How Effective is Peer Review?

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NIH Priority Setting Meeting, September 22, 2015

We have two broad ways of encouraging innovation

"Pull" mechanisms: Reward innovations (e.g. patents)

- Benefit: gives people incentives to pursue highest potential projects
- Concern:
  - Distorts access to innovations afterward (high price of on patent drugs, etc.)
  - Only incentivizes commercially viable projects (less research in basic science, conditions important to people who can't afford to pay, etc.)

"Push" mechanisms: Subsidize innovations (e.g. grants, tax credits)

- Benefit: Resolves some issues with the above
- Concern: Can the government pick winners?

Today: Will talk about recent work in *Science* on the efficacy of NIH peer review.

Assessing the Efficacy of NIH peer review

Good peer review can be defined in many ways. We need:

1. **A notion of what good peer review means**
   - Give the best scores to the best projects
   - Give the best scores to the best projects that wouldn't be funded otherwise?
2. **Measures of what "best project" means**
   - Produces the most citations
   - Produces patents, drug candidates, medical devices, clinical trials, clinical protocols, etc.?
   - Leads to drugs and treatments that produce the most QALYs saved?

Research question: How well do scores predict outcomes?

Bottom Line: Peer review adds value

Percentile scores provide information about grant quality not available elsewhere.

- Among observably similar applicants, a 1 std dev improvement in percentile score predicts 16% more citations and 8% more publications.

Percentile scores predict high impact research

- Among observably similar applicants, a 1 std dev improvement in percentile score predicts 20% more high-impact publications and 15% more follow-on patents

What we do

1. **Start with more data**: all NIH-funded R01 grants from 1980-2008

2. **Track grant outcomes**
   - # Publications: all articles that acknowledge funding from a grant.
   - # of Citations: all citations to those publications, through 2013.
   - # Hit Publications: very highly cited publications
   - # Patents: all patents that acknowledge funding from a grant.
   - # Patents building off this grant: all patents that cite publications that acknowledge a grant

3. **Control for applicant characteristics** (does peer review predict outcomes among observably similar candidates?)
   - Past publications, citations, grant history
   - Institutional affiliation

Publication Outcomes

Step 1: NIH Grants → Publications

Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions

JAMES U. BOWIE,* JOHN F. REIDHAAR-OLSON, WENDELL A. LIM, ROBERT T. SAUER

An amino acid sequence encodes a message that determines the shape and function of a protein. This message is highly degenerate in that many different sequences can code for proteins with essentially the same structure and activity. Comparison of different sequences with similar messages can reveal key features of the code and improve understanding of how a protein folds and how it performs its function.

specific positions in a cloned gene and uses selections or screens to identify functional sequences. This approach has been used to great advantage for proteins that can be expressed in bacteria or yeast, where the appropriate genetic manipulations are possible (*3, 8–11*). The end results of both methods are lists of active sequences that can be compared and analyzed to identify sequence features that are essential for folding or function. If a particular property of a side chain, such as charge or size, is important at a given position, only side chains that have the required property will be allowed. Conversely, if the chemical identity of the side chain is unimportant, then many different substitutions will be permitted

46. We thank C. O. Pabo and S. Jordan for coordinates of the NH_2-terminal domain of λ repressor and its operator complex. We also thank P. Schimmel for the use of his graphics system and J. Burnbaum and C. Francklyn for assistance. Supported in part by NIH grant AI-15706 and predoctoral grants from NSF (J.R.-O.) and Howard Hughes Medical Institute (W.A.L.).

Patenting Outcomes

Step 1: NIH Grants → Patents

United States Patent [19]
Evans et al.

[11] **Patent Number: 4,820,816**
[45] **Date of Patent: Apr. 11, 1989**

[54] **3-TRIFUOROMETHYLSULFONYLOXY-SUBSTITUTED 1-CARBACEPHALOSPORINS AS INTERMEDIATES FOR ANTIBIOTICS**

[75] Inventors: **David A. Evans**, Concord; **Eric B. Sjogren**, Arlington, both of Mass.

