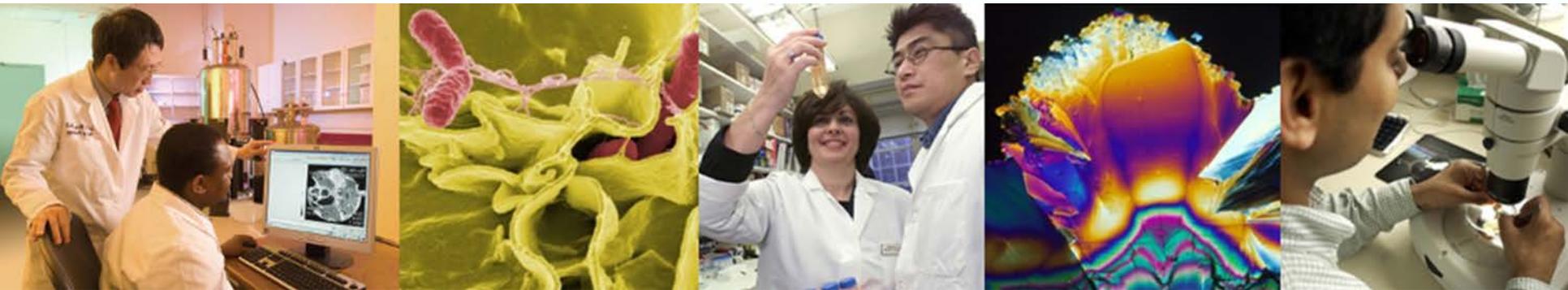


Enhancing Reproducibility and Transparency of Research Findings

Reproducibility and Reliability of Biomedical Research Symposium
April 2, 2015



Lawrence A. Tabak, DDS, PhD
Principal Deputy Director, NIH
Department of Health and Human Services



The Growing Challenge

- Noted by research community; in multiple publications
 - Across research areas
 - Especially in preclinical research

Beware the creeping cracks of bias

Evidence is mounting that research is riddled with unchecked, this could erode public trust, warns

Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khusru Asadullah

False-Positive Psychology: Undisclosed Flexibility in Data Collection and Analysis Allows Presenting Anything as Significant

Reforming Science: Methodological and Cultural Reforms

Why animal research needs to improve

Many of the studies that use animals to model human diseases are too small and too prone to bias to be trusted, says Malcolm Macleod.

The Economist

World politics Business & finance Economics Science & technology Culture

Unreliable research

Trouble at the lab

Scientists like to think of science as self-correcting. To an alarming degree, it is not

Oct 19th 2013 | From the print edition

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Raise standards for preclinical cancer research

C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

Challenges to Ensuring Rigor and Transparency in Reporting Science: Science and “Self-Correction”

- Science often viewed as “self-correcting”; immune from reproducibility problems
 - Principle remains true over the long-term
- Checks and balances for reproducibility in the short- and medium-term are hobbled by interrelated factors
 - Results in compromised ability to reproduce findings of others, particularly in preclinical research studies involving animal models of disease

Challenges to Ensuring Rigor and Transparency in Reporting Science: Additional Contributors

- Insufficient Reporting
- “P-Hacking”
- Lack of Consideration of Sex as a Biological Variable
- Problems with authentication of cell lines

Insufficient reporting of methodological approaches is evident for pre-clinical studies

Table 3. Prevalence of selected quality characteristics in other experimental models

	Number of publications	Randomisation (%)	Blinded assessment of outcome (%)	Sample-size calculation (%)
Transgenic stroke studies	157	n/a	3	0
Stroke pathophysiology studies	166	5	18	0
Parkinson's disease	118	12	15	0
Multiple sclerosis	183	2	11	0

Trends Neurosci 2007; 30: 433-439

“P-hacking”

1521-0103/351/1/200–205\$25.00
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<http://dx.doi.org/10.1124/jpet.114.219170>
J Pharmacol Exp Ther 351:200–205, October 2014

