15-161
February 9, 2015

Funding Breakthrough Research at the National Institutes of Health

Pierre Azoulay

On December 1, 2014, Dr. Joan Smith, Director of the Center for Scientific Review at the National Institutes of Health (NIH), rushed into the boardroom where her top deputies were already assembled. "Thanks for coming in on such a short notice," she said, "This is now top priority for everyone. I want all hands on deck."

Dr. Smith had called an emergency meeting after a grueling session with her boss, Dr. Francis Collins, the Director of the NIH. He had made it clear he was tired of leading an agency accused of being hostile to high-risk, "transformative" research. As the primary US government organization and the single largest funder for health-related research, the NIH had been faulted by many—from journalists to rank-and-file academics to policymakers in the halls of congress—for the "creativity deficit" in American science. The slow and imperfect peer review process was blamed for limiting funding to only the most incremental, safe proposals. (See **Exhibit 1** for a sampling of media reports on this topic.)

Both Dr. Collins and Dr. Smith knew the criticisms, though often lacking concrete evidence,[1] contained a kernel of truth: most NIH grants were relatively short-term (three to five years), and funded investigators had to file thorough annual reports, which grant officers carefully combed through in an effort to make sure grantees delivered on the aims of their proposals. In this setting, meandering exploration was a risky choice for any scientist, and bordered on career suicide for an untenured faculty member.

[1] A recent analysis of the scores used by NIH's funding committees to rank research proposals showed that these scores were strongly correlated with future research success (Li and Agha 2014).

This case was prepared by Professor Pierre Azoulay. Pierre Azoulay is the Sloan Distinguished Associate Professor of Technological Innovation, Entrepreneurship, and Strategic Management. This case is fictitious, with the exception of certain details that are sourced. Jane Wu and Cate Reavis provided helpful suggestions and editorial assistance.

Dr. Smith understood exactly why she had been called into the director's office: her center oversaw the workings of NIH's massive peer review operation. Dr. Collins was counting on her to propose a solution. However, he was not after some pie-in-the-sky grand plan to "revolutionize"—or even abandon—peer review. Instead, the proposed solution needed to be a credible, implementable response to the more thoughtful critiques of the agency.

Given just two weeks to draft the proposal, Dr. Smith knew there was no time to waste. With grants totaling over $30 billion per year, the NIH played a key role in shaping the rate and direction of biomedical research. At the same time, the NIH had evolved into a large, complex organization. Thus, any change to the review process would be scrutinized by many, both inside and outside the agency.

As Dr. Smith scanned the anxious faces around the room, she knew that these coming weeks were going to be the biggest test of her career.

Background on the National Institutes of Health (NIH)

The National Institutes of Health (NIH) was founded in 1887 with the goals of fostering innovative scientific research and supporting high-level training of the scientific workforce in order to protect and improve human health. In 2014, the NIH comprised 27 Institutes or Centers that were typically organized around body systems (e.g., the National Heart, Lung, and Blood Institute), or disease areas (e.g., the National Cancer Institute). Each institute received its own Congressional appropriation and was responsible for funding research that was potentially relevant to its mission (see **Exhibit 2**).[2]

Eighty percent of the budget was usually allocated to extramural funding, i.e., competitive grants awarded to researchers working for public and private universities, academic medical centers, and other research institutions. NIH extramural funding was awarded through a large number of distinct grant mechanisms, each designed to accomplish a specific objective.[3] The common thread that ran through all of NIH's funding activities was the belief that scientific inquiry should be driven from the bottom up, with individual scientists proposing innovative research programs that were then evaluated by a panel of volunteer experts from related fields.[4] Imitated by so many funding agencies around the world to the point of appearing unremarkable, the twin principles of investigator initiative and peer review were nothing short of revolutionary when the current system was put in place shortly after World War II.[5]

[2] For example, the National Institute for Mental Health (NIMH), the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Allergy and Infectious Diseases (NIAID), etc.

[3] For instance, F grants were fellowship grants used to fund pre-doctoral and post-doctoral fellows; T grants were training grants; P grants were program grants for large group of investigators; K grants were grants specifically targeted to young investigators, etc.

[4] The NIH regularly issues requests for proposals on its priority areas, but investigators are free to submit applications on unsolicited topics.

[5] Azoulay et al. 2013.

The most important grant mechanism was the R01, a project-based, renewable research grant which constituted 50% of all extramural expenditures. With an average award size of $1.7 million spread over three to five years, the R01 served as the primary funding source for most academic laboratories in the United States. In 2014, the NIH had received 51,073 applications for research project grants across all its component institutes and 9,241 of these had been awarded—a success rate equal to 18.1%. But this figure hid a great deal of heterogeneity. The success rate for new grant applications at the National Cancer Institute, for example, was only 13.4%.[6]

The Grant Application Process

All grant applications went through a similar process (see **Exhibit 3**):

Assignment to study sections. Each proposal was assigned to a committee comprised of scientific peers, known as a study section. Each study section was organized around a scientific topic (for example, "Behavioral Genetics and Epidemiology" or "Cellular Signaling and Regulatory Systems") and was responsible for evaluating the quality of applications in its area. Study sections reviewed grant applications from multiple disease areas as long as they shared similar scientific underpinnings (see **Exhibit 4**).