[73] Assignee: **President and Fellows of Harvard College**, Cambridge, Mass.

[21] Appl. No.: **233,088**

[22] Filed: **Aug. 17, 1988**

Related U.S. Application Data

[62] Division of Ser. No. 18,668, Feb. 25, 1987, Pat. No. 4,778,884, which is a division of Ser. No. 761,647, Aug. 2, 1985, Pat. No. 4,643,737.

[51] **Int. Cl.**[4] **C07D 221/02**
[52] **U.S. Cl.** **540/205**; 544/316; 544/362
[58] **Field of Search** 540/205

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,673,737 6/1987 Evans et al. 540/205

FOREIGN PATENT DOCUMENTS

211540 2/1987 European Pat. Off. 540/205

OTHER PUBLICATIONS

Evans et al, Chem. Abst 104–5677b (1986).
Evans et al, Chem. Abst. 107–7004r (1987).
Evans et al, Tetrahedron Letters vol. 26, No. 32, pp. 3787–3790 (1985).

Primary Examiner—Donald G. Daus
Assistant Examiner—Cecilia Shen
Attorney, Agent, or Firm—William B. Scanlon; Leroy Whitaker

[57] **ABSTRACT**

7β-Acylamino-3-trifluoromethylsulfonyloxy-1-carba-3-cephem-4-carboxylic acid antibiotic compounds, esters and salts thereof, and the corresponding 7-amino and protected 7-amino 1-carbacephalosporins are provided. The 3-trifluoromethylsulfonyloxy-substituted 1-carbacephalosporins also are useful in a process for preparing 3-halo-1-carbacephalosporins which comprises reacting a 3-triflate ester with a lithium halide in an aprotic polar solvent.

5 Claims, No Drawings

3-TRIFUOROMETHYLSULFONYLOXY-SUBSTITUTED 1-CARBACEPHALOSPORINS AS INTERMEDIATES FOR ANTIBIOTICS

The United States government has rights in this invention by virtue of Grant No. GM-33328 awarded by the National Institutes of Health.

This application is a division of application Ser. No. 018,668, filed 2-25-87 now U.S. Pat. No. 478,884, which is a division of application Ser. No. 08/761,647, filed 8/2/85, now U.S. Pat. No. 4,673,737.

Follow on Patenting Outcomes

Step 1: NIH Grants → Publications

Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions

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specific positions in a cloned gene and uses selections or screens to identify functional sequences. This approach has been used to great advantage for proteins that can be expressed in bacteria or yeast, where the appropriate genetic manipulations are possible (*3, 8–11*). The end results of both methods are lists of active sequences that can be compared and analyzed to identify sequence features that are essential for folding or function. If a particular property of a side chain, such as charge or size, is important at a given position, only side chains that have the required property will be allowed. Conversely, if the chemical identity of the side chain is unimportant, then many different substitutions will be permitted

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Step 2: Publications → Patents

(12) **United States Patent**
Li et al.

(10) **Patent No.: US 6,867,006 B2**
(45) **Date of Patent: Mar. 15, 2005**

(54) **ANTIBODIES TO HUMAN CHEMOTACTIC PROTEIN**

(75) Inventors: **Haodong Li**, Gaithersburg, MD (US); **Steven M. Ruben**, Olney, MD (US); **Granger Sutton, III**, Columbia, MD (US)

(73) Assignee: **Human Genome Sciences, Inc.**, Rockville, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 230 days.

