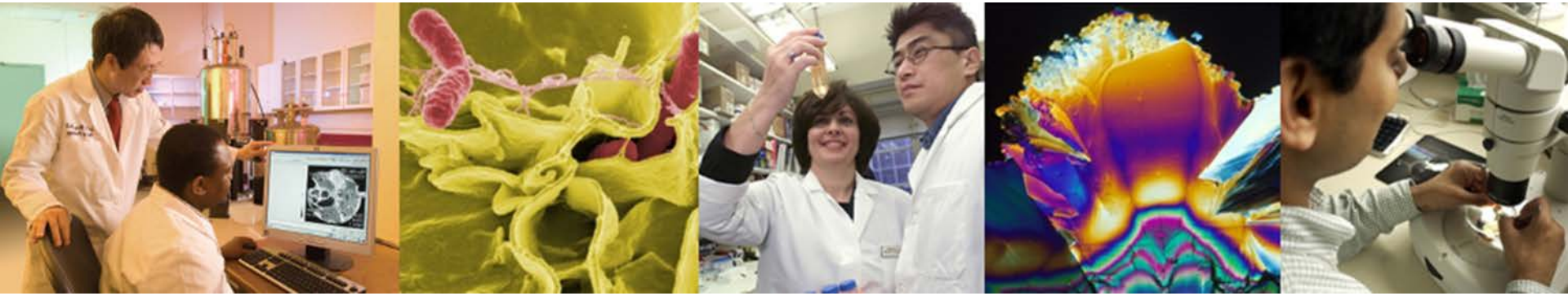
NIH Update

Council of Councils Meeting
September 9, 2016



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

Topics for Today

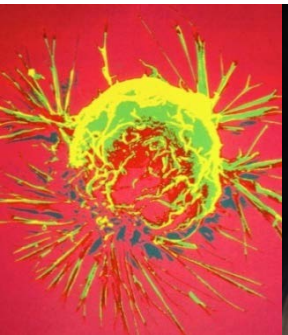
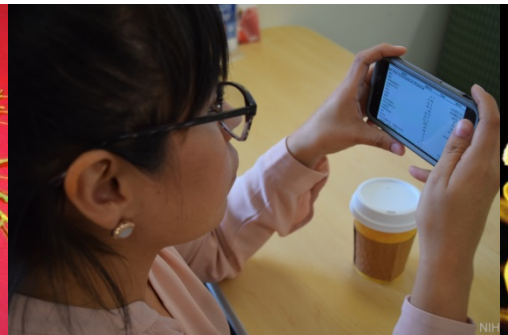
- Budget Update
- Enhancing Reproducibility and Transparency of Research Findings
- Transitioning to a New Administration

Topics for Today

- **Budget Update**
- Enhancing Reproducibility and Transparency of Research Findings
- Transitioning to a New Administration

FY 2016 Increase Highlights

- $2 billion increase
- Allows highest level of new and competing Research Project Grants since FY 2003 (10,753)
- Precision Medicine Initiative $200 M
  - *Cohort* *130 M*
  - *Cancer* *70 M*
- Antimicrobial Resistance 100 M
- BRAIN Initiative 85 M
- Alzheimer's Disease 350 M


NIH's FY 2017 Budget Request

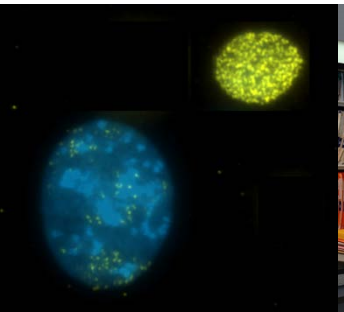
Year	FY 2015	FY 2016	FY 2017 Request
Program Level ($B)	$30.311	$32.311	$33.136
Competing RPGs (est.)	9,540	10,753	9,946
Total RPGs (est.)	34,379	35,840	36,440
Applicant Success Rate (est.)	18.3%	19.2%	17.5%

- The proposed increase of $825 million in FY 2017 would continue the progress achieved in FY 2016 and allow the highest total number of Research Project Grants (competing and noncompeting) in seven years

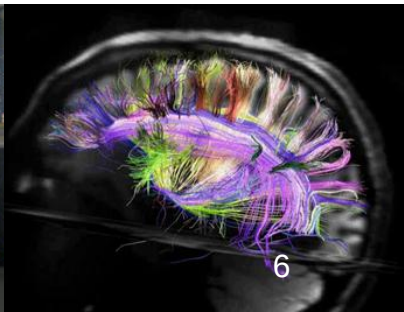
FY 2017 Request:
Targeted Increases – from Mandatory Funds*

- National Cancer Moonshot $680 M
- Precision Medicine Initiative Cohort $100 M
- BRAIN Initiative $45 M

*Remainder of NIH budget request is at the same overall program level as FY 2016, but $1 billion of that is from mandatory funds ($1.825 billion total)