Commentary

Common Misconceptions about Data Analysis and Statistics

Harvey J. Motulsky

GraphPad Software Inc., La Jolla, California

Received August 8, 2014; accepted August 8, 2014

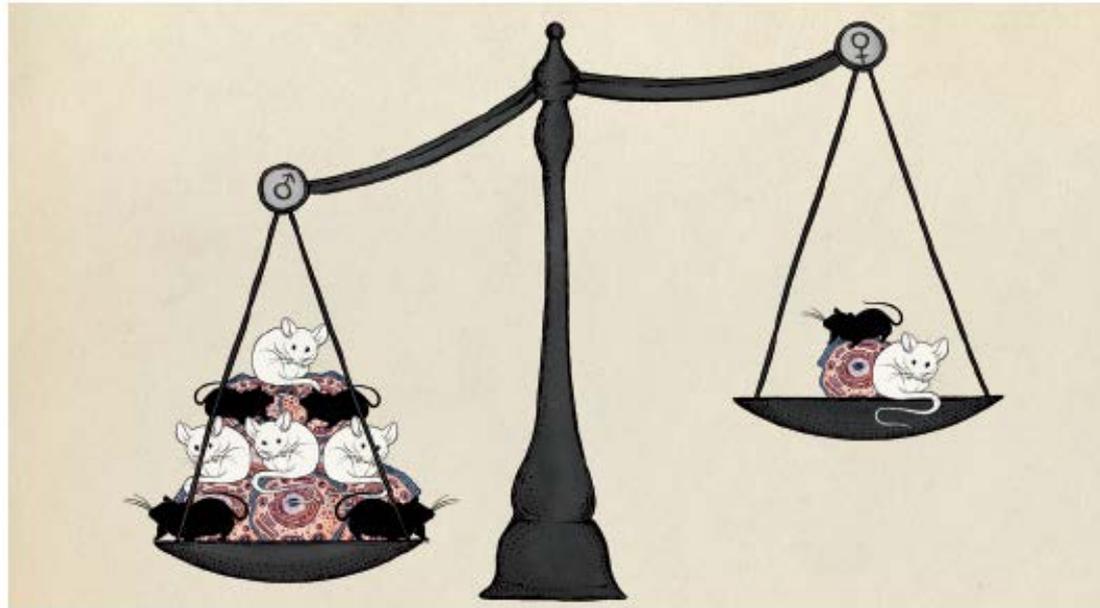
ABSTRACT

Ideally, any experienced investigator with the right tools should be able to reproduce a finding published in a peer-reviewed biomedical science journal. In fact, however, the reproducibility of a large percentage of published findings has been questioned. Undoubtedly, there are many reasons for this, but one reason may be that investigators fool themselves due to a poor understanding of statistical concepts. In particular, investigators

often make these mistakes: 1) P-hacking, which is when you reanalyze a data set in many different ways, or perhaps reanalyze with additional replicates, until you get the result you want; 2) overemphasis on *P* values rather than on the actual size of the observed effect; 3) overuse of statistical hypothesis testing, and being seduced by the word “significant”; and 4) over-reliance on standard errors, which are often misunderstood.

