Council of Councils

NIH Reproducibility Initiative

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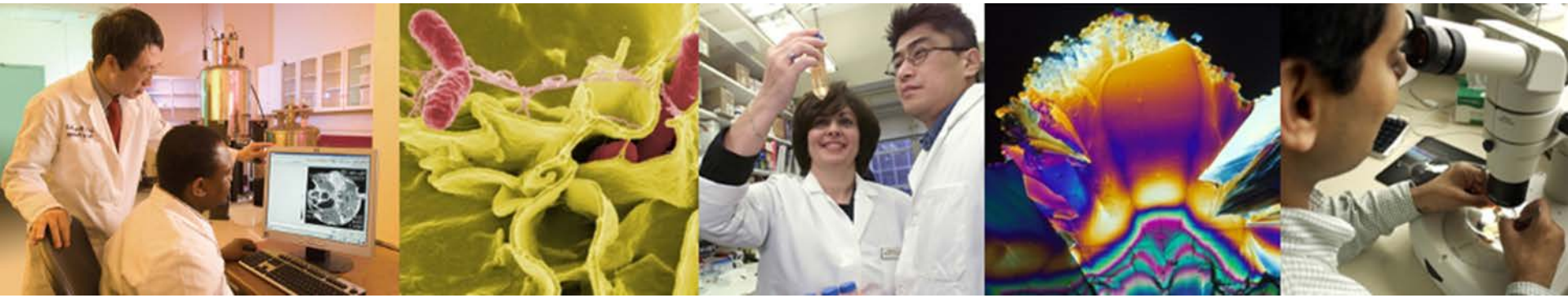

NIH plans to enhance reproducibility

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

Feedback on Commentary

- Range of respondents: Investigators, reagent suppliers, professional associations, industry
- Reaction: mostly supportive
- Ideas/materials shared:
  - Dedicated funding for replication studies
  - Additional literature on reproducibility issues (books, publications)

Underlying Issues

- Poor training
- Poor evaluation
- Difficulty in publishing negative findings
- Perverse reward incentives

Principles for Addressing the Underlying Issues

1. Raise community awareness
2. Enhance formal training
3. Protect the quality of funded and published research by adoption of more systematic review processes (Study Sections and Journals)
4. Increase stability for investigators

Trans-NIH Actions
Stakeholder Engagement

- Meeting with Journal Editors to identify common opportunity areas
  - Work with and encourage journals to publish follow-up papers that point out scientific flaws in previously published work
- Developing workshop with PhRMA to identify areas of common interest with industry
- Envisioning workshop with Academia
- Considering workshop with reagent suppliers

EDITORIAL

nature biotechnology

Receptive to replication

"Replication is a difficult and thankless task. Until now, journals, funders and academics have shown little interest in it. *Nature Biotechnology* will remain open to publishing replication studies and rigorous efforts that fail to reproduce findings from other publications of high interest to our readers. **It is our view, however, that the best practice is to publish such replication failures in the journal where the original findings were published. That way, the power of the scientific process to consolidate and modify our understanding of initial findings in a report is clearly visible to all.**"

contradict western blots from the Zhang paper that suggested miR168a directly suppressed levels of low-density lipoprotein receptor adapter protein 1 (LDLRAP1) in mice. Finally, the miRagen study suggests differences in diet composition, rather than miRNA-mediated cross-kingdom gene regulation, likely account for alterations in low-density lipoprotein in mouse plasma.

But why put the paper in *Nature Biotechnology* rather than *Cell Research*, where the original report was published? In fact, the miRagen investigators did submit their paper to that journal but were told that "it is a bit hard to publish a paper of which the results are largely negative."

We differ with this assessment and believe the paper is worthy of publication precisely because it is a negative result throwing light on a key research question.

findings must surely be industry. Companies have the deepest financial resources, and they have the most to gain. And it was groups at Amgen and Bayer that raised the recent chorus of concern about irreproducibility of the literature in the first place. Then again, corporations have few incentives to jump through all the hoops of peer review when they fail to reproduce results; in this respect, miRagen deserves praise for seeking to publish its negative findings.

Apart from the above post-publication correction mechanisms, efforts are also underway to improve reproducibility before findings become papers. For example, one idea being floated by certain funders is to set aside a portion of a research grant specifically for independent verification of the main study's results before publication; in this scheme, submission to a journal would proceed only after the results were corroborated.

Trans-NIH Actions
Stakeholder Engagement

Meetings with/Presentations to:

- Life Sciences Subcommittee of Committee on Science – May 28th, 2014
- Virginia Commonwealth University – September 22nd, 2014
- Society for Neuroscience (SfN) – November 2014, led by NINDS
- Clinical Research Forum and Association for Clinical and Translational Sciences (ACTS) – joint meeting in April 2014
- American Society for Pharmacology & Experimental Therapeutics (ASPET) – April 2014
- Coalition for the Life Sciences (CLS) – March 2014
- Health Research Alliance (HRA) – January 2014
- Consortium of Social Science Associations (COSSA) – November 2013

Trans-NIH Actions
Development of Training Resources

- NINDS working with IRP on training module in experimental design
  - Basic module expected to be road-tested with IRP staff (trainees, fellows, and faculty) by summer of 2014
  - Film version expected to be completed by end of 2014
- IRP working on TEDMED-like talks on data interpretation considerations for various experimental techniques
  - Talks expected to begin in summer of 2014
- Potential NIH course/resources on experimental design; could be done through FAES and adapted for online use
  - Options being explored for implementation by end of 2014

IC Pilot Summary

Pilot Focus	Types of Efforts Being Developed
Evaluation of scientific premise/grant applications	New FOAs with additional review criteria regarding scientific premise
Checklist/Reporting Guidelines	Reviewer checklists regarding reporting standards/scientific rigor
Changes to Biosketch	Biosketch pilot coordinated by the Office of Extramural Research
Approaches to reduce "perverse incentives"	Exploring award options with a longer period of support for investigators
Supporting replication studies	New FOAs or collaborations for replication studies, and exploring options to assess (at the time of application) whether pre-clinical findings should be replicated
Training	Developing materials for the new training module on research integrity
Other efforts	PubMed Commons Pilot system, use of prize challenges to encourage reproducibility of results

Potential Changes

- Changes in policy (to FOAs and/or to review)
  - Standards for experimental design – include requirements in FOAs?
  - Add review criteria to align with new requirements
  - Cell line authentication (NIGMS)
  - Antibody authentication, e.g., standards for different types of reagents
  - Sex differences in animal research

Ideas for Additional Reproducibility Initiatives

- Have we done enough for now?
- What other ideas would you recommend NIH pursue that are?
  - Transformative
  - Synergistic
  - Catalytic
  - Cross-cutting
  - Unique




NIH...

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Turning Discovery Into Health