

# Strengthening Research Rigor and Reproducibility

- Update on NIH efforts to improve rigor
- Outcomes of NINDS training workshop
- Discuss the role of Institutions

## Disclaimer

Opinions I will voice are not official opinions of NIH

Shai D. Silberberg

National Institute of Neurological Disorders and Stroke  
National Institutes of Health

**Beware the creeping cracks of bias**

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

**Evaluation of Excess Significance Bias in Animal Studies of Neurological Diseases**

Raise standards for preclinical cancer research

**Why animal research needs to improve**

**When Mice Mislead**

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

**Helping editors, peer reviewers and authors improve the clarity, completeness and transparency of reporting health research**

**Bringing rigour to translational medicine**

**Drug targets slip-sliding away**

Unreliable research

**Trouble at the lab**

**Translating animal research into clinical benefit**

Reproducibility of science: Fraud, impact factors and carelessness

D.A. Eisner

October 2017

# Research health required

*The creation of a US Research Integrity Advisory Board is long overdue. Such a leadership body would mitigate bad practices and strengthen good research.*

November 2017

## Fighting fraud

*An Austrian success story shows one way to tackle misconduct.*

September 2018

“High-profile cases of exposed malpractice continue to pile up, and **surveys** of researchers regularly confirm that poor behaviour is shockingly more common than many who promote the values of science might want to accept.”



# Barking up the wrong tree!

(PNAS, 2012; 109:17028-17033)

## Misconduct accounts for the majority of retracted scientific publications

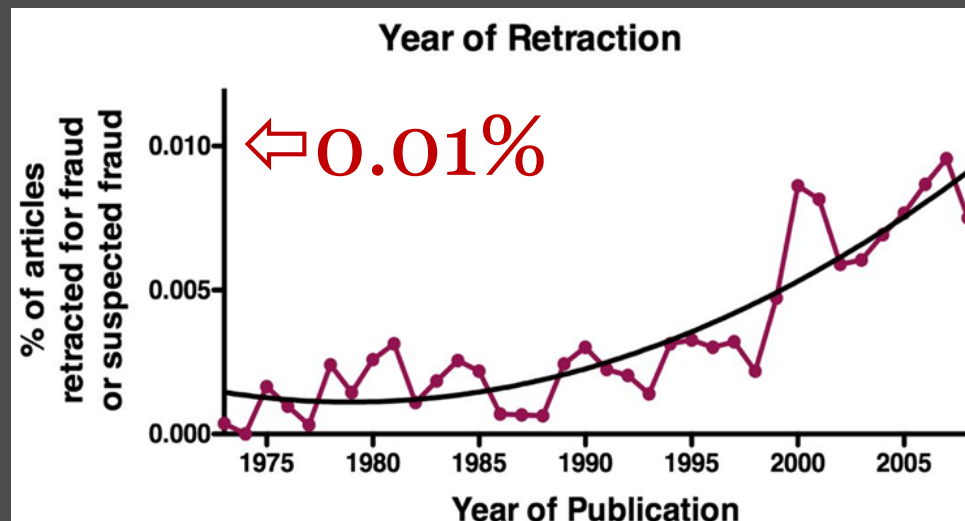
“The percentage of scientific articles retracted because of fraud has increased ~10-fold since 1975.”



## Stop ignoring misconduct

Efforts to reduce irreproducibility in research must also tackle the temptation to cheat, argue Donald S. Kornfeld and Sandra L. Titus.

*Nature*, 2016; 537: 29-30



# Human Nature

“Once a man’s understanding has settled on something (....), **it** draws everything else also to support and agree with it”

The New Organon, 1620

Unconscious bias



FRANCIS BACON

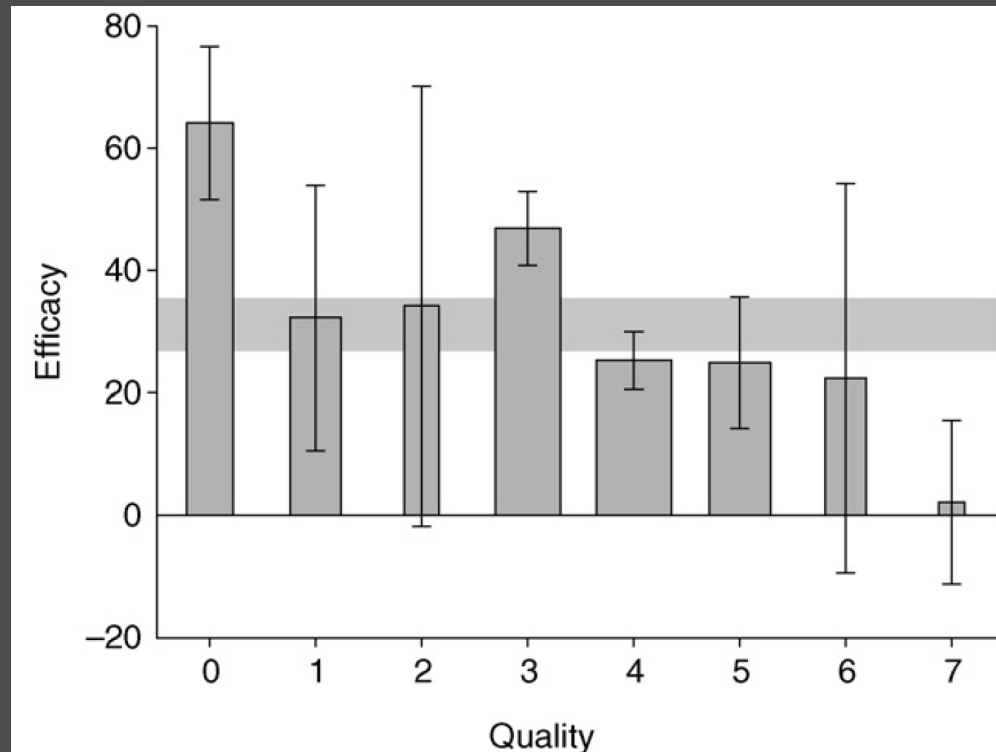
“I used to think that the brain was the most wonderful organ in my body. Then I realized who was telling me this.”