Initial scientific review. Three members of the study section, who focused on scientific and technical merits rather than other factors such as the amount of funding requested, reviewed each proposal. NIH emphasized five main criteria for its reviewers:

1. Significance: Did the project address an important issue?
2. Approach: Was the methodology sound?
3. Innovation: Was the research novel?
4. Investigators: Were the skills of the research team well matched to the project?
5. Environment: Was the lab or research location conducive to project success?

Full study section review. Grants with the highest initial review scores (typically the top half) were discussed in a full study section meeting. After deliberations, each member anonymously assigned a final score,[7] and initial reviewers were allowed to revise their evaluations. The overall score for the proposal (called the "priority score" in NIH lingo) was the average across all members of the study section. To make priority scores comparable across study sections, they were normalized through the assignment of percentile rankings.

Funding decision. Once a study section evaluated an application, it was then routed to one of NIH's 27 institutes. Within each institute, the funding rule was mechanical: an institute was required to fund

[6] Office of Extramural Research (OER), Division of Statistical Analysis and Reporting (DSAR), http://www.report.nih.gov, Table #206.

[7] The applications are typically scored on a scale of 1.0 (best) to 5.0 (worst) with 0.1 increments.

the applications it was assigned in the order of their percentile rank until its budget had been exhausted.[8] The lowest score that received funding was known as an institute's "payline." If a proposal was not funded in a given grant cycle, it could be amended (using feedback from the study section) and resubmitted up to two times.

Over the past 10 years, overall funding had declined in inflation-adjusted terms. As a result, even established scientists often found themselves unable to continue operating their laboratories. Disgruntled and demoralized, they tended to lash out against the funding machine they deemed responsible for grinding their research efforts to a halt. At its best, however, the R01 peer review system provided high-powered incentives to individual scientists while maintaining intellectual freedom. Judged over a long period of time, the system had been immensely successful: NIH had funded research that expanded societal understanding of the human body and its interaction with the environment. Examples included novel vaccines, pharmaceutical cures for multiple types of cancer, and research that had greatly reduced the number of deaths from cardiovascular diseases.[9]

NIH's Funding Practices and Scientific Risk-taking

Back in her office, Dr. Smith read through a batch of rejected R01 applications. She wondered whether the institution that had served the biomedical research community so well during 20th century would prove itself ill-suited for the challenges of the 21st century. Did NIH's funding practices tend to reward incremental research at the expense of work that could be more innovative?

A knock at her door interrupted her thoughts; her assistant had found a copy of an old article she had requested. The article detailed the story of Mario Capecchi, a scientist from the University of Utah, who in 1980 had sought R01 funding with a grant proposal outlining three distinct projects. The NIH peer-reviewers liked the first two as they built on Capecchi's past research efforts, but they were unanimously negative towards the third project, in which he proposed to develop gene targeting in mammalian cells. They deemed the probability that the newly introduced DNA would find its matching sequence within the host genome to be vanishingly small, and the experiment not worthy of pursuit. The NIH still funded the grant, but strongly recommended that Capecchi drop the third project. The scientist later explained that despite this unambiguous advice, he chose to put almost all his efforts into the third project. "It was a big gamble," Capecchi later admitted. "Had I failed to obtain strong supporting data within the designated time frame, our NIH funding would have come to an abrupt end and we would not be talking about gene targeting today."[10]

Fortunately, within four years, Capecchi and his team obtained strong evidence for the feasibility of gene targeting in mammalian cells, and the grant was renewed enthusiastically in 1984. Dispelling any

[8] Institute directors have the discretion to fund applications out of order if, for example, they are especially important to the institute's mission. These exceptions appeared to be rare (Jacob and Lefgren 2011).

[9] Sampat and Lichtenberg 2011.

[10] Capecchi 2008.

doubt that he had misinterpreted the feedback from reviewers, the critique for the 1984 competitive renewal stated, "We are glad that you didn't follow our advice." The story did not stop there. In 2007, Capecchi shared the Nobel Prize for developing the techniques behind the knockout mouse. Such mice have allowed scientists to learn the roles of thousands of mammalian genes and have provided laboratory models of human afflictions for testing therapies.

Dr. Smith remembered Capecchi's story very well. The scientist had been undeterred by his peers' advice to "play it safe," and eventually saw his ideas prevail. But was this heroic story typical? Dr. Smith feared that scientists like Capecchi were the exception rather than the norm. NIH's study sections put a great amount of weight on preliminary results when evaluating grant applications. Over time, this had led to a situation in which grants recognized competent investigations that had already been concluded, rather than serving as inputs into the production of novel research results. The danger was that, in their eagerness to step onto (or stay ensconced in) the funding treadmill, NIH-funded researchers were encouraged to pursue relatively safe avenues that built directly on previous results, at the expense of truly exploratory research.

