Number of Years	6	6	N/A	18
Publication Rate	9	9.666667	N/A	7.56

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Xie published more articles in the post-NDPA period as compared to the pre-NDPA one. In his interview, Xie said that he thought the NDPA emphasized quality over quantity in terms of publication outputs. He believes that his NDPA research generated more high impact publications in journals such as *Science* and *Nature*.

Of the 58 articles Xie published in the post-NDPA period, 8 were attributed to NDPA funding. The publications attributed to NDPA funding are listed in Table 176.

Table 176. Publications Attributed to NDPA Funding (Xie)

Title	Journal	Year Published
A stochastic single-molecule event triggers phenotype switching of a bacterial cell	Science	2008
Chemically specific imaging of cryptosporidium oocysts using coherent anti-Stokes Raman scattering (CARS) microscopy	Journal of Microscopy-Oxford	2009
Coherent Anti-Stokes Raman Scattering Microscopy: Chemical Imaging for Biology and Medicine	Annual Review of Analytical Chemistry	2008
Label-Free Biomedical Imaging with High Sensitivity by Stimulated Raman Scattering Microscopy	Science	2008
Nonspecifically bound proteins spin while diffusing along DNA	Nature Structural & Molecular Biology	2009
Probing Dynein and Kinesin Stepping with Mechanical Manipulation in a Living Cell	ChemPhysChem	2009
Probing transcription factor dynamics at the single-molecule level in a living cell	Science	2007
Single-Molecule Study of DNA Polymerization Activity of HIV-1 Reverse Transcriptase on DNA Templates	Journal of Molecular Biology	2010

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of Fall 2010, Xie's 129 original publications excluding reviews had been cited a total of 7,125 times. In the post-NDPA period, The statistics on this publication set are shown in Table 177.

Table 177. Summary of Citation Analyses (Xie)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (129 pubs)	7,125	30.76	43
Pre-NDPA (51 pubs)	3,257	18.79	N/A
Post-NDPA (56 pubs)	2,172	21.77	N/A
Attributed to NDPA Funding (8 pubs)	313	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Xie published 54 publications in nineteen different sources in the pre-NDPA time period and 58 publications in twenty-eight sources in the post-NDPA period. Detailed data on Xie's most published-in journals for the pre- and post-NDPA time periods are shown in the tables Table 178and Table 179, respectively.

Table 178. Most Published-in Journals in the Pre-NDPA Period, 1999-2004 (Xie)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
14	Abstracts of Papers of The American Chemical Society	N/A	N/A
8	Biophysical Journal	0.187695	99.28
6	Physical Review Letters	1.2816	99.95
4	Optics Letters	0.132863	98.76
3	Journal of Chemical Physics	0.327329	99.71
2	Journal of Biological Chemistry	1.32919	99.96
2	Journal of Physical Chemistry B	0.438558	99.81
2	Journal of The Optical Society of America B-Optical Physics	0.029932	92.19
2	Review of Scientific Instruments	0.066896	97.17
2	Science	1.58309	99.98

Source: Eigenfactor.org, Journal names came from Web of Science

Table 179. Most Published-in Journals in the Post-NDPA Period, 2005-2010 (Xie)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
6	Abstracts of Papers of The American Chemical Society	N/A	N/A
5	Optics Express	0.168236	99.15
4	Chemphyschem	0.044627	94.93
4	Journal of Physical Chemistry B	0.438558	99.81
4	Optics Letters	0.132863	98.76
3	Nano Letters	0.252897	99.51
3	Nature	1.76345	100
3	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99
3	Science	1.58309	99.98

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 32 of Xie's 54 publications, 63.64%, were in journals at or above the 98th percentile (Table 180). In the post-NDPA period, 37 of 58 publications, 63.79%, were in journals of the same caliber. Four NDPA-attributed publications had Eigenfactor values above the 98th percentile.