Lack of Consideration of Sex as a Biological Variable

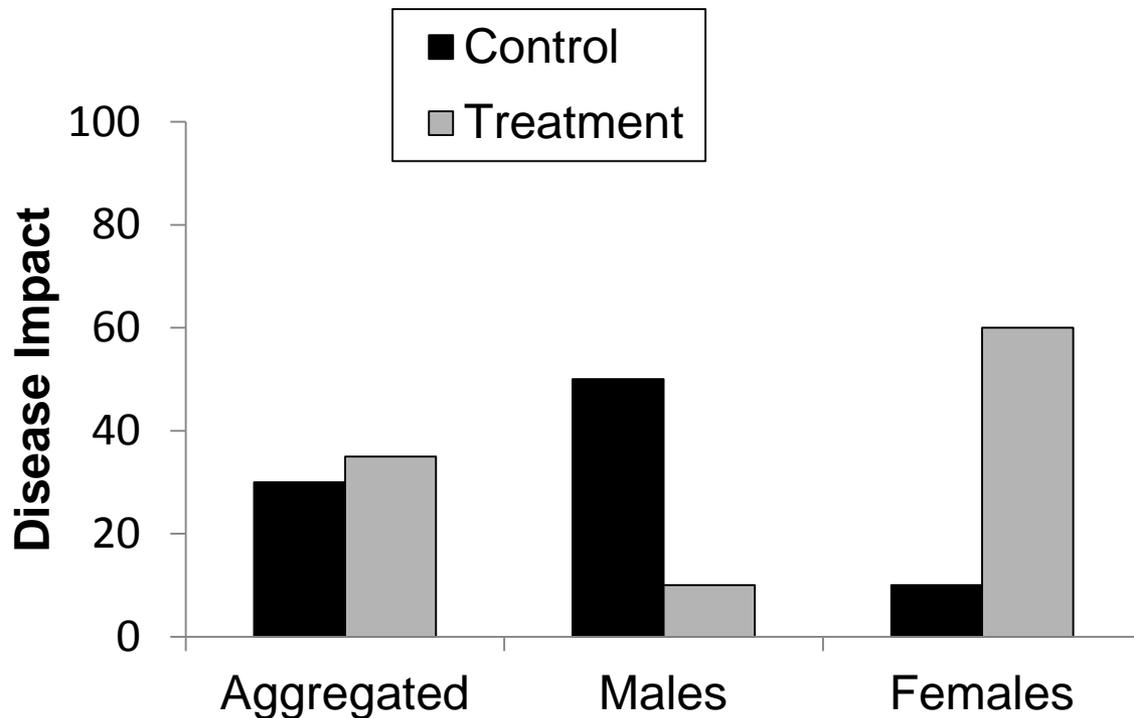
COMMENT



NIH to balance sex in cell and animal studies

Janine A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

Biological/Disease Impact of Experimental Design



Real Life

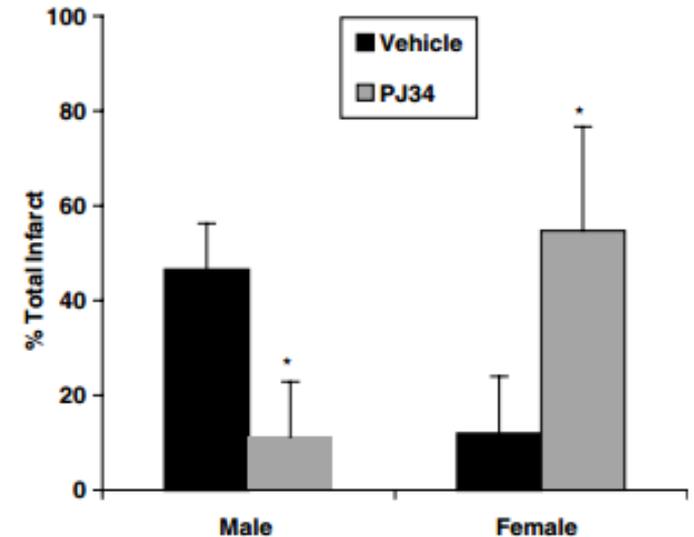


Figure 9 The effects of the selective poly-ADP ribose polymerase (PARP-1) inhibitor PJ-34 in wild-type (WT) mice of both genders. Treatment with PJ-34 at ischemic onset reduced total infarction in male mice compared with saline-treated controls (* $P < 0.001$). A significant increase in ischemic damage was seen in PJ-34-treated females compared with control (* $P < 0.001$).

Problems with Authentication of Cell Lines

PERSPECTIVES



CELL BIOLOGY

Fixing problems with cell lines

Technologies and policies can improve authentication

By Jon R. Lorsch^{1*}, Francis S. Collins²,
Jennifer Lippincott-Schwartz^{2,4}

Despite the important role of cell culture in the study of biology and medicine, evidence has accumulated that cell lines are frequently misidentified or contaminated by other cells or microorganisms. This can

concerns, developing corrective measures for cell line misidentification and contamination warrants renewed attention.

Since the 1960s, more than 400 widely used cell lines worldwide have been shown to have been misidentified (2, 3). Cells originally thought to have been derived from one tissue type have later been found to be from a different tissue. In some cases, even

For example, studies using just two misidentified cell lines were included in three grants funded by the U.S. National Institutes of Health (NIH), two clinical trials, 11 patents, and >100 papers (6). Nonetheless, the need for validation and accurate reporting of cell line identity does not appear to be widely recognized by researchers; a 2013 study found that fewer than half of cell lines were unambiguously identified in published articles (7).