An Alternative Funding Model: The Howard Hughes Medical Institute (HHMI) Medical Investigator Program

The HHMI, a non-profit medical research organization, played a powerful role in advancing biomedical research and science education in the United States. HHMI committed almost $700 million a year to biomedical research with a goal of pushing the boundaries of knowledge in some of the most important areas of biological research. Each year, HHMI selected and funded a group of high-potential researchers that, once selected, continued to be based at their home institutions, leading a research group of 10 to 25 students, postdoctoral associates and technicians. The program urged its investigators to take risks, explore unproven avenues, and embrace the unknown—even if it meant courting failure.

HHMI's award cycles were long (five years), and typically renewed at least once; the review process provided detailed, high-quality feedback to the researcher; and, the program selected "people not projects," which allowed (and in fact encouraged) the quick reallocation of resources to new approaches when the initial ones proved unfruitful. In contrast, NIH's typical R01 grant cycle lasted three years, and grant renewal was not forgiving of failure. (See **Exhibits 5** and **6** for a comparison between the main features of the funding process at NIH and HHMI, respectively.)

At the time of the second review—typically ten years after the initial appointment—HHMI investigators were at risk of losing their coveted status if a jury of elite scientists was not sufficiently impressed with their accomplishments. Even upon termination, however, HHMI put in place a two-year phase-down period during which researchers continued to be funded, allowing them to search for alternative sources of funding without having to close down their laboratory.

The contrast between HHMI's and NIH's funding models naturally led to the question of which approach resulted in a higher rate of exploration? An independent academic study, published in 2011,

hinted at the superiority of HHMI's funding practices.[11] It found that HHMI investigators published more highly cited papers after their award (see **Exhibit 7**), but also "flopped" more often than comparable NIH-funded scientists selected as controls. Moreover, HHMI investigators used more novel keywords in their research after their HHMI appointment, consistent with the hypothesis that the program allowed them to explore new research themes they would not otherwise have followed.

Though the study had become exhibit one for the argument in favor of a radical reform of NIH's approach to peer review, the agency's most vociferous critics often failed to read beyond the abstract and the top-line results. Yet, it was not difficult to poke holes in the study's design. First, it was not a randomized controlled trial, usually considered the "gold standard" for program evaluation. Second, the HHMI investigators in the study, just like their NIH-funded controls, were often running large, well-financed laboratories. Yet, because of incomplete budget data, the study's authors were unable to break down their results by lab size. As a result, it was difficult to conclude whether it was the funding itself, rather than the manner in which it was used in program design (e.g., "people not projects," long term horizon, rich feedback, etc.) that explained the apparent superiority of the HHMI program over NIH's traditional funding practices.

Finally, HHMI selected investigators at the rate of about 20 per year. In contrast, focusing only on the flagship R01 grant, NIH funded on the order of 2,000 new investigators every year. Among NIH staff, there was great skepticism that HHMI-style peer review practices could be scaled up to tackle the volume of grant applications typically processed by a public funding agency.

Public Sector Alternatives

For many decades, the need to encourage high-risk scientific exploration had been a recurring theme for all research agencies within the US federal government. A number of public sector attempts had been made to design research programs that encouraged scientific risk-taking, including:

NIH's MERIT awards. Initiated in 1987, the MERIT (Method to Extend Research in Time) R37 Award program extended funding for up to five years (three years, however, was more typical) to a select number of NIH-funded investigators "who have demonstrated superior competence, outstanding productivity during their previous research endeavors and are leaders in their field with paradigm-shifting ideas." The specific details varied across NIH's component institutes, but the essential feature of the program was that only researchers holding an R01 grant in its second or later cycle were eligible. Further, the application for renewal had to score in the top percentile in a given funding cycle. A particular R01 grant could receive MERIT status only once.

NIH Director's Pioneer Awards. Perhaps stung by the recent attention garnered by the HHMI investigator program, NIH sought to emulate its success by creating a grant mechanism, the NIH Director's Pioneer Award, which espoused the same "transformative" rhetoric. Every year since

[11] Azoulay et al. 2011.

2006, NIH selected a cohort of approximately 15 scientists "who propose pioneering—and possibly transforming approaches—to major challenges in biomedical and behavioral research." In contrast to HHMI investigator status, however, Pioneer Award status was not renewable.