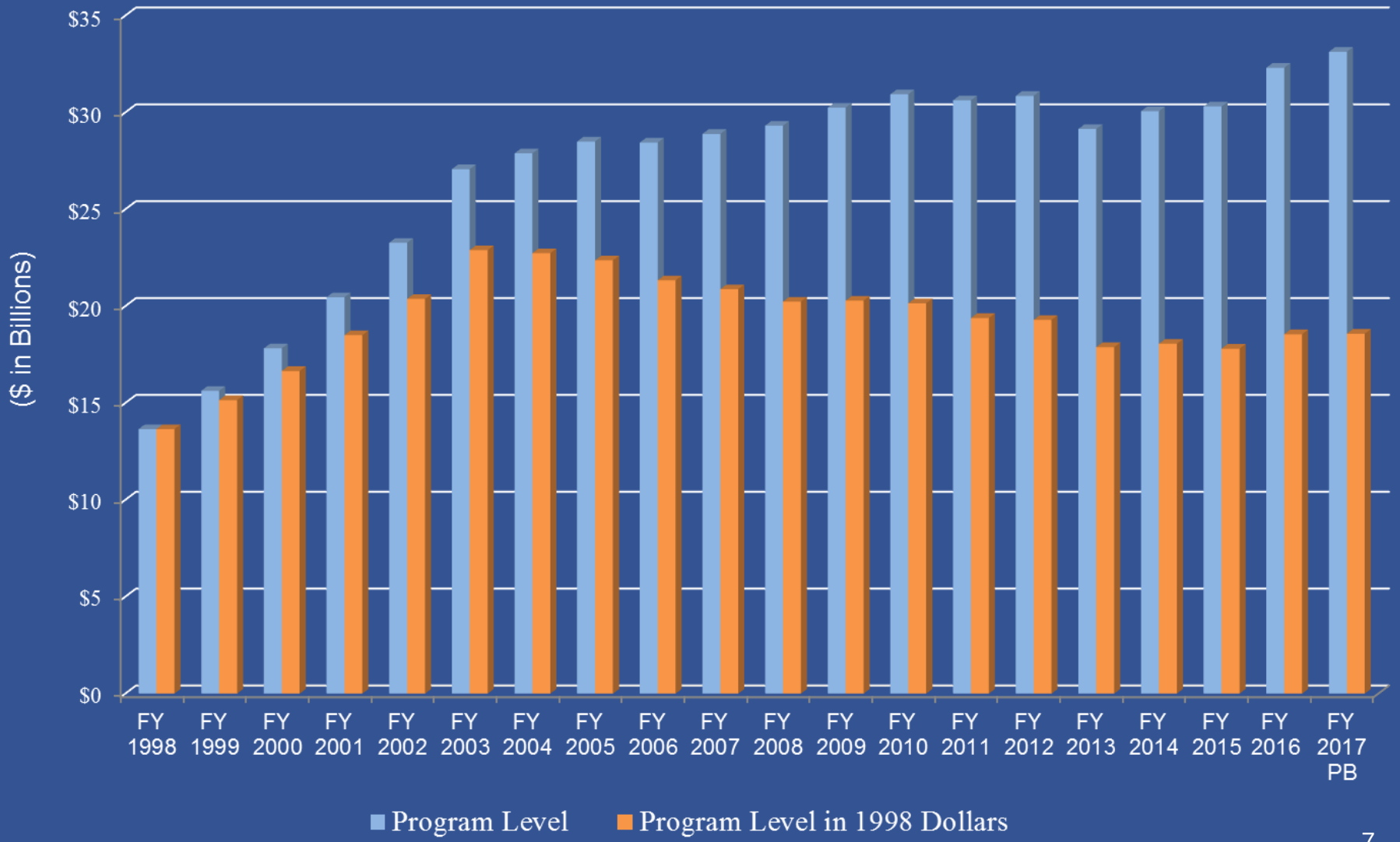




NIH Program Level

in Nominal Dollars and Constant Dollars



Topics for Today

- Budget Update
- **Enhancing Reproducibility and Transparency of Research Findings**
- Transitioning to a New Administration

The Growing Challenge: Ensuring the Rigor and Reproducibility of Science

- Noted by research community and beyond in several publications
  - Across research area
  - Especially in preclinical research

The Growing Challenge: Ensuring the Rigor and Reproducibility of Science

- Noted by research community and beyond in several publications
  - Across research area
  - Especially in preclinical research

The Growing Challenge: Ensuring the Rigor and Reproducibility of Science

- Noted by research community and beyond in several publications
  - Across research area
  - Especially in preclinical research

LAST WEEK TONIGHT WITH JOHN OLIVER

Deficiencies in Experimental Procedures

- Insufficient Reporting in Publications
- “P-Hacking”
- Researcher’s “Degrees of Freedom”
- Lack of Consideration of Sex as a Biological Variable
- Cell Lines

Deficiencies in Experimental Procedures

- Insufficient Reporting in publications – blinding, replication & randomization, sample size outliers and exclusion criteria

Insufficient Reporting of Methodological Approaches is Evident for Pre-Clinical Studies

Table 3. Prevelence 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

Adapted from Dr. S. Silberberg, NINDS

Amyotrophic Lateral Sclerosis

ISSN: 1748-2968 (Print) 1471-180X (Online) Journal homepage: http://www.tandfonline.com/loi/iafd19

Design, power, and interpretation of studies in the standard murine model of ALS

Sean Scott, Janice E. Kranz, Jeff Cole, John M. Lincecum, Kenneth Thompson, Nancy Kelly, Alan Bostrom, Jill Theodoss, Bashar M. Al-Nakhala, Fernando G. Vieira, Jeyanthi Ramasubbu & James A. Heywood

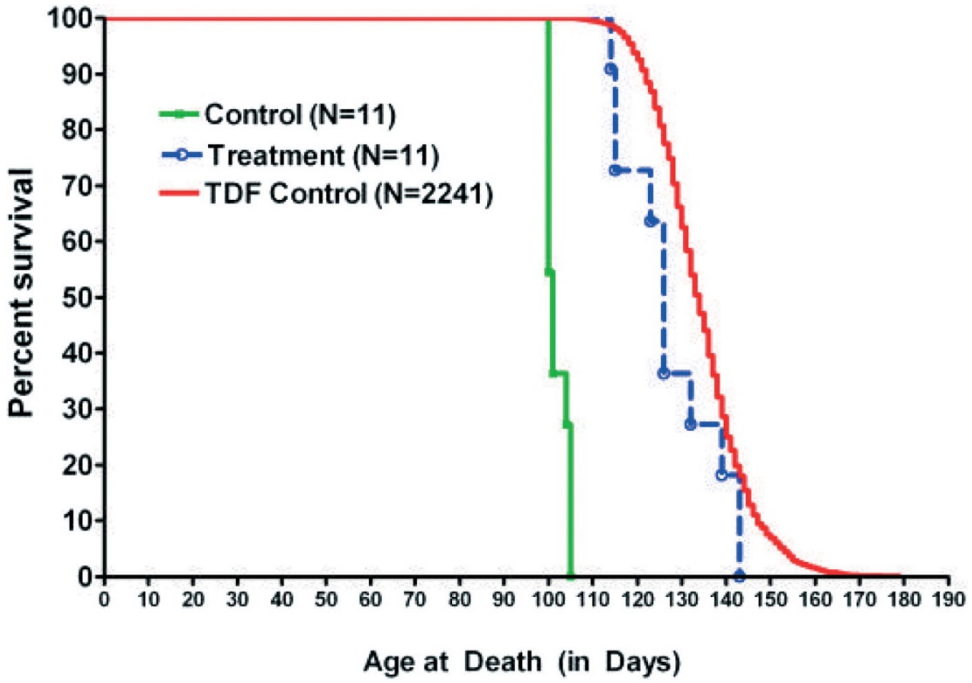


Figure 4. Survival analysis. Control and treated SOD1^{G93A} mice from one publication compared to all of our 2241 control animals (acquired over four years – data from Table S2) that died of ALS.

Amyotroph Lateral Scler 2008; 9: 4-15

Deficiencies in Experimental Procedures (cont.)

- Insufficient Reporting in publications – blinding, replication & randomization, sample size outliers and exclusion criteria
- "P-Hacking"

1521-0103/351/1/200–205$25.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 2014 Creative Commons Attribution-NoDerivatives 4.0 International (CC-BY-ND 4.0)
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

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 results 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.