Table 180. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Xie)

Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (54 pubs)	32	63.64%
Post-NDPA (58 pubs)	37	63.79%
Attributed to NDPA Funding (8 pubs)	4	50.00%

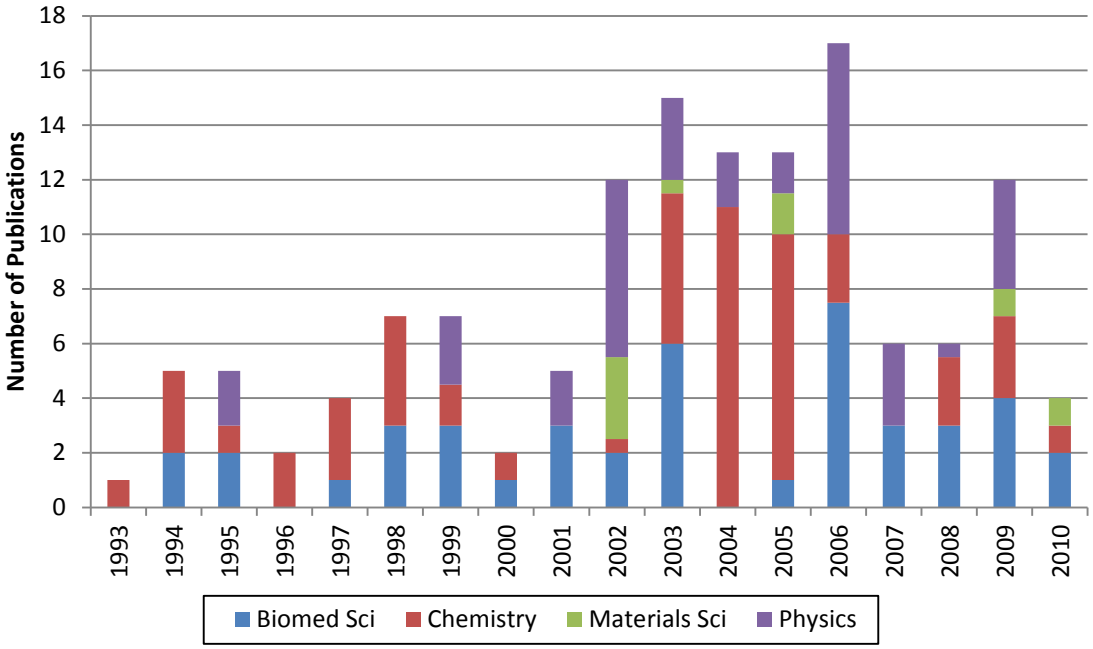
Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data are from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org.

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Xie's 136 publications over the duration of his career can be categorized into a total of four different macro-disciplines. He published in four macro-disciplines over his 54 pre-NDPA publications and his 58 post-NDPA publications. The distribution of Xie's

publications into macro-disciplines over the full length of his career is shown in Figure 73.



Source: Web of Science

Figure 73. Distribution of Publications into Macro-disciplines over Time (Xie)

Throughout Xie's career, no one macro-discipline dominated his publications. He published fairly equally in Biomedical Science, Chemistry, and Physics.

2) Body of Knowledge Cited

Xie cited fourteen different macro-disciplines over the 3,378 references of his 136 publications. This included twelve macro-disciplines over the 1,186 references of his 54 pre-NDPA publications and over the 1,775 references of his 58 post-NDPA publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I scores is 0.572 and the mean S score is 0.486. The Integration and Specialization scores for Xie are displayed in Table 181.

Table 181. Integration and Specialization Scores (Xie)

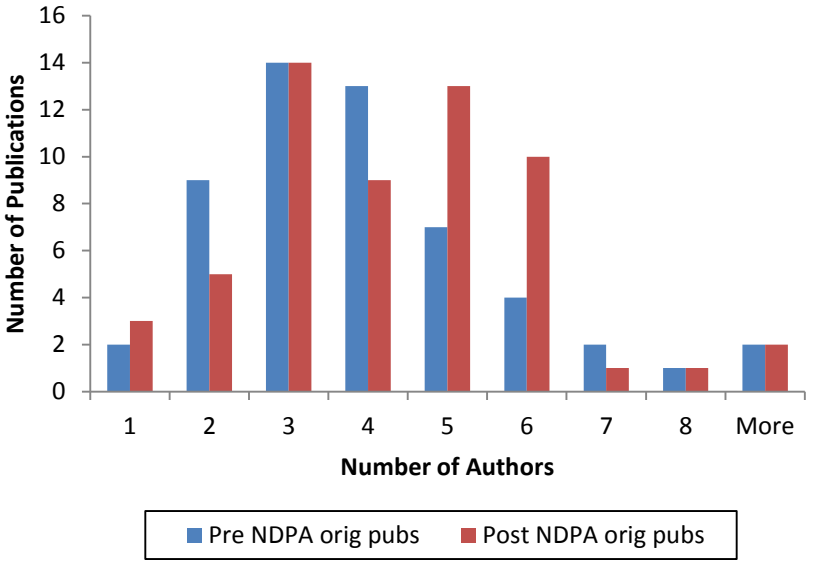
	Full Career (3378 cited references)	Pre-NDPA (1186 cited references)	Post-NDPA (1775 cited references)
Integration	0.613	0.645	0.553
Specialization	0.391	0.405	0.389

Source: Publication data are from Web of Science, scores were calculated using VantagePoint.