(21) Appl. No.: **10/141,965**

(22) Filed: **May 10, 2002**

WO	WO 96/38559	12/1996
WO	WO 96/40762	12/1996
WO	WO 97/15594	5/1997
WO	WO-98/44118	10/1998

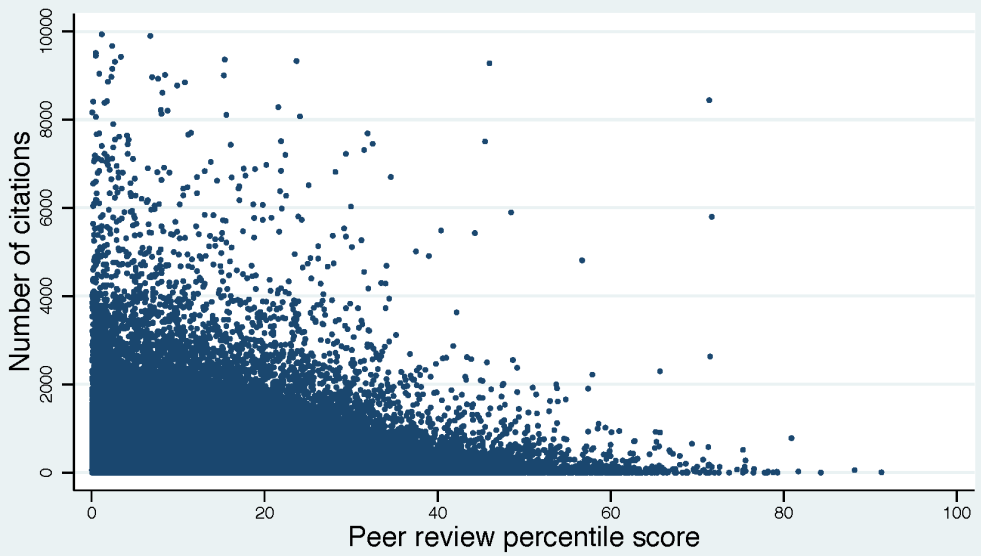
OTHER PUBLICATIONS

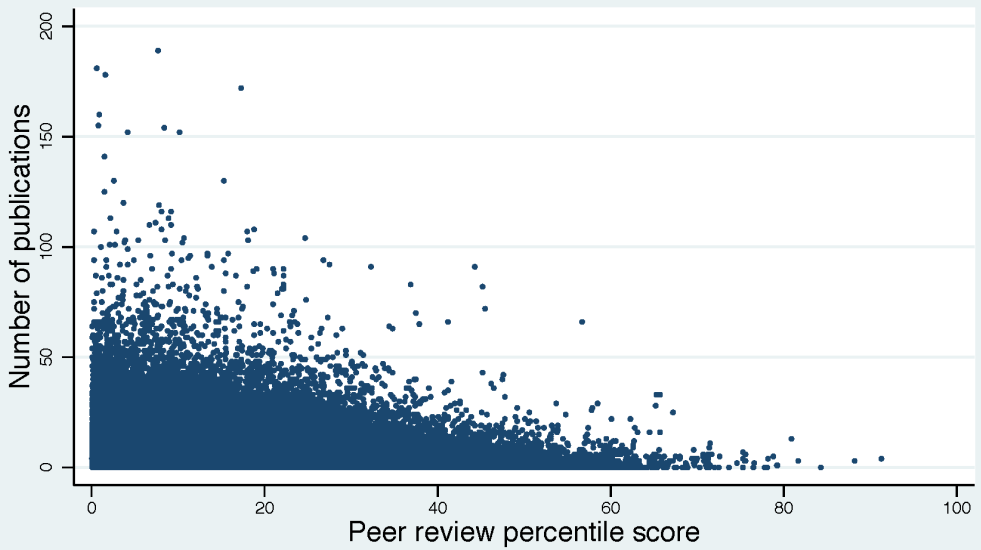
Beall, C.J., et al., "Conversion of Monocyte Chemoattractant Protein–1 into a Neutrophil Attractant by Substitution of Two Amino Acids," *J. Biol. Chem. 267*:3455–3459, American Society for Biochemistry and Molecular Biology, Inc. (1992).