NIH's Intramural Campus. Approximately 10% of the overall NIH budget was dedicated to the intramural research program. This program directly supported about 6,000 scientists working within the federal laboratories on NIH campuses. The main campus in Bethesda, Maryland was also home to the largest hospital in the world exclusively dedicated to clinical research—the NIH Clinical Center. The intramural program provided long-term funding and considerable intellectual freedom with the intention of supporting high-risk/high-reward research that would be difficult to support in the broader research community through the extramural program.[12] While the intramural program was responsible for numerous groundbreaking discoveries in the 1960s and 1970s, critics inside and outside the agency argued that its quality had slowly deteriorated. In particular, they pointed out that the rigidity in pay scales and promotion policies (intramural scientists were federal employees) made it extremely difficult to hire or retain top investigators.[13]

DARPA. The Defense Advanced Research Projects Agency (DARPA) was an agency of the United States Department of Defense (DoD) responsible for the development of new technologies for use by the military. DARPA was responsible for funding the development of many technologies which had had a major effect on the world, including the early Internet, computer networking, and NLS—the first hypertext system. DARPA had greater independence from the government than more conventional military R&D organizations and its officials reported directly to senior DoD management. Three features of DARPA were noteworthy. First the agency was small and flexible, presenting itself as "100 geniuses connected by a travel agent."[14] Second, it prominently portrayed itself as accepting of failure "if the payoff from potential success is great enough."[15] Third, DARPA historically focused not on incremental but rather radical innovation. It emphasized high-risk investment, moved from fundamental technological advances to prototyping, and then handed off the production stage to the armed services or the commercial sector.[16]

Towards a Grant Mechanism for "Breakthrough Research"

As she contemplated the enormity of the task before her, Dr. Smith knew that her options were heavily constrained by NIH's existing structure, as well as by its distinctive culture. The challenge was to come up with a proposal that was audacious enough to meet the challenge head-on, yet still politically feasible

[12] NIH 2009.

[13] Shapiro et al. 1988.

[14] Nichols 2009.

[15] Bonvillian 2006.

[16] Bonvillian 2006.

for there were sure to be many proponents of the status quo. With her team she was planning to develop a blueprint for a novel grant mechanism, tentatively named "R99."

Dr. Smith knew the proposal needed to clearly articulate why NIH's traditional practices would benefit from increased experimentation, and why previous attempts at solving the problem had not been successful. As the comparison to HHMI could not be avoided, her team would also need to explain their decisions as to what attributes, if any, NIH should import from the alternative models.

The design of the R99 award needed to be well thought-out along multiple dimensions:

Eligibility. Would every scientist be able to apply? If not, what would be the criteria for individual eligibility? Would R99 select projects, as was traditional for NIH, or people, as was the practice at HHMI?

Review Process. How would applications be evaluated? Should they be reviewed in NIH's standing study sections, or by a different set of committees empaneled for this precise purpose? If the latter, what was the profile of a good committee member? What criteria should committee members use to rank proposals? Should the scores of committee members be averaged or aggregated taking into account the level of support or skepticism for a particular proposal?

Timeline and Renewal. Would the grant cycle be the traditional three to five years, or a different length of time? Would the R99 be renewable? If so what should be the criteria for renewal?

Evaluation. If the R99 were implemented, how would its success be evaluated? What was the right benchmark? What was the right metric, or set of metrics?

With only eleven days left before her presentation to Dr. Collins and the rest of NIH leadership, an event that could determine the future of her career, Dr. Smith poured herself another cup of coffee and settled in for a long night ahead.

Exhibit 1 Sampling of Recent Media Articles

Source: Kaplan 2005; Kolata 2009; McKnight 2009; Ioannidis 2011; Nicholson and Ioannidis 2012; McNeil 2014.