Deficiencies in Experimental Procedures (cont.)
Researcher's "Degrees of Freedom"

Table 2. Simple Solution to the Problem of False-Positive Publications

Requirements for authors

1. Authors must decide the rule for terminating data collection before data collection begins and report this rule in the article.
2. Authors must collect at least 20 observations per cell or else provide a compelling cost-of-data-collection justification.
3. Authors must list all variables collected in a study.
4. Authors must report all experimental conditions, including failed manipulations.
5. If observations are eliminated, authors must also report what the statistical results are if those observations are included.
6. If an analysis includes a covariate, authors must report the statistical results of the analysis without the covariate.

Guidelines for reviewers

1. Reviewers should ensure that authors follow the requirements.
2. Reviewers should be more tolerant of imperfections in results.
3. Reviewers should require authors to demonstrate that their results do not hinge on arbitrary analytic decisions.
4. If justifications of data collection or analysis are not compelling, reviewers should require the authors to conduct an exact replication.

Simmons et al. *Psychological Science* 2011;22:1359-1366

Deficiencies in Experimental Procedures (cont.)

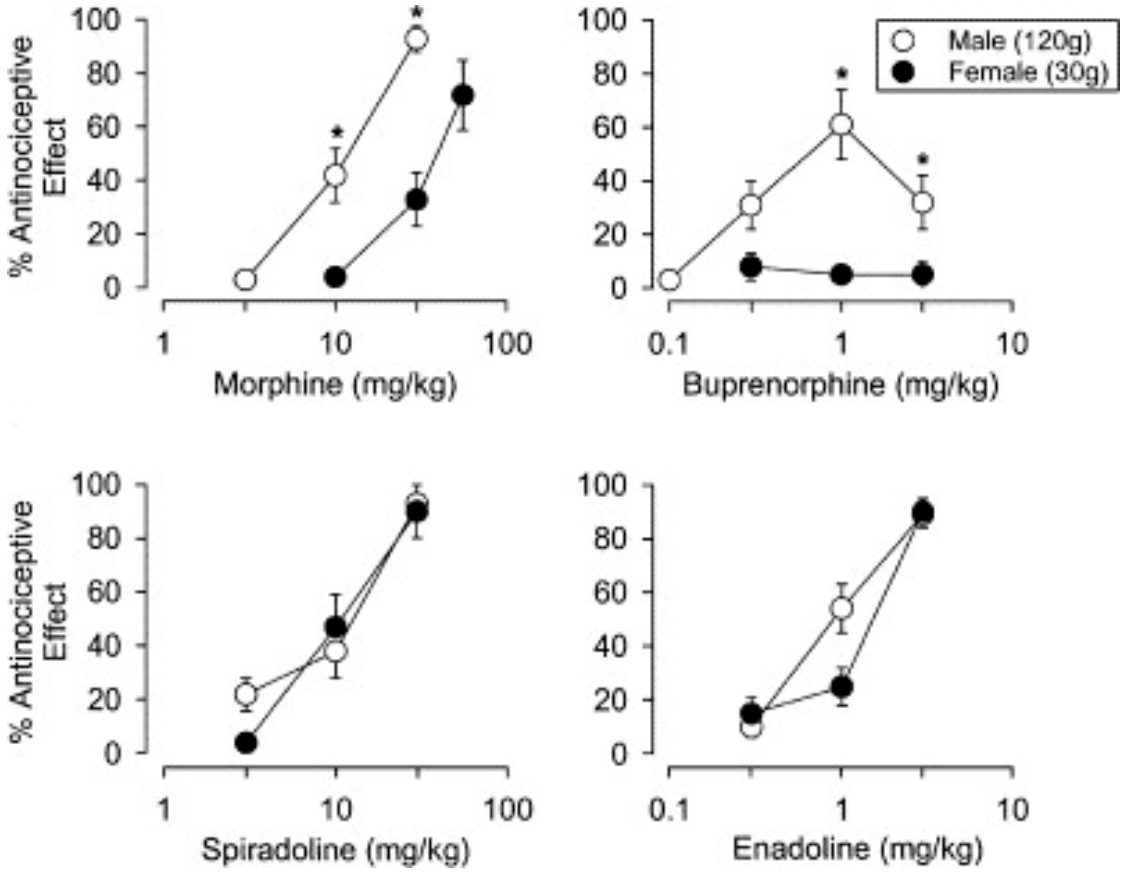
- Insufficient Reporting in publications – blinding, replication & randomization, sample size outliers and exclusion criteria
- "P-Hacking"
- Researcher's "Degrees of Freedom"
- Lack of Consideration of Sex as a Biological Variable


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.

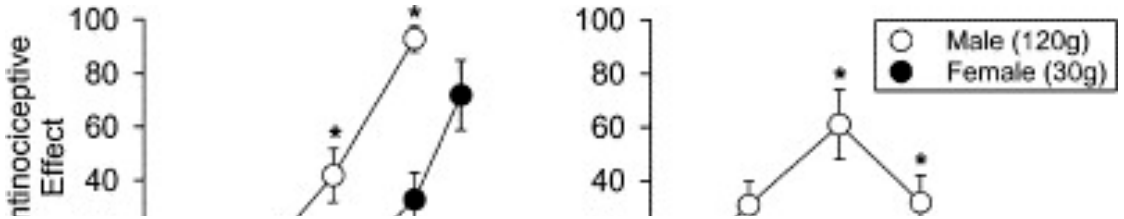
Importance of Sex as a Biological Variable



Morphine was 2.3-fold more potent in males and buprenorphine produced a 61% effect in males and only a 5% effect in females

Barrett AC, et al. *European Journal of Pharmacology* (2002) **452,** 163–173.

Importance of Sex as a Biological Variable



1521-0081/68/2/242–263$25.00
PHARMACOLOGICAL REVIEWS
U.S. Government work not protected by U.S. copyright

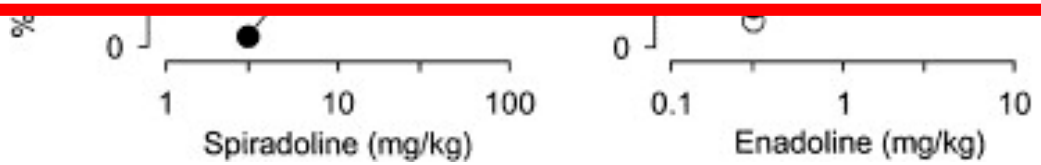
http://dx.doi.org/10.1124/pr.115.011163
Pharmacol Rev 68:242–263, April 2016

ASSOCIATE EDITOR: MICHAEL M. GOTTESMAN

Sex Differences in Animal Models: Focus on Addiction

Jill B. Becker[1] and George F. Koob[1]

Molecular & Behavioral Neuroscience Institute, Department of Psychiatry, Department of Psychology, University of Michigan, Ann Arbor, Michigan (J.B.B.); and Director, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland (G.F.K.)