Problems with Authentication of Cell Lines

PERSPECTIVES



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Challenges to Ensuring Rigor and Transparency in Reporting Science: Underlying Issues

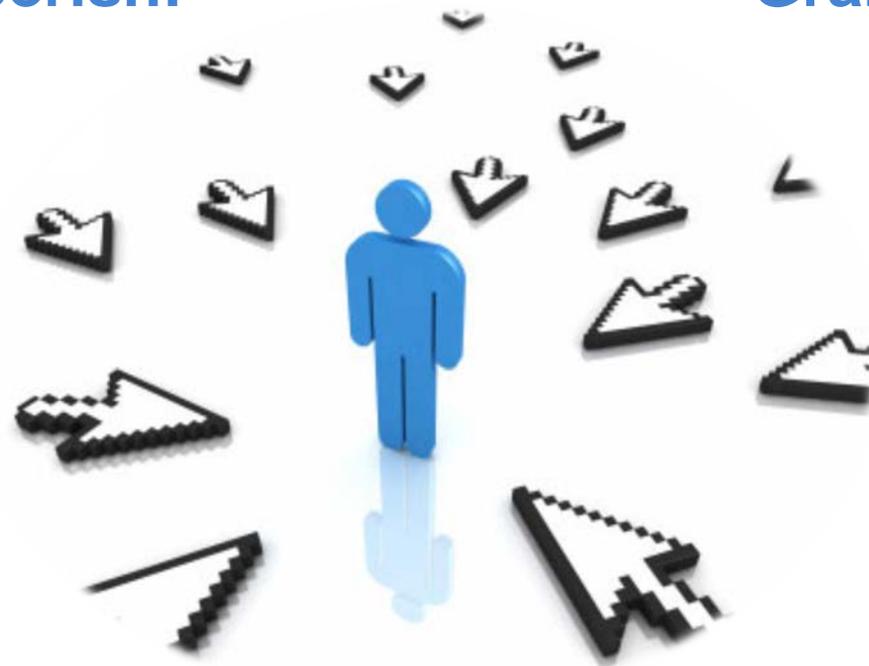
Incentives

Publish or perish!