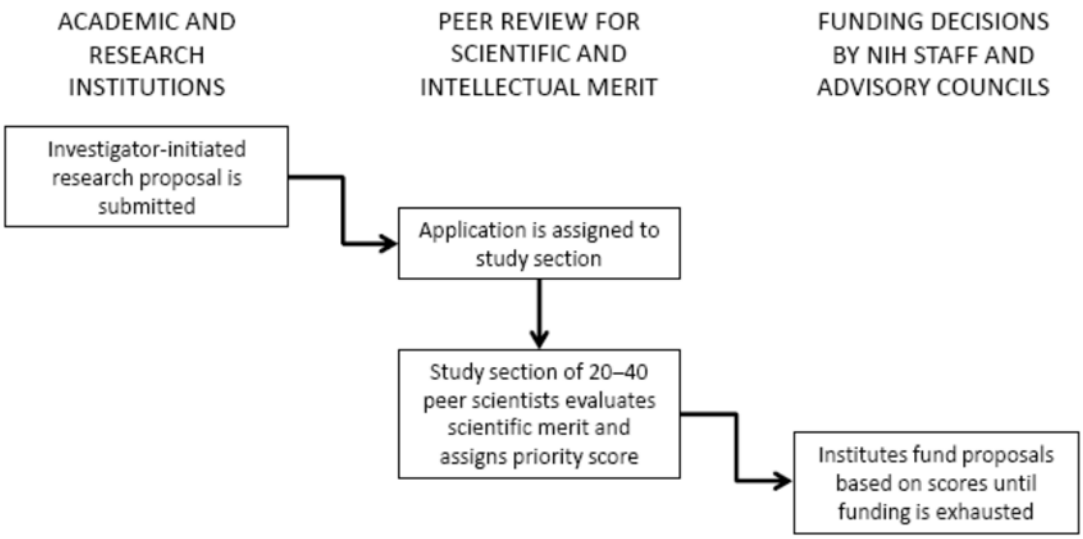
Exhibit 2 NIH Component Institutes

Institute	Abbrev.	Established	Avg. Budget*
National Cancer Institute	NCI	1937	$4,019,793
National Heart, Lung, and Blood Institute	NHLBI	1948	$2,489,629
National Institute of Allergy and Infectious Diseases	NIAID	1948	$2,070,634
National Institute of Dental and Craniofacial Research	NIDCR	1948	$325,861
National Institute of Mental Health	NIMH	1949	$1,378,636
National Institute of Diabetes and Digestive and Kidney Diseases	NIDDK	1950	$1,491,613
National Institute of Neurological Disorders and Stroke	NINDS	1950	$1,244,241
National Eye Institute	NEI	1968	$562,126
National Institute on Alcohol Abuse and Alcoholism	NIAAA	1970	$423,341
National Institute on Drug Abuse	NIDA	1974	$960,637
National Institute of Arthritis and Musculoskeletal and Skin Diseases	NIAMS	1986	$458,273
National Institute of Child Health and Human Development	NICHD	1962	$1,043,447
National Institute of Environmental Health Sciences	NIEHS	1969	$557,645
National Institute on Aging	NIA	1974	$702,184
National Institute on Deafness and Other Communication Disorders	NIDCD	1988	$347,646
National Institute of General Medical Sciences	NIGMS	1962	$1,629,056
National Human Genome Research Institute	NHGRI	1989	$375,451
National Institute of Biomedical Imaging and Bioengineering	NIBIB	2000	$316,430
National Library of Medicine	NLM	1956	$229,442
National Institute of Nursing Research	NINR	1986	$106,880
National Institute on Minority Health and Health Disparities	NIMHD	1993	$228,287

*Over the 1980-2005 time period, In thousands of 2010 dollars (amounts deflated by the Biomedical R&D PPI)

Source: Casewriter.

Exhibit 3 Overview of the Extramural Research Review and Funding Process



Source: Azoulay et al. (2013).