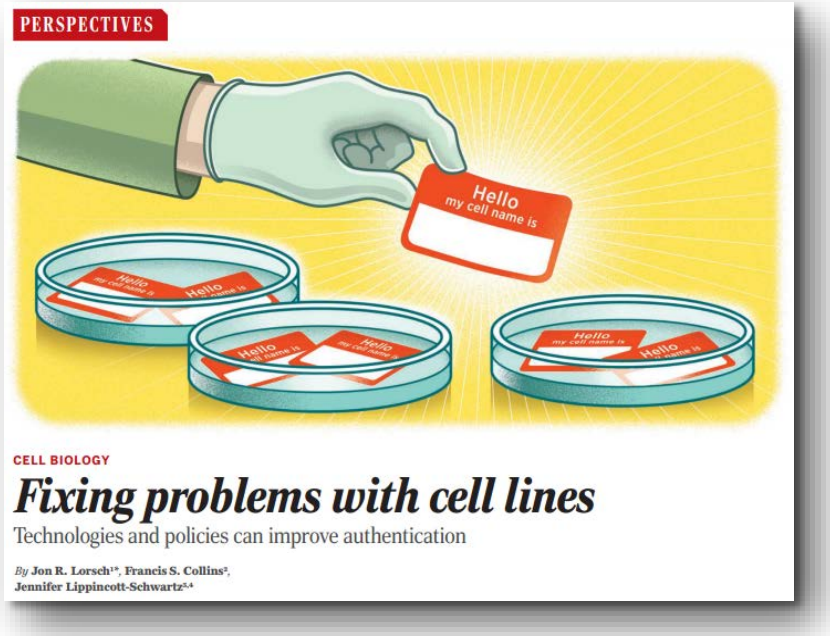


Morphine was 2.3-fold more potent in males and buprenorphine produced a 61% effect in males and only a 5% effect in females

Barrett AC, et al. *European Journal of Pharmacology* (2002) **452,** 163–173.

Deficiencies in Experimental Procedures (cont.)

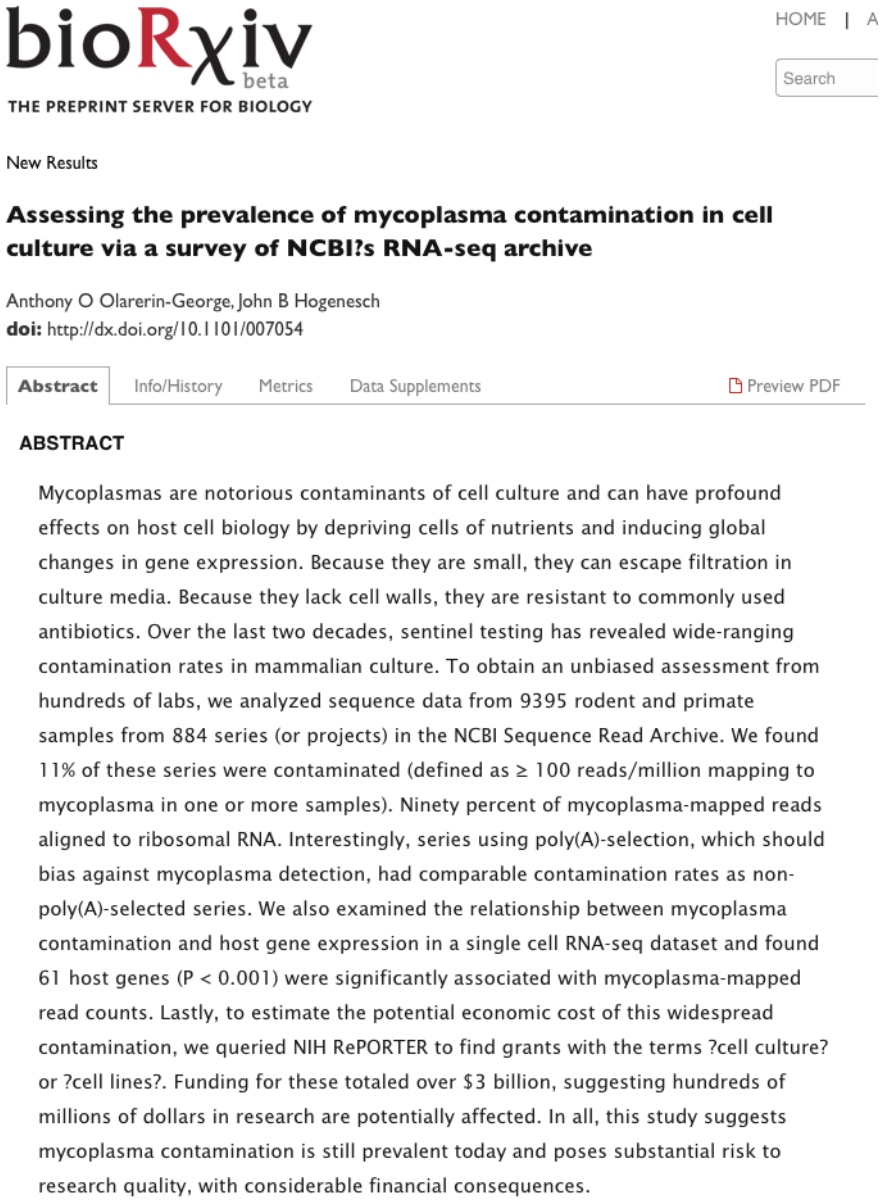
- Insufficient Reporting in publications – blinding, replication & randomization, sample size outliers and exclusion criteria
- "P-Hacking"
- Researcher's "Degrees of Freedom"
- Lack of Consideration of Sex as a Biological Variable
- Problems with Authentication of Cell Lines



Reproducibility in Cell Culture Studies

- >400 misidentified cell lines have been cataloged, dating back to the 1960s
- ~70% of researchers surveyed in 2004 had never checked the identity of their cell lines
- Major repositories report that 14-30% of cell lines submitted are contaminated
- In a 2013 survey <50% of cell lines had an unambiguous identifier and source in publications
- Standards for cell line authentication and affordable methods for cell authentication now available

Reproducibility in Cell Culture Studies



bioRxiv beta
THE PREPRINT SERVER FOR BIOLOGY

HOME | A

Search

New Results

Assessing the prevalence of mycoplasma contamination in cell culture via a survey of NCBI?s RNA-seq archive