Compared to the other Pioneers, Xie generally appears to be a "Renaissance Integrator" and "Grazer" due to his lack of specialization in one field.

d. Collaboration

The median number of total authors in Xie's publication set was three. In both the pre- and post-NDPA period this median was four. A comparison of the pre- and post-NDPA distributions of the total number of authors can be seen in Figure 74.



Source: Web of Science

Figure 74. Distribution of Number of Authors in Original Publication Set (Xie)

The number of unique authors in a researcher's publishing network is another metric that captures co-authorship patterns. Xie has published with approximately 157 unique individuals throughout his full career. He co-authored with 74 researchers in the pre-NDPA period and 96 researchers in the post-NDPA period. Over his eight NDPA-attributed publications, Xie co-authored with 22 unique researchers.

V. Junying Yuan (2005)

1. Research Summary

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.

2. NDPA Reviewer Panel Opinions

The NDPA panel of reviewers "considered the project to be of very high risk but to have a potentially very high impact." Yuan's proposal was based on her preliminary finding that an autosomal deafness disorder may involve the aggregation of a mutant form of a protein which is normally expressed in the ear, and she proposed to pursue the finding as a potential model for a protein-conformational disease. Although the panel considered the proposed idea to be of substantially high risk, it was the previous track record of the investigator that secured their support of the proposal. The final recommendation of the panel stated, "In view of Dr. Yuan's past scientific breakthroughs, they were very enthusiastic about the potential for significant advances in a very important area."

3. Nature of Project Risks and Outcomes

Both the Pioneer and the three experts were asked to characterize the ways in which the risks and outcomes of the awardee's research were pioneering (Table 182 and Table 183).

a. Typology of Project Risks

Table 182. Characterization of Unique Project Risk (Yuan)

Please indicate which of the following risks are applicable to the NDPA-funded project	Expert 1	Expert 2	Expert 3
Conceptual Risk		x	x
Technical Risk			
Experience Risk		x	
Multidisciplinary Risk	x		x
None of these risks			

Source: Expert review

At least two of three experts thought Yuan's research had conceptual and multidisciplinary risks. Below is a selection of comments from the experts which demonstrate how they interpreted the risks associated with Yuan's NDPA research.

> "The notion that transmissible infectious prion agents play a broader role in disease was (and remains) controversial. In order to test this idea, the PI needed to conduct experiments that were outside of her area of expertise."

> "The original research proposed concerned the mechanism of behavior of the product of the DFNA9 gene, known as cochlin, in producing adult-onset sensorineural hearing loss. Yuan proposed that misfolding and aggregation of cochlin in this context might be an example of prion behavior in mammals, i.e., that the mutant protein might co-opt wild-type into aggregates and be infectious."

The experts recognized that the theories in the proposal were in dispute within their scientific field, and that the project required knowledge beyond Yuan's previous expertise. The experts also acknowledged that Yuan's Pioneer proposal cut across multiple scientific fields.

b. Typology of Potential Outcomes

Table 183. Characterization of Potential Pioneering Outcomes (Yuan)

Please indicate which of the following potential or realized outcomes apply to the NDPA research	Expert 1	Expert 2	Expert 3
New Idea	x	x	x
New Phenomenon		x	
New Methodology			
New Technology			
New Framework			
None of these outcomes			

Source: Expert review

All three experts agreed that Yuan's research had the potential to result in the formulation of a new idea. Below is a selection of comments from the expert panel which reflect how the reviewers identified the potential outcomes of Yuan's research:

> "The research did have the potential to provide evidence that infectious protein play a broader role in pathology than had been previously thought. That being said, the actual research conducted fell far short of this goal. In general, I would characterize the actual research done as being solid work in an interesting field. In other words precisely the kind of research that the normal R01 route does a good job at funding."