Exhibit 4 NIH Study Sections

Study Section	Description	Study Section	Description	Study Section	Description
ACE	AIDS Clinical Studies and Epidemiology	CPDD	Child Psychopathology and Developmental Disabilities	MSFA	Macromolecular Structure and Function A
ACTS	Arthritis, Connective Tissue and Skin	CRFS	Clinical Research and Field Studies of Infectious Diseases	MSFB	Macromolecular Structure and Function B
ADDT	AIDS Discovery and Development of Therapeutics	CSRS	Cellular Signaling and Regulatory Systems	MSFC	Macromolecular Structure and Function C
AICS	Atherosclerosis and Inflammation of the Cardiovascular System	DBD	Developmental Brain Disorders	MSFD	Macromolecular Structure and Function D
AIP	AIDS Immunology and Pathogenesis	DDNS	Drug Discovery for the Nervous System	MSFE	Macromolecular Structure and Function E
AMCB	AIDS Molecular and Cellular Biology	DDR	Drug Discovery and Mechanisms of Antimicrobial Resistance	MTE	Musculoskeletal Tissue Engineering
ANIE	Acute Neural Injury and Epilepsy	DEV1	Development - 1	NAED	NeuroAIDS and other End-Organ Diseases
AOIC	AIDS-associated Opportunistic Infections and Cancer	DEV2	Development - 2	NAL	Neurotoxicology and Alcohol
APDA	Adult Psychopathology and Disorders of Aging	DIRH	Dissemination and Implementation Research in Health	NAME	Neurological, Aging and Musculoskeletal Epidemiology
ASG	Aging Systems and Geriatrics	DMP	Drug Discovery and Molecular Pharmacology	NANO	Nanotechnology
AUD	Auditory System	DPVS	Diseases and Pathophysiology of the Visual System	NCF	Neurogenesis and Cell Fate
BACP	Bacterial Pathogenesis	DT	Developmental Therapeutics	NCSD	Nuclear and Cytoplasmic Structure/Function and Dynamics
BBM	Biochemistry and Biophysics of Membranes	EBIT	Enabling Bioanalytical and Imaging Technologies	NDPR	Neurodifferentiation, Plasticity, Regeneration and Rhythmicity
BCHI	Biomedical Computing and Health Informatics	EPIC	Epidemiology of Cancer	NMB	Neurobiology of Motivated Behavior
BDMA	Biodata Management and Analysis	ESTA	Electrical Signaling, Ion Transport, and Arrhythmias	NNRS	Neuroendocrinology, Neuroimmunology, Rhythms and Sleep
BGES	Behavioral Genetics and Epidemiology	GCAT	Genomics, Computational Biology and Technology	NOIT	Neuroscience and Ophthalmic Imaging Technologies
BINP	Brain Injury and Neurovascular Pathologies	GDD	Gene and Drug Delivery Systems	NOMD	Neural Oxidative Metabolism and Death
BMBI	Biomaterials and Biointerfaces	GHD	Genetics of Health and Disease	NPAS	Neural Basis of Psychopathology, Addictions and Sleep Disorders
BMCT	Basic Mechanisms of Cancer Therapeutics	GMPB	Gastrointestinal Mucosal Pathobiology	NRCS	Nursing and Related Clinical Sciences
BMIO	Behavioral Medicine, Interventions and Outcomes	GVE	Genetic Variation and Evolution	NTRC	Neurotransporters, Receptors, and Calcium Signaling
BMIT-A	Biomedical Imaging Technology A	HAI	Hypersensitivity, Autoimmune, and Immune-mediated Diseases	ODCS	Oral, Dental and Craniofacial Sciences
BMIT-B	Biomedical Imaging Technology B	HBPP	Hepatobiliary Pathophysiology	PBKD	Pathobiology of Kidney Disease
BMRD	Biostatistical Methods and Research Design	HDEP	Health Disparities and Equity Promotion	PCMB	Prokaryotic Cell and Molecular Biology
BNVT	Bioengineering of Neuroscience, Vision and Low Vision Technologies	HIBP	Host Interactions with Bacterial Pathogens	PDRP	Psychosocial Development, Risk and Prevention
BPNS	Biophysics of Neural Systems	HM	Hypertension and Microcirculation	PMDA	Pathophysiological Basis of Mental Disorders and Addictions
BRLE	Biobehavioral Regulation, Learning and Ethology	HSOD	Health Services Organization and Delivery	PN	Pregnancy and Neonatology
BSCH	Behavioral and Social Consequences of HIV/AIDS	HT	Hemostasis and Thrombosis	PRDP	Psychosocial Risk and Disease Prevention
BSPH	Behavioral and Social Science Approaches to Preventing HIV/AIDS	ICER	Integrative and Clinical Endocrinology and Reproduction	PTHE	Pathogenic Eukaryotes
BTSS	Bioengineering, Technology and Surgical Sciences	ICI	Intercellular Interactions	RIBT	Respiratory Integrative Biology and Translational Research
BVS	Biology of the Visual System	ICP1	International and Cooperative Projects - 1	RPIA	Risk, Prevention and Intervention for Addictions
CADO	Cellular Aspects of Diabetes and Obesity	IHD	Immunity and Host Defense	RTB	Radiation Therapeutics and Biology
CAMP	Cancer Molecular Pathobiology	III	Innate Immunity and Inflammation	SAT	Surgery, Anesthesiology and Trauma
CASE	Cardiovascular and Sleep Epidemiology	INMP	Integrative Nutrition and Metabolic Processes	SBCA	Synthetic and Biological Chemistry A
CBSS	Cancer Biomarkers	IPOD	Integrative Physiology of Obesity and Diabetes	SBCB	Synthetic and Biological Chemistry B
CCHF	Cardiac Contractility, Hypertrophy, and Failure	IRAP	Infectious Diseases, Reproductive Health, Asthma and Pulmonary Conditions	SBDD	Skeletal Biology Development and Disease
CDD	Cardiovascular Differentiation and Development	ISD	Instrumentation and Systems Development	SBSR	Skeletal Biology Structure and Regeneration
CDIN	Chronic Dysfunction and Integrative Neurodegeneration	KMBD	Kidney Molecular Biology and Genitourinary Organ Development	SCS	Somatosensory and Chemosensory Systems
CDP	Chemo/Dietary Prevention	KNOD	Kidney, Nutrition, Obesity and Diabetes	SEIR	Societal and Ethical Issues in Research
CE	Cancer Etiology	LAM	Neurobiology of Learning and Memory	SMEP	Skeletal Muscle and Exercise Physiology
CG	Cancer Genetics	LCMI	Lung Cellular, Molecular, and Immunobiology	SMI	Sensorimotor Integration
CICS	Clinical and Integrative Cardiovascular Sciences	LCOM	Language and Communication	SPC	Mechanisms of Sensory, Perceptual, and Cognitive Processes
CIDO	Clinical and Integrative Diabetes and Obesity	LIRR	Lung Injury, Repair, and Remodeling	SPIP	Social Psychology, Personality and Interpersonal Processes
CIHB	Community Influences on Health Behavior	MABS	Modeling and Analysis of Biological Systems	SSPA	Social Sciences and Population Studies A
CII	Cancer Immunopathology and Immunotherapy	MBPP	Membrane Biology and Protein Processing	SSPB	Social Sciences and Population Studies B
CIMG	Clinical, Integrative and Molecular Gastroenterology	MCE	Molecular and Cellular Endocrinology	SYN	Synapses, Cytoskeleton and Trafficking
CLHP	Community-Level Health Promotion	MCH	Molecular and Cellular Hematology	TAG	Therapeutic Approaches to Genetic Diseases
CMAD	Cellular Mechanisms in Aging and Development	MEDI	Medical Imaging	TCB	Tumor Cell Biology
CMBG	Cellular and Molecular Biology of Glia	MESH	Biobehavioral Mechanisms of Emotion, Stress and Health	TME	Tumor Microenvironment
CMIA	Cellular and Molecular Immunology - A	MFSR	Motor Function, Speech and Rehabilitation	TPM	Tumor Progression and Metastasis
CMIB	Cellular and Molecular Immunology - B	MGA	Molecular Genetics A	TTT	Transplantation, Tolerance, and Tumor Immunology
CMIP	Clinical Molecular Imaging and Probe Development	MGB	Molecular Genetics B	UGPP	Urologic and Genitourinary Physiology and Pathology
CMIR	Cellular, Molecular and Integrative Reproduction	MIM	Myocardial Ischemia and Metabolism	VACC	HIV/AIDS Vaccines
CMND	Cellular and Molecular Biology of Neurodegeneration	MIST	Molecular and Integrative Signal Transduction	VB	Vector Biology
CNBT	Clinical Neuroimmunology and Brain Tumors	MNG	Molecular Neurogenetics	VCMB	Vascular Cell and Molecular Biology
CNN	Clinical Neuroscience and Neurodegeneration	MNPS	Molecular Neuropharmacology and Signaling	VIRA	Virology - A
CNNT	Clinical Neuroplasticity and Neurotransmitters	MONC	Molecular Oncogenesis	VIRB	Virology - B
CONC	Clinical Oncology	MRS	Musculoskeletal Rehabilitation Sciences	VMD	Vaccines Against Microbial Diseases
CP	Cognition and Perception			XNDA	Xenobiotic and Nutrient Disposition and Action