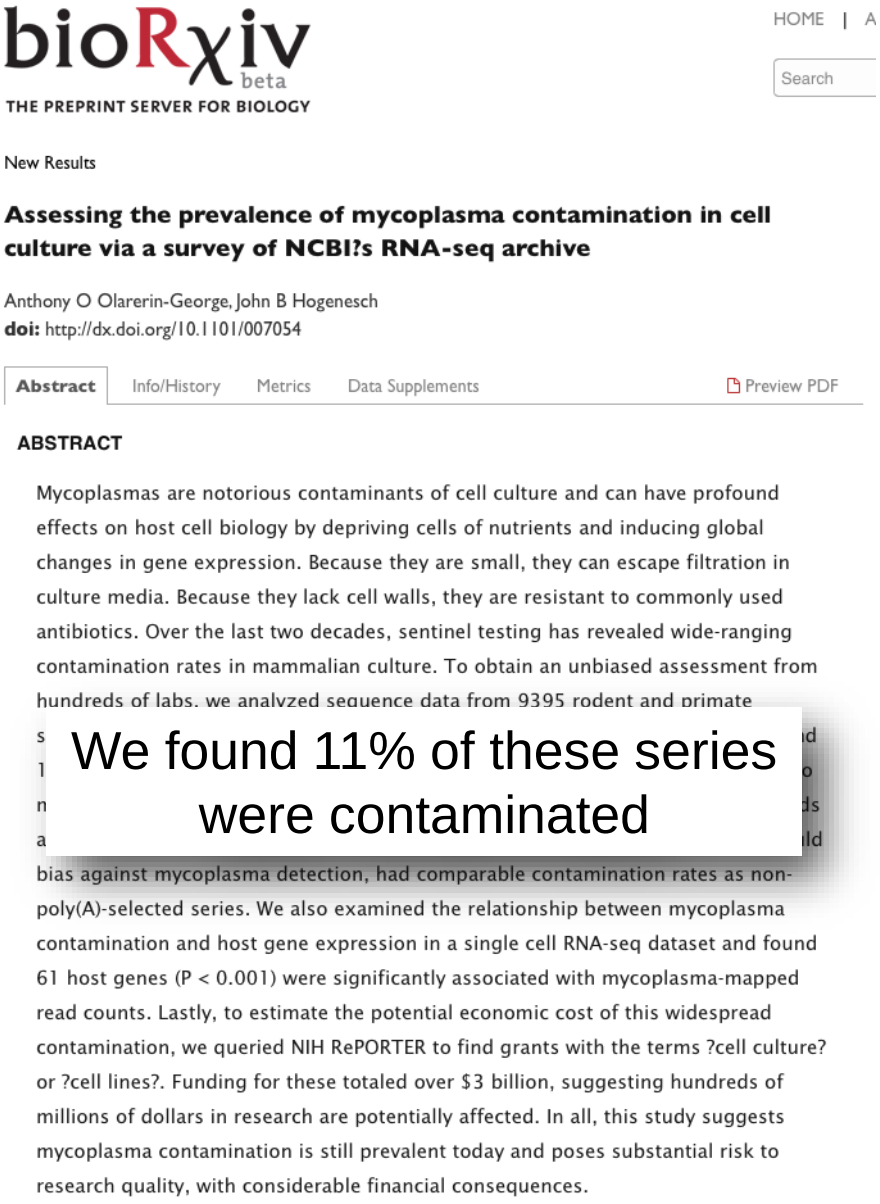
Anthony O Olarerin-George, John B Hogenesch
doi: http://dx.doi.org/10.1101/007054

Abstract | Info/History | Metrics | Data Supplements | Preview PDF

ABSTRACT

Mycoplasmas are notorious contaminants of cell culture and can have profound effects on host cell biology by depriving cells of nutrients and inducing global changes in gene expression. Because they are small, they can escape filtration in culture media. Because they lack cell walls, they are resistant to commonly used antibiotics. Over the last two decades, sentinel testing has revealed wide-ranging contamination rates in mammalian culture. To obtain an unbiased assessment from hundreds of labs, we analyzed sequence data from 9395 rodent and primate samples from 884 series (or projects) in the NCBI Sequence Read Archive. We found 11% of these series were contaminated (defined as ≥ 100 reads/million mapping to mycoplasma in one or more samples). Ninety percent of mycoplasma-mapped reads aligned to ribosomal RNA. Interestingly, series using poly(A)-selection, which should bias against mycoplasma detection, had comparable contamination rates as non-poly(A)-selected series. We also examined the relationship between mycoplasma contamination and host gene expression in a single cell RNA-seq dataset and found 61 host genes ($P < 0.001$) were significantly associated with mycoplasma-mapped read counts. Lastly, to estimate the potential economic cost of this widespread contamination, we queried NIH RePORTER to find grants with the terms ?cell culture? or ?cell lines?. Funding for these totaled over $3 billion, suggesting hundreds of millions of dollars in research are potentially affected. In all, this study suggests mycoplasma contamination is still prevalent today and poses substantial risk to research quality, with considerable financial consequences.

Reproducibility in Cell Culture Studies



bioRxiv beta
THE PREPRINT SERVER FOR BIOLOGY

HOME | A

Search

New Results

Assessing the prevalence of mycoplasma contamination in cell culture via a survey of NCBI?s RNA-seq archive

Anthony O Olarerin-George, John B Hogenesch
doi: http://dx.doi.org/10.1101/007054

Abstract | Info/History | Metrics | Data Supplements | Preview PDF

ABSTRACT

Mycoplasmas are notorious contaminants of cell culture and can have profound effects on host cell biology by depriving cells of nutrients and inducing global changes in gene expression. Because they are small, they can escape filtration in culture media. Because they lack cell walls, they are resistant to commonly used antibiotics. Over the last two decades, sentinel testing has revealed wide-ranging contamination rates in mammalian culture. To obtain an unbiased assessment from hundreds of labs, we analyzed sequence data from 9395 rodent and primate

We found 11% of these series were contaminated

bias against mycoplasma detection, had comparable contamination rates as non-poly(A)-selected series. We also examined the relationship between mycoplasma contamination and host gene expression in a single cell RNA-seq dataset and found 61 host genes ($P < 0.001$) were significantly associated with mycoplasma-mapped read counts. Lastly, to estimate the potential economic cost of this widespread contamination, we queried NIH RePORTER to find grants with the terms ?cell culture? or ?cell lines?. Funding for these totaled over $3 billion, suggesting hundreds of millions of dollars in research are potentially affected. In all, this study suggests mycoplasma contamination is still prevalent today and poses substantial risk to research quality, with considerable financial consequences.