> "The results presented [in the articles] would indicate that mutant cochlin is an aggregation-prone and cellular toxic protein, consistent with the clinical observations. Whether it exhibits any prion-like behavior is not resolved with the data at hand… In this case, cochlin appears to have toxicity unique to the inner ear and whether this is a function simply of its abundant expression there or a function of additional receptors or other components in the inner ear apparatus remains to be demonstrated. In a clinical context, a prion-like behavior seems remote."

> "The concept of necroptosis and identification of components of this pathway is highly novel and presents a new idea in cell death research."

The experts recognized that Yuan's NDPA project proposed an expanded role for prion diseases, but that the accomplished research was insufficient to substantiate the claims. However, the research conducted implies a unique role in cellular death mechanisms which could be further investigated in future research.

c. Assessing Whether the Research Was Pioneering

In addition to characterizing the associated risks, and identifying the potential outcomes of the research, experts were also asked to assess whether the accomplished work was pioneering. One expert strongly agreed, one moderately agreed, and one strongly disagreed that Yuan's accomplished research was pioneering. Below are examples of explanations given by the experts on why they thought the research accomplished was or was not pioneering:

> "The stuff she cited in the Cell paper was fairly novel, but not really an outgrowth of this program. Maybe she was funded by something else and this was the most novel thing she was working on during the time period so she decided to go with it. What she proposed to do was way out there, maybe kinda crazy. She set up a bold hypothesis but she didn't stick to it."

> "The results are unexpected and highly novel."

> "The proposal that self propagating (prion-like) aggregates play a broader role in neurodegenerative disease has gained some traction (although the jury is still out on this one). However, the PIs research was NOT

responsible for these advances. Instead the PI focused on interesting but less conceptual novel areas and made solid progress."

Two out of the three experts found to the work proposed by Yuan to be high-risk, but thought the actual research accomplished actually fell short of the original goals. The third expert focused on the concept of necroptosis, which was not included in the original proposal, but was developed during the time of the award; this reviewer found the work to be novel.

4. Value of the NDPA Program

a. Pioneer Perspective

During her interview, Yuan admitted that she probably could not have pursued the proposed idea without the NDPA, because she did not have enough preliminary data to substantiate her claims before a traditional study section. Yuan also explained that "the project has been modified as [they have] gone along," because they could not have predicted exactly what would be. The flexibility of the award enabled Yuan and her lab to "afford to do more experiments" and to have access to "machines, and reagents that [she] didn't think [she] would have been able to buy otherwise."

b. Expert Perspective

Experts were asked to rate whether Yuan's results were a unique output of the Pioneer Award, and whether the Pioneer Award is adding value to NIH (Figure 75).

Note: Experts were asked to score these questions on a rating scale: 1 is strongly disagree, 2 is moderately disagree, 3 is moderately agree, and 4 is strongly agree. Source: Expert review

Figure 75. Experts' Opinions of the NDPA (Yuan)

One expert moderately agreed and one strongly disagreed that it is unlikely that Yuan's research outcomes could have been achieved under traditional funding mechanisms. One strongly agreed and one moderately disagreed that the NDPA is adding value to NIH. Below is a selection of comments from reviewers about the value of the NDPA program:

> "In sum, if one considers Yuan's studies of necroptosis, this clearly ranks as pioneering type of work/observations in my view, whereas the dfna9 was an interesting proposal but not really validated as prion disease at this point. Insofar as Pioneer would award funds to established creative investigators and set them loose to do good things, I believe Yuan's output is consistent with that. I believe that the necroptosis work could have been funded by a more conventional NIH mechanism, albeit not to the dollar level that the Pioneer Award offers. With an N=1 here it is not straightforward to more globally evaluate whether the Program is adding value to the NIH portfolio. On a dollars per output basis, I would agree that a close inspection is called for."
>
> The recent trend in NIH funding has been towards predictable, more conservative projects. The NDPA program is extremely valuable because it provides funding for highly innovative, high-risk projects that have the potential for unexpected breakthrough discoveries."
>
> "The present [work] did not achieve these goals and I am not aware of other examples of successes of the NDPA program although I base this judgment on a very limited view of the program as a whole."