Berkhout, T.A., et al., "Cloning, in Vitro Expression, and Functional Characterization of a Novel Human CC Chemokine of the Monocyte Chemotactic Protein (MCP) Family (MCP–4) That Binds and Signals through the CC Chemokine Receptor 2B," *J. Biol. Chem. 272*:16404–16413, American Society for Biochemistry and Molecular Biology, Inc. (Jun. 1997).

Bowie, J.U., et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science 247*:1306–1310, American Association for the Advancement of Science (1990).

Raw Correlation, Scores and Citations/Publications





Statistically significant relationship: 5.8 fewer citations for every 1pp increase in percentile rank.

This could mean:

- Reviewers are contributing unique insights about the quality of an application
- Reviewers are aggregating information that is available elsewhere.
- Reviewers are doing anything that is better than random.

Defining Value-Added in Peer Review

Value-added: Can peer review tell us something about the quality of an application we couldn't have figured out otherwise?

- No value added: "This person has a strong publication record so this current proposal is likely to be serious as well."
  - Might be true, but could figure that out from a CV
- Value added: "This is just more of the same and is less likely to have the same impact because we know it already."
  - Would be hard to figure out without reading the application or some kind of human review.

Quantifying Value-added

Raw Correlation

$$\text{Research Outcomes}_g = a_0 + a_1 \text{Score}_g + \text{Error}_g$$

- a_1 is the average change in future outcomes for a 1 unit increase in score (want this negative)

Value Added

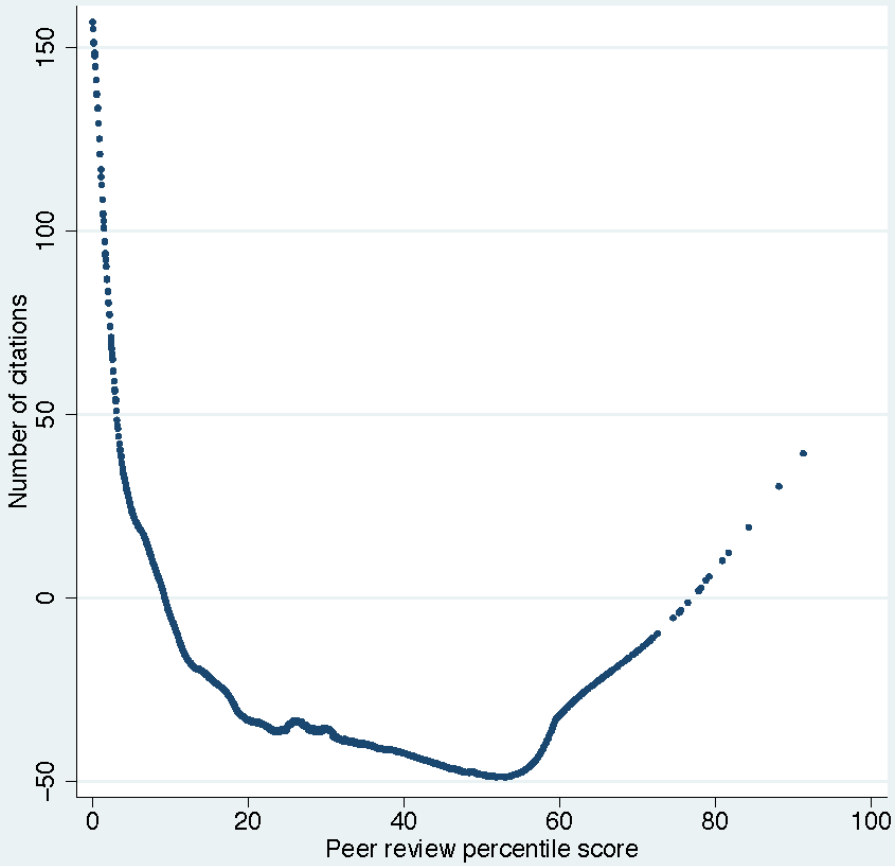
$$\text{Research Outcomes}_g = b_0 + b_1 \text{Score}_g + [\text{Applicant Characteristics}] + \text{Error}_g$$