Principles for Addressing Underlying Issues

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

Principles for Addressing Underlying Issues

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

Raise Community Awareness

NIH Rigor and Reproducibility Web-portal

http://www.nih.gov/science/reproducibility

Raise Community Awareness

- Workshop in Summer 2014 with PhRMA to identify areas of common interest with industry
- Workshop in Summer 2014 with Journal Editors to identify common opportunity areas
- **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://www.nih.gov/science/reproducibility/principles-guidelines.htm

Raise Community Awareness

Efforts by Other Organizations: Recent Example

ASA News
AMERICAN STATISTICAL ASSOCIATION
Promoting the Practice and Profession of Statistics®
732 North Washington Street, Alexandria, VA 22314 • (703) 684-1221 • Toll Free: (888) 231-3473 • www.amstat.org • www.twitter.com/AmstatNews

AMERICAN STATISTICAL ASSOCIATION RELEASES STATEMENT ON STATISTICAL SIGNIFICANCE AND *P*-VALUES

Provides Principles to Improve the Conduct and Interpretation of Quantitative Science

March 7, 2016

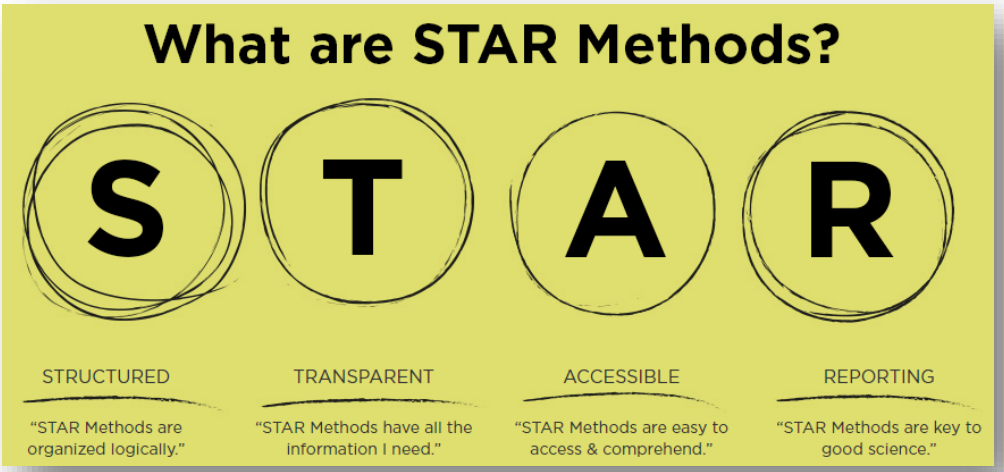
"We teach it because it's what we do; we do it because it's what we teach."

"The *p*-value was never intended to be a substitute for scientific reasoning"

http://amstat.tandfonline.com/doi/abs/10.1080/00031305.2016.1154108

Raise Community Awareness

CellPress



http://www.cell.com/star-methods

Principles for Addressing Underlying Issues

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

Enhance Formal Training

- NINDS, IRP, and Office of the Director (OD) developed training modules in experimental design, which are being used within the IRP and are available publicly

- NIGMS (with 9 other ICs) is supporting the development of training modules to enhance reproducibility
  - Funded 6 awards, supported by 8 ICs
  - 26 administrative supplements to develop curricula
- IRP workshops on data interpretation considerations for various experimental techniques – “potentials and pitfalls”

http://www.nih.gov/science/reproducibility/training.htm

Principles for Addressing Underlying Issues

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

Application and Review Processes

- The NIH Office of Extramural Research (OER) **clarified and revised application instructions and review criteria** to enhance reproducibility of research findings
- Enhancing reproducibility through rigor and transparency
  - Scientific premise of proposed research
  - Rigorous experimental design
  - Consideration of sex and other relevant biological variables
  - Authentication of key biological and/or chemical resources
- Considering sex as a biological variable in NIH-funded research
- Applies to application submitted **Jan. 25, 2016** and beyond
  - Coming soon – updates to institutional training grants, institutional career development awards, and individual fellowships