The experts agreed that the theory of necroptosis developed by Yuan was novel and worthy of pursuit, but two of the experts felt that original high-risk idea was abandoned, and that the necroptosis work could have been funded through traditional mechanisms. The tension that arose among the experts was whether the NDPA program adds value if the awardees propose to break new ground, but end up pursuing sound research which is an extension of their previous work, or something "safe" that could have been funded through traditional mechanisms.

5. Descriptive Bibliometrics

Terms of comparison in the following bibliometric analyses include "pre-NDPA" and "post-NDPA." Since Yuan received the Pioneer Award in 2005, the pre-NDPA range refers to activity between 2001 and 2005 while the post-NDPA range refers to activity between 2006 and 2010.

a. Productivity

Yuan has published a total of 156 original articles over the 21 years of her research career for an average of 7.43 articles per year (Table 184). In the pre-NDPA period, Yuan

published 33 original articles for a rate of 6.6 per year. In the post-NDPA period, she published 49 articles for a rate of 9.8 per year.

Table 184. Summary of Publication Activity (Yuan)

	Pre-NDPA	Post-NDPA	Attributed to NDPA Funding	Full Career
Number of Publications	33	49	7	156
Number of Years	5	5	N/A	21
Publication Rate	6.6	9.8	N/A	7.428571

Note: The publication rates shown in this table are mean averages of the number of publications over a specified duration of time. No consideration was given to the distribution of publications in specific years. Source: Web of Science, NIH RePORTER.

Yuan published more original articles in the post-NDPA period than in the pre-NDPA period. Interestingly, Yuan noted that her NDPA research was resulting in a slower rate of publication because it was a completely new project and a high-risk project. She explained that there is always a publishing lag and that researchers do not start publishing immediately after receiving funding. Although six publications were attributed to NDPA funding, Yuan stated that none of her current publications pertain to her NDPA research.

Of the 49 articles Yuan published in the period after receiving the award, the publications attributed to NDPA funding are listed in Table 185.

Table 185. Publications Attributed to NDPA Funding (Yuan)

Title	Journal	Year Published
A critical role of eEF-2K in mediating autophagy in response to multiple cellular stresses	Autophagy	2009
Divergence from a dedicated cellular suicide mechanism: Exploring the evolution of cell death	Molecular Cell	2006
Identification of a Molecular Signaling Network that Regulates a Cellular Necrotic Cell Death Pathway	Cell	2008
Necroptosis as an alternative form of programmed cell death	Current Opinion in Cell Biology	2010
Neuroprotective strategies targeting apoptotic and necrotic cell death for stroke	Apoptosis	2009
Role of Protein Misfolding in DFNA9 Hearing Loss	Journal of Biological Chemistry	2010
The Jekyll and Hyde Functions of Caspases	Developmental Cell	2009

Source: Web of Science, NIH RePORTER.

b. Impact

1) Citation Analyses

Throughout his career, as of Fall 2010, Yuan's 131 original articles excluding reviews had been cited a total of 18,617 times. In the post-NDPA period, Yuan published Statistics on this publication set are shown in Table 186.

Table 186. Summary of Citation Analyses (Yuan)

Publication Set	Number of Citations	Age-Weighted Citation Rate (AWCR)	H-index
Full Career (131 pubs)	18,617	40.01	57
Pre-NDPA (26 pubs)	2,217	16.70	N/A
Post-NDPA (41 pubs)	740	14.45	N/A
Attributed to NDPA Funding (7 pubs)	134	N/A	N/A

Note: H-indices are only relevant for a researcher's full career. The "Attributed to NDPA Funding" publication set includes all original publications. Source: Web of Science, NIH RePORTER.

2) Journal Impact Factors

Yuan published 33 publications in twenty-five different sources in the pre-NDPA time period and 49 publications in twenty-nine different sources in the post-NDPA time period. Detailed data on Yuan's most published-in journals for the pre- and post-NDPA time periods are shown in Table 187 and Table 188, respectively.