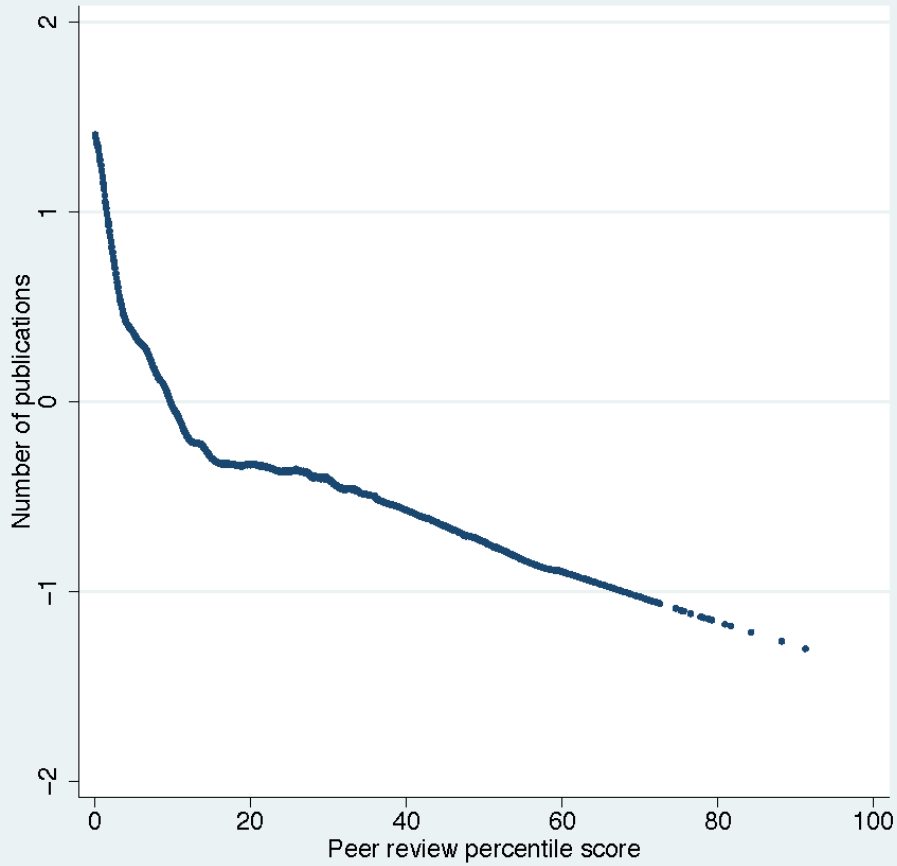
- Applicant Characteristics: publication history, grant history, degrees, age, institutional affiliation, etc.
- b_1 is the average change in future outcomes for a 1 unit increase in score – among **similar** applicants.