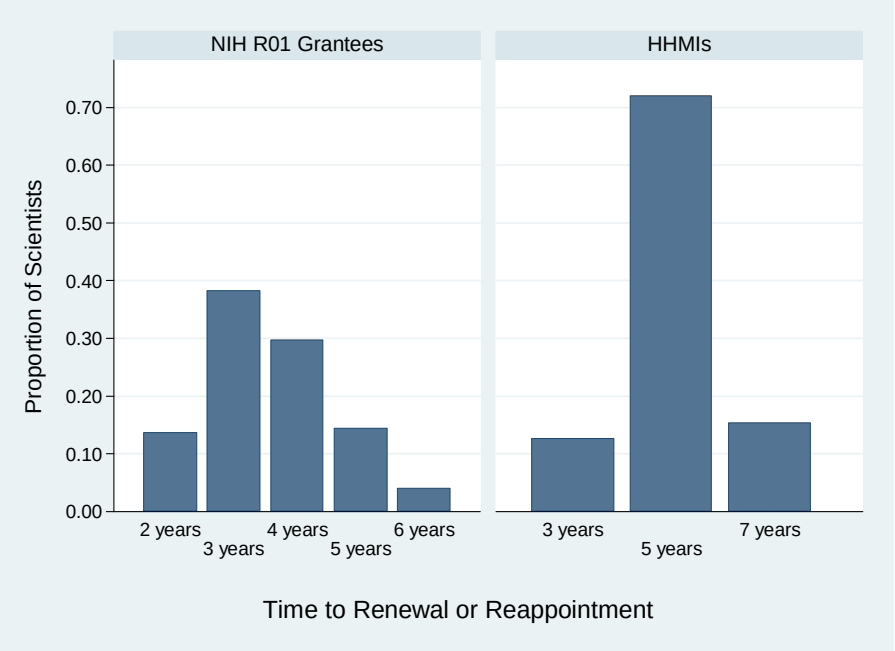
Source: NIH, Center for Scientific Review.

Exhibit 5 NIH R01 Grants vs. HHMI Appointments—Comparison of Salient Features

NIH R01 Grants	HHMI Investigator Program
3- to 5-year funding	5-year funding
first review is similar to any other review	first review is rather lax
funds dry up upon non-renewal	two-year phase-down upon non-renewal
some feedback in the renewal process	feedback from renowned scientists
funding is for a particular project	"people, not projects"

Source: Casewriter; Azoulay et al. (2011).

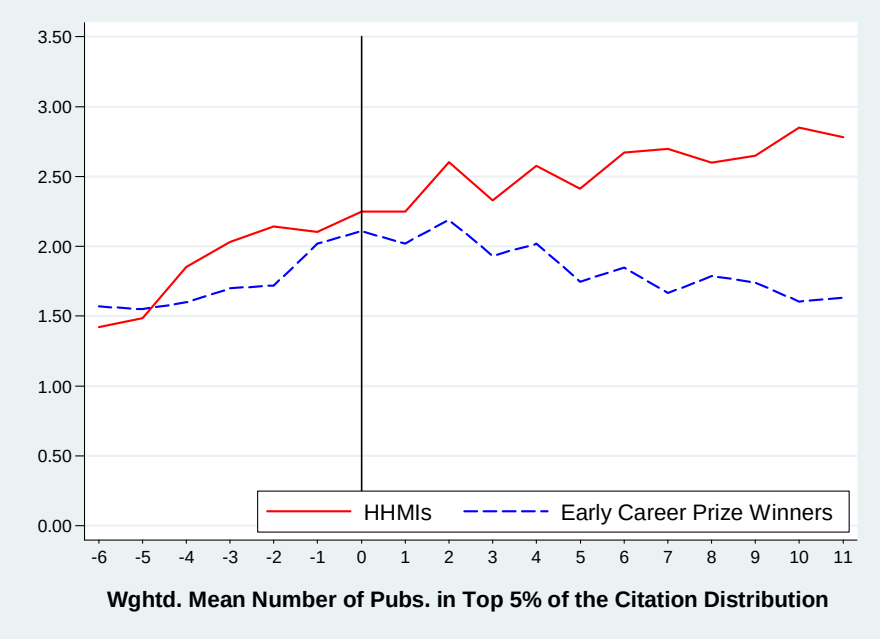
Exhibit 6 NIH R01 Grants vs. HHMI Appointments—Time Horizon