Table 187. Most Published-in Journals in the Pre-NDPA Period, 2001-2005 (Yuan)

Number of Publications	Source	2008 Eigenfactor score	Eigenfactor Percentile
3	Cell Death and Differentiation	0.06284	96.84
3	Journal of Neuroscience	0.521789	99.87
2	Bioorganic & Medicinal Chemistry Letters	0.072746	97.51
2	Journal of Biological Chemistry	1.32919	99.96
2	Neuron	0.28702	99.62
2	Oncogene	0.259466	99.54

Source: Eigenfactor.org, Journal names came from Web of Science

Table 188. Most Published-in Journals in the Post-NDPA Period, 2006-2010 (Yuan)

Number of Publications	Source	2008 Eigenfactor Score	Eigenfactor Percentile
5	Journal of Biological Chemistry	1.32919	99.96
4	Bioorganic & Medicinal Chemistry Letters	0.072746	97.51
4	Cell Death and Differentiation	0.06284	96.84
3	Autophagy	0.013479	83.82
3	Journal of Cell Biology	0.247793	99.47
3	Proceedings of The National Academy of Sciences of The United States of America	1.69817	99.99

Source: Eigenfactor.org, Journal names came from Web of Science

In the pre-NDPA period, 21 of Yuan's 33 publications, 63.64%, were in journals at or above the 98th percentile (Table 189). In the post-NDPA period, 27 of 49 publication, 55.10%, were in journals of the same caliber. Four of Yuan's seven NDPA-attributed publications had Eigenfactor values above the 98th percentile.

Table 189. Publications in Journals with Eigenfactor Values ≥ 98 Percentile (Yuan)

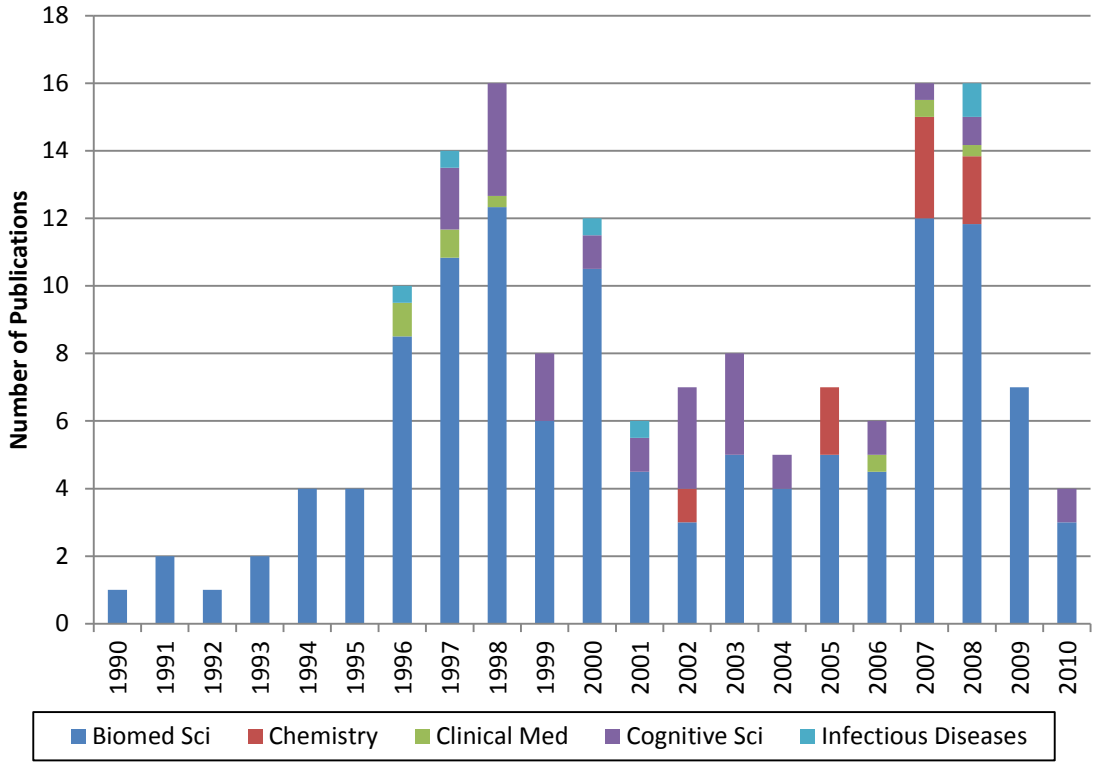
Publication Set	Number of Publications	Percentage of Publications
Pre-NDPA (33 pubs)	21	63.64%
Post-NDPA (49 pubs)	27	55.10%
Attributed to NDPA Funding (7 pubs)	4	57.14%

Note: *Eigenfactor* score percentiles are based on 2008 *Eigenfactor* scores, Source: Publication data are from Web of Science, *Eigenfactor* percentiles are from Eigenfactor.org

c. Interdisciplinarity

1) Body of Knowledge of Publication Set

Yuan's 156 publications over the duration of her career can be categorized into a total of five different macro-disciplines. She published in four macro-disciplines over her 33 pre-NDPA publications and five macro-disciplines over her 49 post-NDPA publications. The distribution of Yuan's publications into macro-disciplines for the full length of her career is shown in Figure 76.