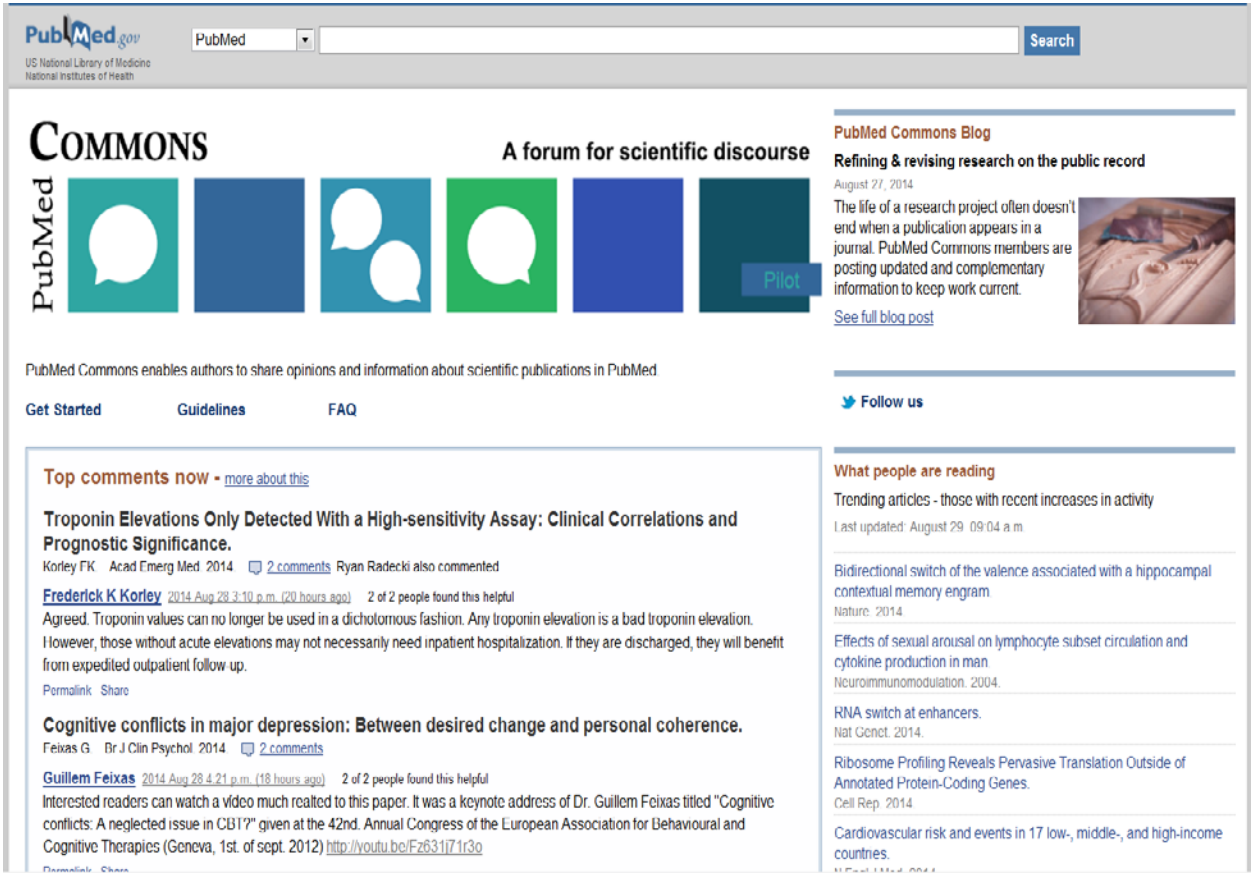
http://grants.nih.gov/reproducibility

Principles for Addressing Underlying Issues

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

Share Information/Data

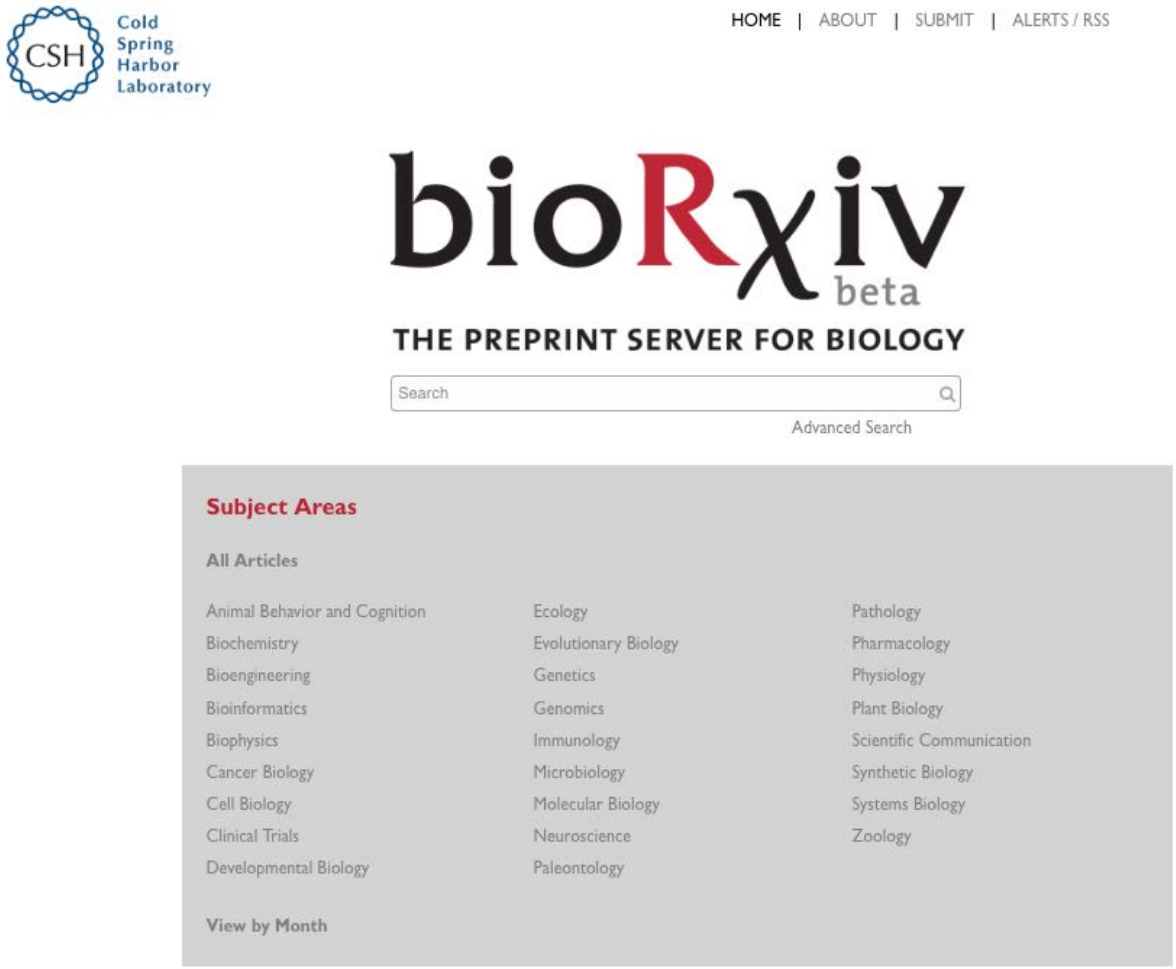
PubMed Commons: System allowing researchers to share opinions on publications indexed by PubMed