Note: NIH tabulations stem from the Compound Grant Applicant File (CGAF). The grants considered are R01 and equivalent whose first cycle began later than 1970, but earlier than 2002.

Source: Azoulay et al. (2011).

Exhibit 7 Dynamics of HHMI Appointment on the Number of Publications



Note: The dashed blue and solid red lines correspond to the average yearly number of articles in the Top 5% of the citation distribution for NIH-funded controls (all early career prize winners) and HHMI investigators, respectively. The averages for the control scientists are weighted by each researcher's inverse probability of selection into the HHMI program. Loosely, the graph depicts the difference between the change in outcomes for the HHMIs and for a pseudo-population of NIH-funded scientists matched on observables. A necessary condition for the plausibility of this exercise is that the treated and control groups display parallel output trends prior to appointment. This appears to be the case here. Interestingly, for three years after appointment, the outcomes for treated and control scientists continue to track each other closely. The graph even suggests that the control group (appropriately selected on observables) briefly outpaces the treatment group following the appointment, consistent with Manso's (2011) theory, which predicts both slower and more variable returns under an exploration incentive scheme. This difference is not statistically significant, however, which is perhaps unsurprising given the sample's relatively small size. HHMI investigators' output begins to diverge from that of the controls only four to five years after appointment.

Source: Azoulay et al. (2011).

References

Advancing Research In Science and Engineering. 2008. *Investing in Early-Career Scientists and High-Risk, High-Reward Research.* Cambridge, MA: American Academy of Arts & Sciences.

Azoulay, Pierre, Joshua Graff Zivin, and Gustavo Manso. 2011. "Incentives and Creativity: Evidence from the Academic Life Sciences." *RAND Journal of Economics* 42(3): 527-554.

Azoulay, Pierre, Joshua Graff Zivin, and Gustavo Manso. 2013. NIH Peer Review: Challenges and Avenues for Reform. *Innovation Policy and the Economy* (edited by Joshua Lerner and Scott Stern), 13: 1-21.

Bonvillian, William B. 2006 "Power Play: The DARPA Model and U.S. Energy Policy." *The American Interest* 2(2): 39-48.

Capecchi, Mario R. 2008. Response. S*cience* 319(5865): 900-1.

Jacob, Brian A., and Lars Lefgren. 2011. "The Impact of Research Grant Funding on Research Productivity." *Journal of Public Economics* 95(9-10): 1168-1177.

Kaplan, David. 2005. "How to Improve Peer Review at NIH." *The Scientist* 19(17): 10.

Kolata, Gina. 2009. "Grant System Leads Cancer Researchers to Play it Safe." *The New York Times*, June 28.

Ioannidis, John P.A. 2011. "Fund People Not Projects." *Nature* 477(7366): 529-531.

Li, Danielle. 2012. "Information, Bias, and Efficiency in Expert Evaluation: Evidence from the NIH." Working Paper, Harvard University.

Li, Danielle and Leila Agha. 2014. "Big Names or Big Ideas: Does Peer Review Select the Best Science?" Working Paper, Harvard University.

Manso, Gustavo. 2011. "Motivating Innovation." *Journal of Finance* 66(5): 1823-1860.

McKnight, Steven L. 2009. "Unconventional Wisdom." *Cell* 138(5): 817-819.

McNeil, Ben. 2014. "Is there a creativity deficit in science?" *arstechnica*, September 3. Retrieved from http://arstechnica.com/science/2014/09/is-there-a-creativity-deficit-in-science/

National Institutes of Health. 2009. "NIH Intramural Research at the Threshold of a New Era." Report, Bethesda, MD.

Nichols, Susan. 2009. "Overview." DARPA SBIR Presentation, Armed Forces Communications and Electronics Association.

Nicholson, Joshua M. and John P.A. Ioannidis. 2012. “Conform and Be Funded.” *Nature* 492(7427): 34-36.

Sampat, Bhaven N., and Frank R. Lichtenberg. 2011. “What Are the Respective Roles of the Public and Private Sectors in Pharmaceutical Innovation?” *Health Affairs* 30(2): 332-339.

Shapiro, Harold T. et al. 1988. “A Healthy NIH Intramural Program: Structural Change or Administrative Remedies?” Institute of Medicine, Division of Health Sciences Policy. Retrieved from http://www.nap.edu/catalog/9929.html