Applicant Characteristics

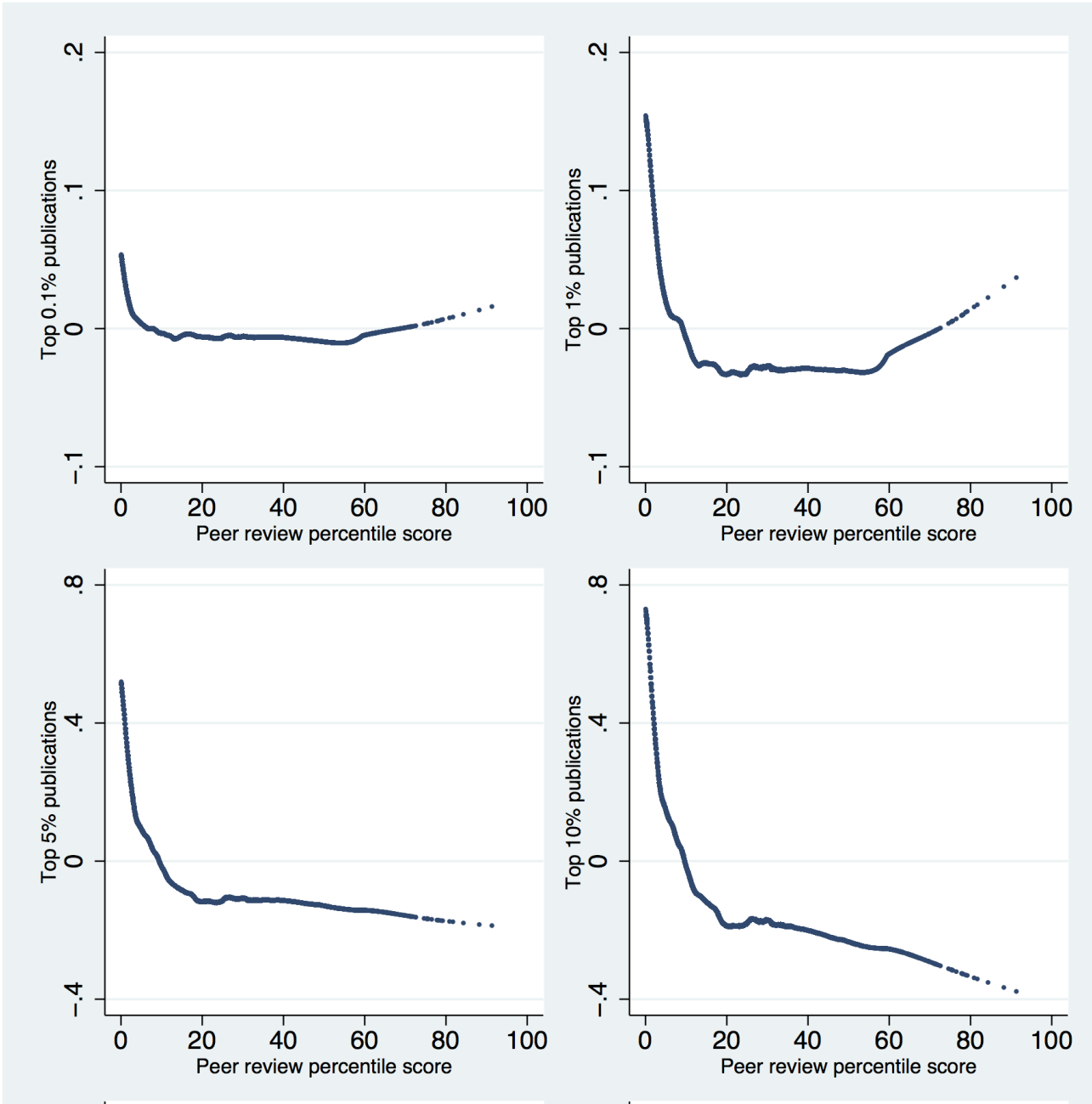
- **# Publications, past 5 years**
- **# of Citations, past 5 years**: all citations to date for those publications
- **# Hit Publications, past 5 years**: publications cited in top 0.1%, 1%, and 5% of the citation distribution for articles published the same year. Based on citations to date.
- Publication variables repeated for first/last author publications only.
- **Degrees**: M.D., Ph.D., or both
- **Grant History**: Prior R01 or other NIH funding recipient
- **Institutional Affiliation**: Ranked by number of NIH grants received.

Value-Added: Do Percentile Scores Predict "Surprise" Grant Outcomes?





Value-Added: Do Percentile Scores Predict "Surprise" Hits?