Note: If a publication is representative of multiple macro-disciplines, the macro-disciplines are displayed as fractions of one. Source: Web of Science

Figure 76. Distribution of Publications into Macro-disciplines over Time (Yuan)

Yuan published primarily in Biomedical Science throughout her career with her work in programmed cell death.

2) Body of Knowledge Cited

Yuan cited sixteen different macro-disciplines in the 7,465 references of her 156 career publications. This included fourteen different macro-disciplines in the 1,746 references of her 33 pre-NDPA publications and twelve macro-disciplines in the 2,360 references of her 49 post-NDPA publications.

3) Integration and Specialization Scores

For the full publication dataset of the Pioneers, the mean I scores is 0.572 and the mean S score is 0.486. The Integration and Specialization scores for Yuan are shown in the table in Table 190.

Table 190. Integration and Specialization Scores (Yuan)

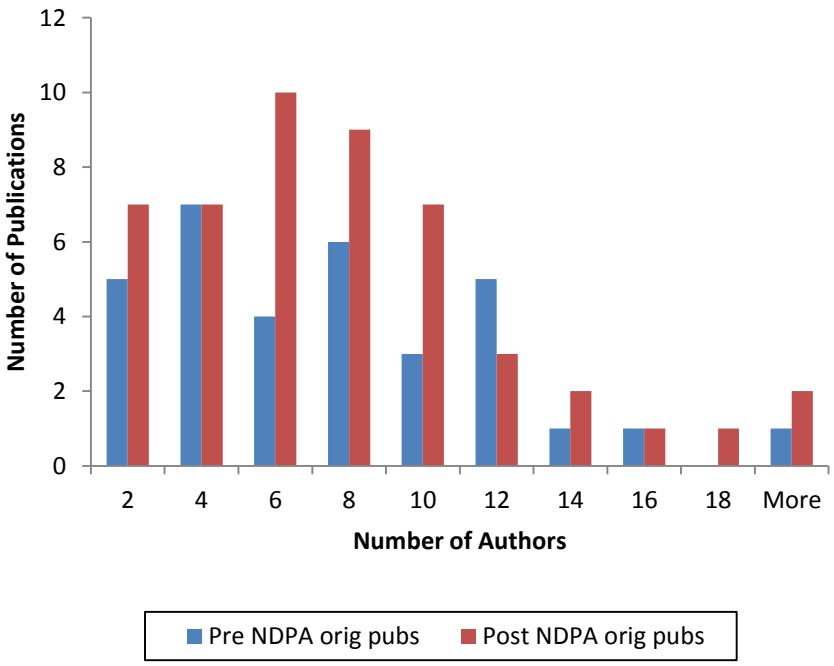
	Full Career (7465 cited references)	Pre-NDPA (1746 cited references)	Post-NDPA (2360 cited references)
Integration	0.370	0.393	0.392
Specialization	0.661	0.605	0.662

Source: Publication data are from Web of Science, scores were calculated using Vantage Point.

Compared to the other Pioneers, Yuan is a "Disciplinarian" for all three time periods.

d. Collaboration

The median number of total authors in Yuan's publication set was six. In the pre- and post-NDPA periods, this median was seven. A comparison of the pre- and psot-NDPA distributions of the total number of authors can be seen in Figure 77.



Source: Web of Science

Figure 77. Distribution of Number of Authors in Original Publication Set (Yuan)

The number of unique authors in a researcher's publishing network is another metric that captures collaboration patterns. Yuan has published with approximately 533 researchers throughout her career. She co-authored with 148 unique researchers in the pre-NDPA period and 276 unique researchers in the post-NDPA period. Over her seven

NDPA-attributed publications, she co-authored with 11 unique researchers. In her interview, Yuan indicated that she had begun to collaborate with immunologists for her NDPA research.

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.[1]

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.

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[1] Leydesdorff, Loet, and Ismael Rafols. 2009. "A Global Map of Science Based on the ISI Subject Categories." *Journal of the American Society for Information Science and Technology* 60(2), 348–362.

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.