http://www.ncbi.nlm.nih.gov/pubmedcommons/

Share Information/Data

Efforts by Other Organizations: Recent Example



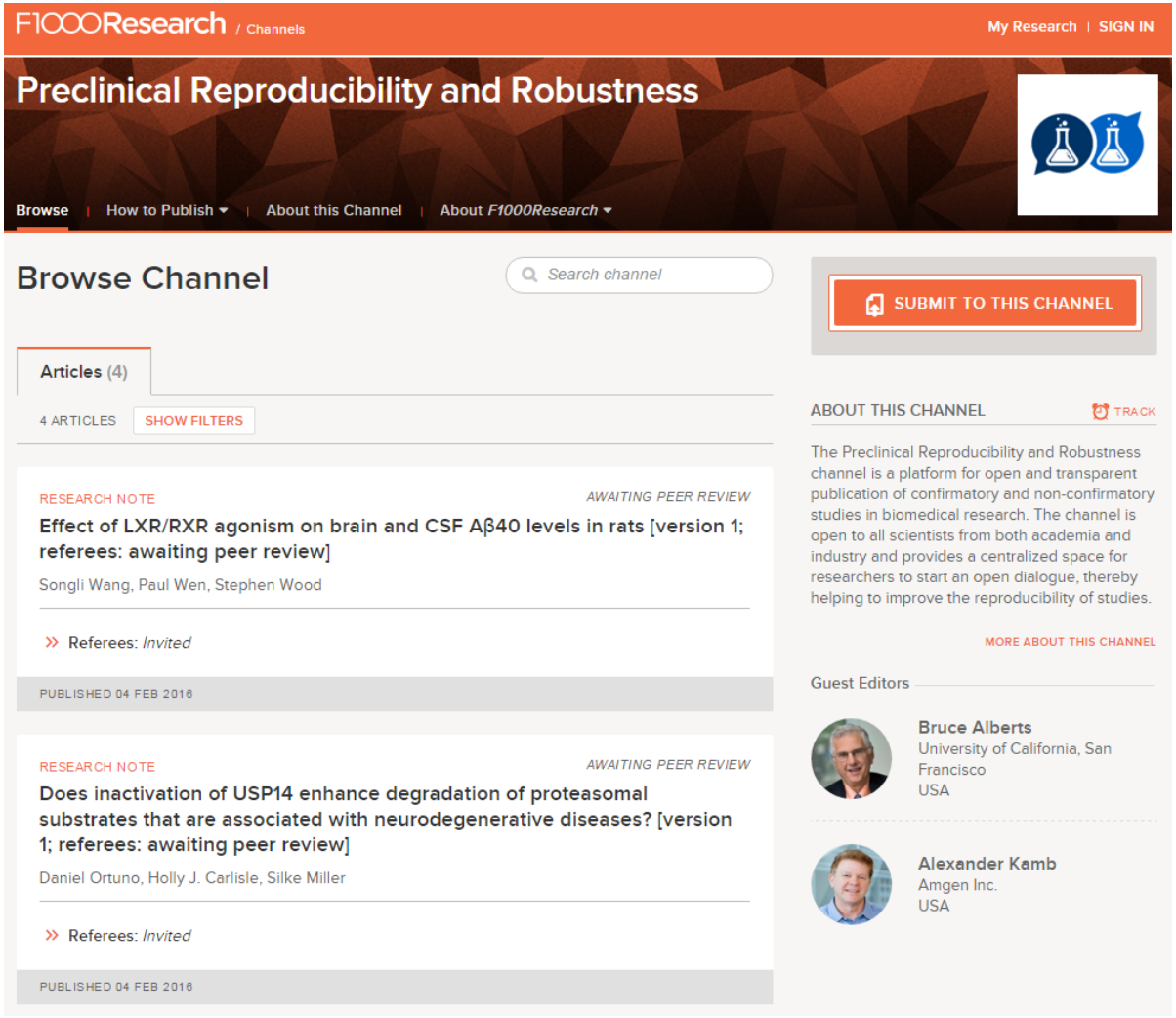
Share Information/Data

Team up with industry

Combining commercial and academic incentives and resources can improve science, argues **Aled Edwards**.

Share Information/Data

Efforts by Other Organizations: Recent Example



http://f1000research.com/channels/PRR

Principles for Addressing Underlying Issues

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

Investigator Stability

NIH is piloting the concept of awarding longer grants that provide more stable support

- Each Institute and Center will decide appropriate size, duration of their award
- Applications will not require specific aims in R01 format
  - Investigators describe research plans; demonstrate how they will translate prior accomplishments into future research approaches
- For investigators at all career stages
- Being pursued at NCI, NINDS, NIGMS

COMMENT

612 | NATURE | VOL 505 | 30 JANUARY 2014

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
balances that onc
have been hobble
the ability of today
others' findings.

Let's be clear:
have no evidenc
ducibility is abo
In 2011, the Offi
the US Departm
Services pursu
Even if this repr
the actual proble

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

Role for Individual Scientists

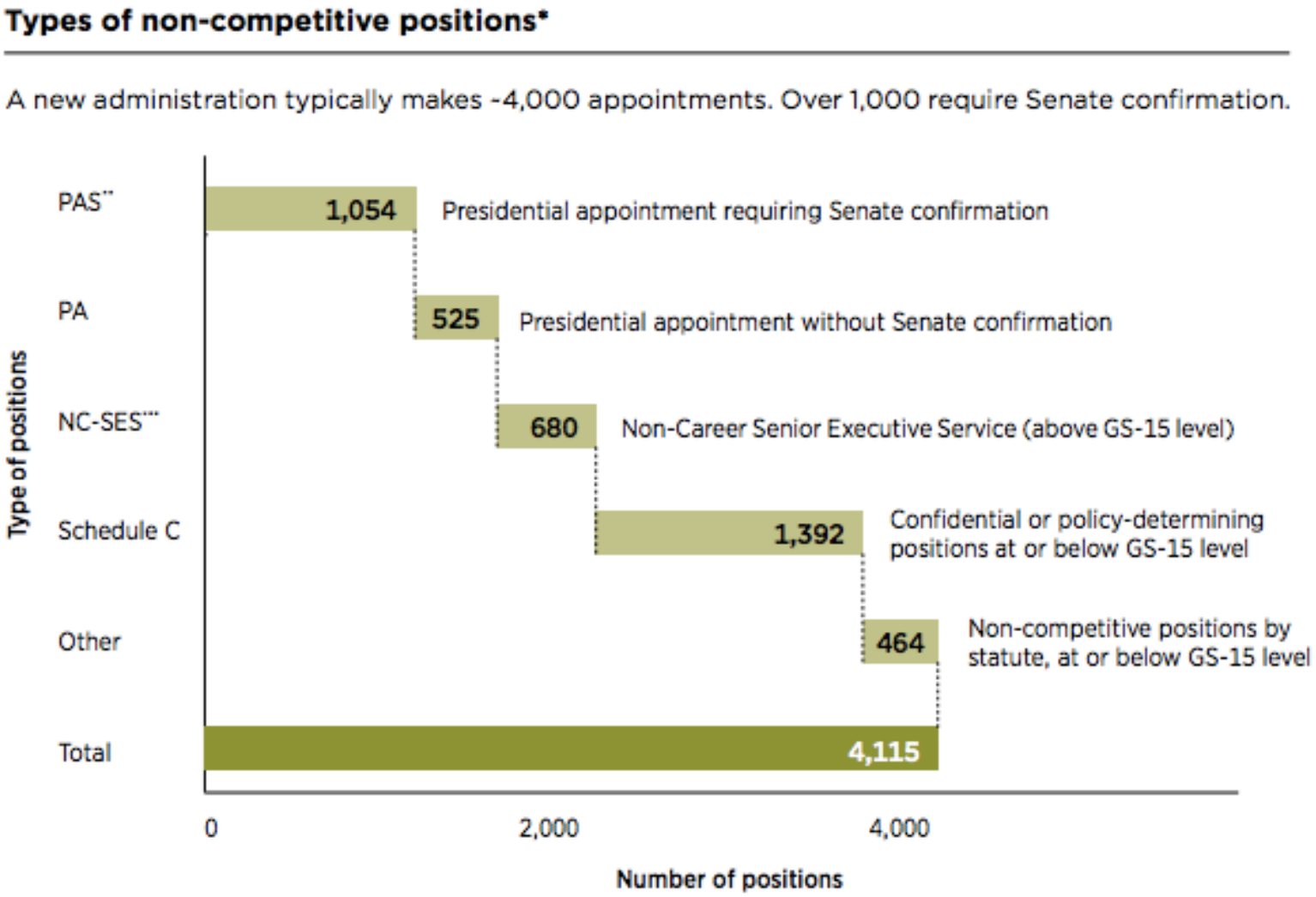
What you can do:

- Stimulate discussion amongst societies/organizations
- Increase transparency
- Promote training in experimental design
- Encourage data and material sharing
- Consider publication of refutations

Topics for Today

- Budget Update
- Enhancing Reproducibility and Transparency of Research Findings
- **Transitioning to a New Administration**

A New Administration: Presidential Transition



A New Administration: Presidential Transition

A New Administration: Presidential Transition

- Obama administration has convened the White House Transition Coordinating Council (WHTCC) and Agency Transition Directors Council (ATDC)
- Both campaigns have access to office space provided by GSA
- Transition leaders will select agency review teams and strategic priorities

A New Administration: Presidential Transition at the NIH

- Designation of "Acting"
- Preparation of materials

- Agency Review Teams arrive
- Selection of incoming Presidential Appointees begins

- Inauguration and onboarding of new Political Appointees begins




NIH...

Lawrence.Tabak@nih.gov

Turning Discovery Into Health