Percentile Scores and Grant Outcomes

	(1)	(2)	(3)	(4)
	Dependent Variable: *Future Citations*			
Independent Variable: *NIH Percentile Score*	-0.0203*** *(0.0006)*	-0.0215*** *(0.0008)*	-0.0162*** *(0.0007)*	-0.0158*** *(0.0007)*
N	137,215	136,076	136,076	128,547
	Dependent Variable: *Future Publications*			
Independent Variable: *NIH Percentile Score*	-0.0155*** *(0.0003)*	-0.0091*** *(0.0003)*	-0.0076*** *(0.0003)*	-0.0076*** *(0.0003)*
N	137,215	136,111	136,111	128,580
Control for subject-year?	No	Yes	Yes	Yes
Control for PI characteristics?	No	No	Yes	Yes
Control for PI publication history?	No	No	No	Yes

Notes: Each reported figure is the coefficient on scores from a single Poisson regression of grant outcomes on NIH peer review scores. The sample includes all NIH-funded R01 grants from 1980-2008. We restrict to new and competing renewal applications that received study section percentile scores. The actual sample size used per regression depends on the number of non-zero observations for the dependent variable. The independent variable is the percentile score: for each funded grant, this refers to the percent of other applications to the same study section - year that received a better study section priority score (lower percentiles represent higher rankings). Future citations

Percentile Scores and Grant Outcomes – Alternative Samples

	Main Estimate	*New Grants*	*Competing Renewal Grants*	*Rare Names*
	(1)	(2)	(3)	(4)
	Dependent Variable: *Future Citations*			
Independent Variable: *NIH Percentile Score*	-0.0158***	-0.0130***	-0.0180***	-0.0157***
	(0.0007)	*(0.0010)*	*(0.0009)*	*(0.0008)*
N	128,547	71,185	56,365	109,592
	Dependent Variable: *Future Publications*			
Independent Variable: *NIH Percentile Score*	-0.0076***	-0.0055***	-0.0091***	-0.0073***
	(0.0003)	*(0.0005)*	*(0.0004)*	*(0.0004)*
N	128,580	71,236	56,367	109,619
Control for subject-year?	Yes	Yes	Yes	Yes
Control for PI characteristics?	Yes	Yes	Yes	Yes
Control for PI publication history?	Yes	Yes	Yes	Yes

Percentile Scores and Tail Grant Outcomes

	Dependent Variable: *High Impact Publications*			Dependent Variable: *Patents*	
	Top 0.1%	Top 1%	Top 5%	Direct	Indirect
	(1)	(2)	(3)	(4)	(5)
Independent Variable: *NIH Percentile Score*	-0.0247*** *(0.0025)*	-0.0210*** *(0.0014)*	-0.0172*** *(0.0008)*	-0.0150*** *(0.0022)*	-0.0154*** *(0.0015)*
N	88,795	118,245	125,021	92,893	122,850
Control for subject-year?	Yes	Yes	Yes	Yes	Yes
Control for PI characteristics?	Yes	Yes	Yes	Yes	Yes
Control for PI publication history?	Yes	Yes	Yes	Yes	Yes

Notes: Each reported figure is the coefficient on scores from a single Poisson regression of grant outcomes on NIH peer review scores. The sample includes all NIH-funded R01 grants from 1980-2008. We restrict to new and competing renewal applications that received study section percentile scores. The actual sample size used per regression depends on the number of non-zero observations for the dependent variable. The independent variable is the percentile score: for each funded grant, this refers to the percent of other applications to the same study section - year that received a better study section priority score (lower percentiles represent higher rankings). High Impact publication is given by the count of publications acknowledging the grant that receive more citations than all but 0.1%, 1%, or 5% of publications from the same year. Direct patents are those that acknowledge funding from a grant; indirect patents are those that cite publications that acknowledge funding from a grant. We control for the same variables as described in Column 3 of Table 1 and in the Supporting Online Materials.

Thank you!

Questions or comments? dli [at] hbs.edu