Grant support

Impact factor

Innovation

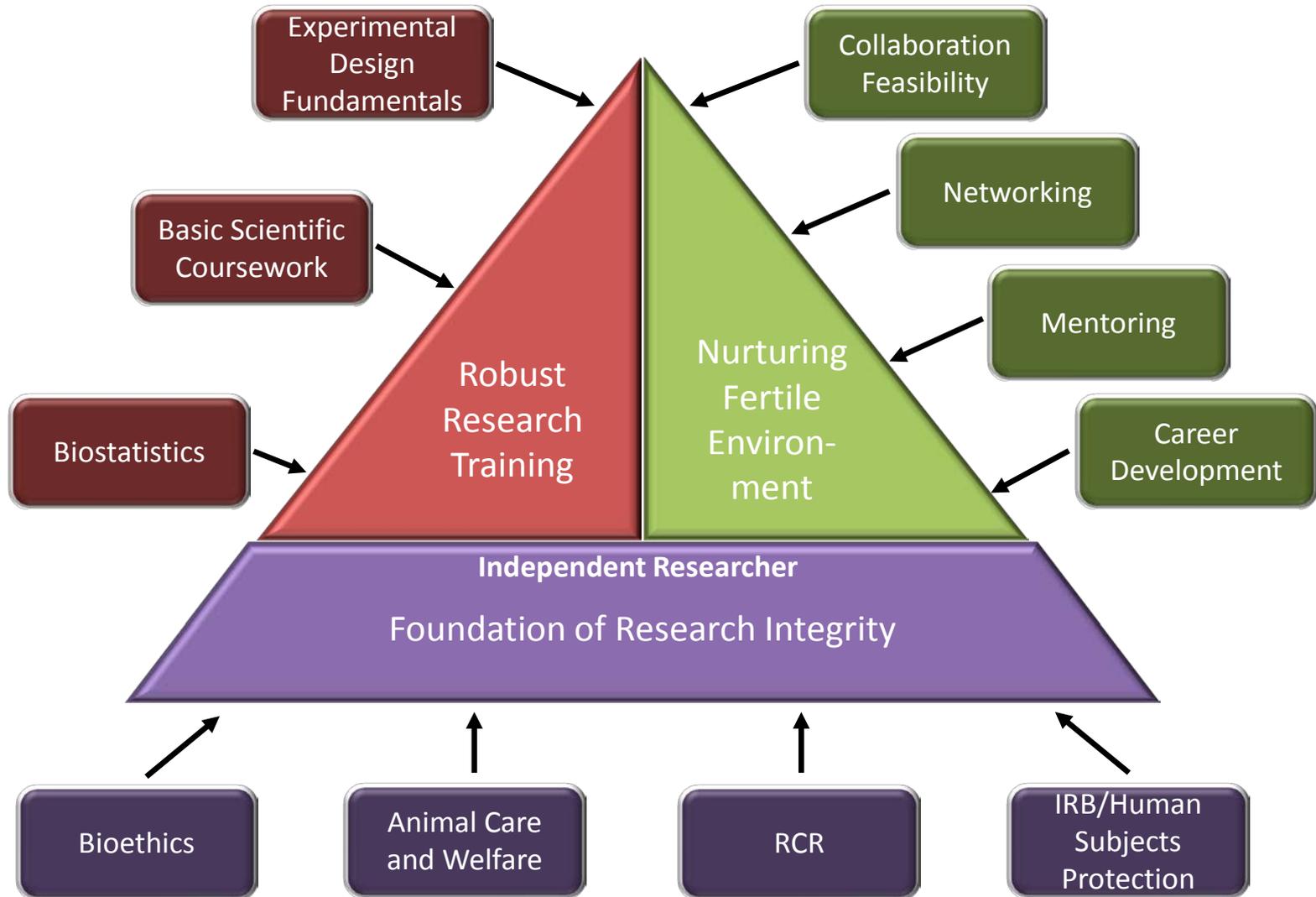


Significance

Poor training

Novelty:
No negative data

Biomedical Research Ecosystem



NIH plans to enhance reproducibility

Francis S. Collins and **Lawrence A. Tabak** discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

A growing chorus of concern, from scientists and laypeople, contends that the complex system for ensuring the reproducibility of biomedical research is failing and is in need of restructuring^{1,2}. As leaders of the US National Institutes of Health (NIH), we share this concern and here explore some of the significant interventions that we are planning.

Science has long been regarded as 'self-correcting', given that it is founded on the replication of prior work. Over the long term, that principle remains true. In the

shorter term, however, imbalances that once have been hobbled by the ability of today's researchers to replicate others' findings.

Let's be clear: we have no evidence that the current system is self-correcting. In 2011, the Office of Science and Technology Policy at the US Department of Health and Human Services pursued a strategy to address this problem. Even if this represents the actual problem

"Efforts by the NIH alone will not be sufficient to effect real change in this unhealthy environment."

Principles for Addressing the Underlying Issues

- Raise community awareness
- Enhance formal training
- Protect the quality of funded and published research by adoption of more systematic review processes
- Increase stability for investigators

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Addressing Underlying Issues: Raise Community Awareness

- Workshop in June 2014 with Journal Editors to identify common opportunity areas
- Workshop in July 2014 with PhRMA to identify areas of common interest with industry
- Obtained input on barriers to reproducibility re: research reagents
- Meetings with professional societies and institutions

Addressing Underlying Issues: Raise Community Awareness

- Over 135 journals endorsed the principles, which were broadly shared in November 2014 through editorials and other notifications

JCB

CellPress

nature

jbc THE JOURNAL OF
BIOLOGICAL CHEMISTRY

 PLOS | ONE

Science

Circulation

The Journal of Neuroscience

<http://nih.gov/about/endorsing-journals.htm>

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Addressing Underlying Issues: Enhance Formal Training

- NINDS, IRP, and Office of the Director (OD) working on training module in experimental design
 - Filmed modules are being used within the IRP
 - Available to NIH staff (intramural researchers and extramural staff), and also are available to the extramural research community



<https://www.youtube.com/watch?v=U4A-ZSTUEUo>

<https://www.youtube.com/watch?v=NEcErxoOVm0>

<https://www.youtube.com/watch?v=Pc0h-GOcBLE>

<https://www.youtube.com/watch?v=wSWunBYzl8c>

Addressing Underlying Issues: Enhance Formal Training

- NINDS, IRP, and Office of the Director (OD) working on training module in experimental design
 - Filmed modules are being used within the IRP
 - Available to NIH staff (intramural researchers and extramural staff), and also are available to the extramural research community
- NIGMS funding opportunity (multiple ICs have signed on) supporting the development of training modules to enhance reproducibility
 - [RFA-GM-15-006](#): Closed late last year
 - 10 IC's, \$3.1M, ~20 awards

Addressing Underlying Issues: Enhance Formal Training

- IRP workshops on data interpretation considerations for various experimental techniques
 - Two workshops held thus far, with a third planned for May
 - First workshop focused on imaging, FRET, FACS, and cell-based models
 - Second workshop focused on structural biology (i.e., Cryo-EM, NMR)
 - Workshops are publically available on the NIH website
- Can explore options for bringing in training expertise for both intramural and extramural staff

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Addressing Underlying Issues: Trans-NIH Pilots

Pilot Focus	Types of Efforts Being Developed
Evaluation of scientific premise in grant applications	New Funding Opportunities with additional review criteria regarding scientific premise
Checklist and reporting guidelines	Reviewer checklists regarding reporting standards and scientific rigor
Changes to biosketch	Biosketch pilot with focus on accomplishments and not just publications
Approaches to reduce "perverse incentives" to publish	Exploring award options with a longer period of support for investigators
Supporting replication studies	New Funding Opportunities for replication studies, and options to assess whether pre-clinical findings should be replicated
Training	Developing materials on experimental design
Other efforts	Use of Prize Challenges to encourage reproducibility of results, PubMed Commons

Addressing Underlying Issues: PubMed Commons

http://pubmed.ncbi.nlm.nih.gov/directors-blog/

NIH DIRECTOR'S BLOG



PubMed Commons

Get Started

Top commen

Troponin Elev
Prognostic Sig
Korley FK Acad En
[Frederick K Korle](#)
Agreed. Troponin v
However, those wit
from expedited out
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Interested readers
conflicts: A neglect
Cognitive Therapie
[Permalink](#) [Share](#)

PubMed Commons: Catalyzing Scientist-To-Scientist Interactions

Posted on August 5, 2014 by [Dr. Francis Collins](#)



Public record



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System

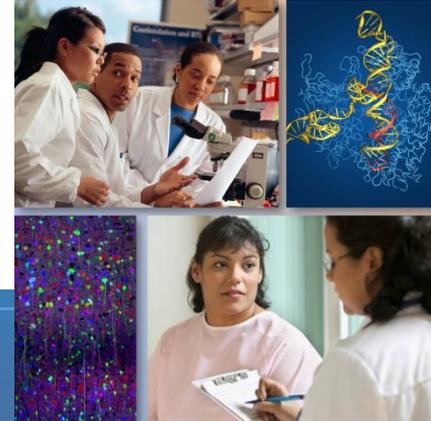
Today's scientists find it tough to keep up with all of the latest journal articles, innovative methods, and interesting projects of colleagues in their fields. That's understandable, because there are tens of thousands of journals, hundreds of conferences in major fields, dozens of emerging

nions on

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Addressing Underlying Issues: Investigator Stability



NIH DIRECTOR'S BLOG

Formula for Innovation: People + Ideas + Time

Posted on July 17, 2014 by [Dr. Sally Rockey](#) and [Dr. Francis Collins](#)

In these times of tight budgets and rapidly evolving science, we must consider new ways to invest biomedical research dollars to achieve maximum impact—to turn scientific discoveries into better health as swiftly as possible. We do this by thinking strategically about the areas of research that we support, as well as the process by which we fund that research.

Addressing Underlying Issues: Investigator Stability

Formula for Innovation – People + Ideas + Time

- Awarding longer grants — e.g., NIH Pioneer Awards
- NCI's **Outstanding Investigator Award**
 - To investigators with extraordinary records
 - \$600,000/yr direct costs for up to 7 yrs
- NIGMS's **Maximizing Investigators' Research Award**
 - Concept stage, awaiting RFI feedback
 - \$150,000–\$750,000/yr direct costs for 5 yrs
- Other NIH ICs may follow with similar opportunities



NIH...

Lawrence.Tabak@nih.gov

Turning Discovery Into Health