Emo Phillips



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The fewer methodological parameters are reported,  
the greater the apparent efficacy!



Effect size for studies of **FK506** (Tacrolimus) in experimental stroke.

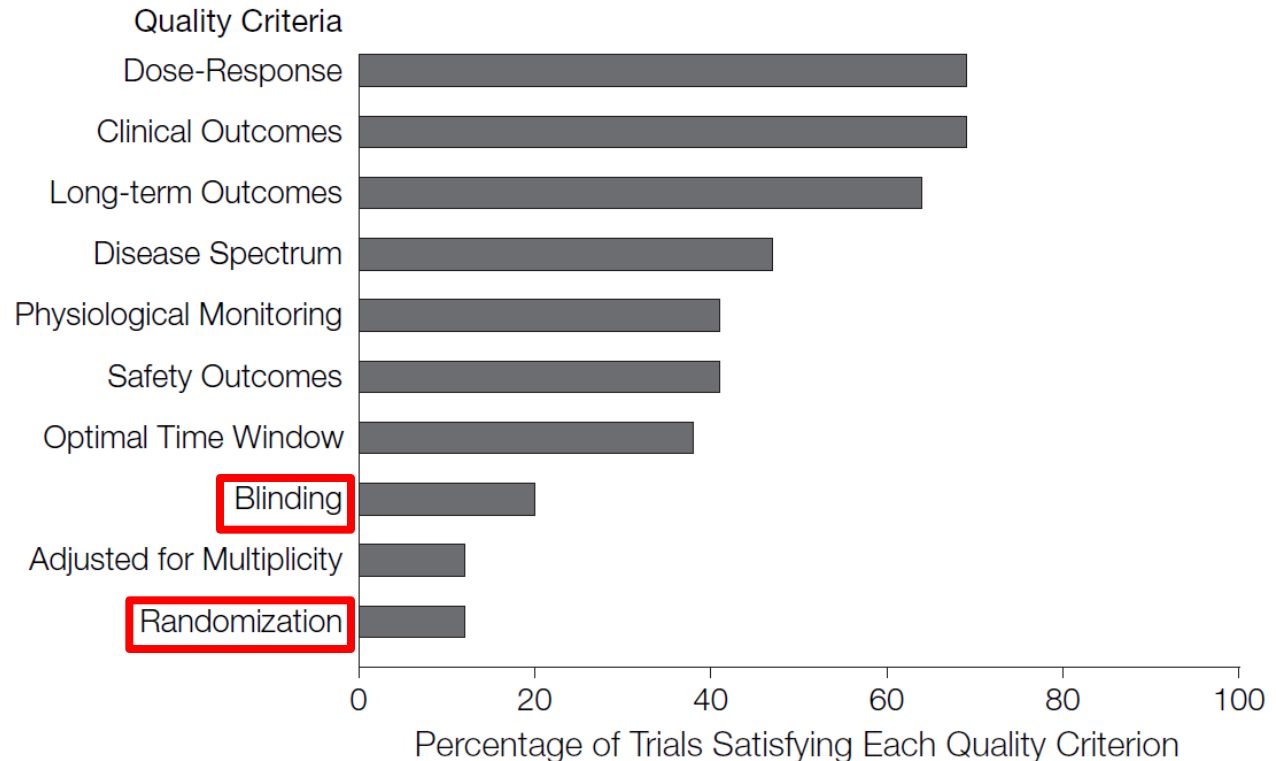
# Inadequate reporting is widespread

## Journals:

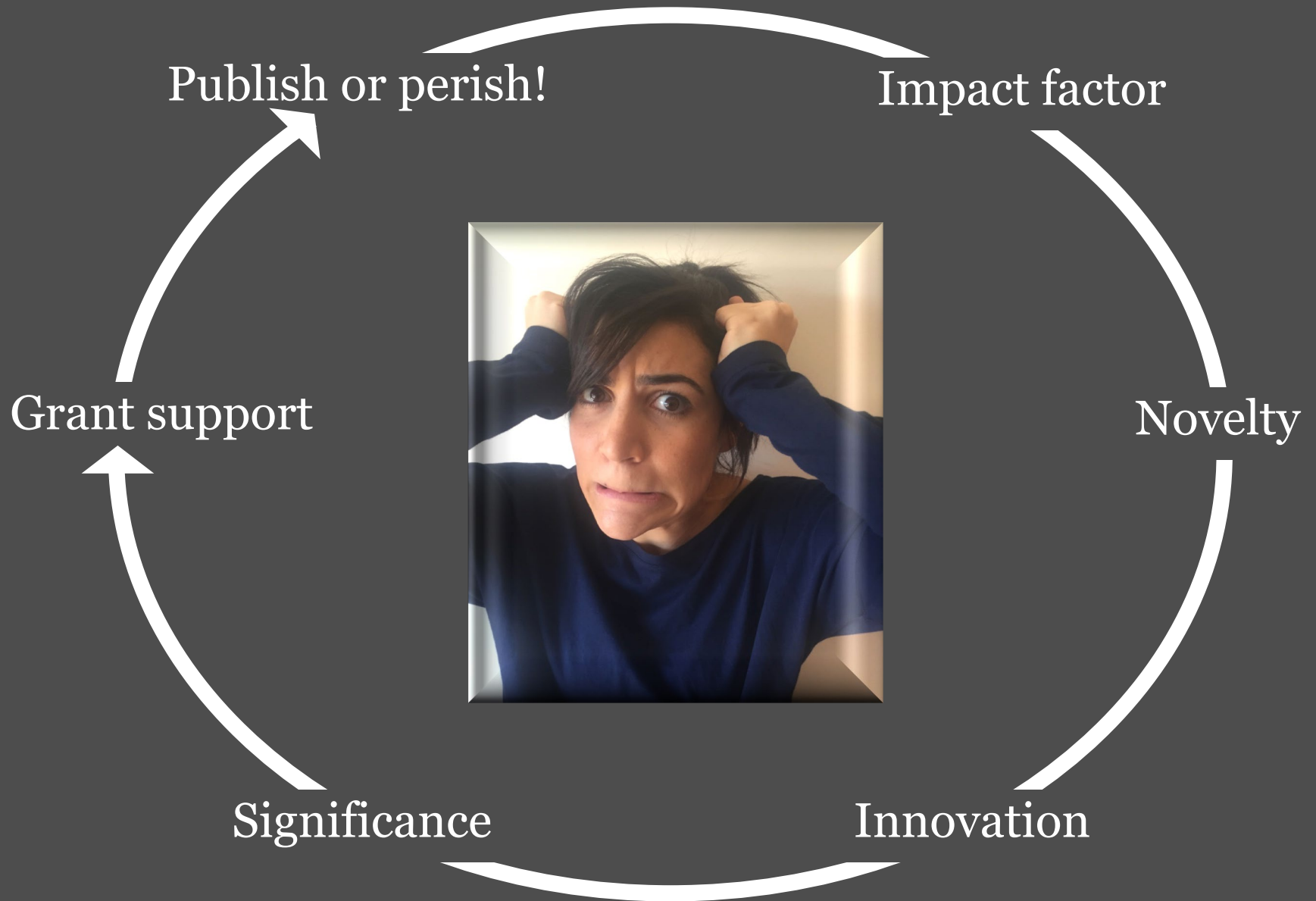
- Cell
- Nature
- Science
- Nature Medicine
- Nature Genetics
- Nature Immunology
- Nature Biotechnology

>500 citations

**Figure 1.** Methodological Quality of Animal Trials (n=76)



Paper money!



Institution  
administration

Funders

Journal editors

Reviewers



# Research Program Award (R35 Clinical Trial Optional)

- ❑ A more stable funding environment, facilitating the pursuit of longer term research goals
- ❑ Flexible funding, enabling investigators to pursue research opportunities as they arise, not tied to specific aims
- ❑ Reduced time spent writing grant applications and managing multiple grant awards, thereby allowing investigators to spend more time conducting and overseeing research
- ❑ More time for PDs/PIs to mentor junior scientists

# Improving the Review of Manuscripts and Grants





# Optimizing the Predictive Value of Preclinical Research

June 20 – 21, 2012  
Washington Plaza Hotel  
Washington DC



Editors



Funders



Investigators



Reviewers

## A call for transparent reporting to optimize the predictive value of preclinical research

Story C. Landis<sup>1</sup>, Susan G. Amara<sup>2</sup>, Khusru Asadullah<sup>3</sup>, Chris P. Austin<sup>4</sup>, Robi Blumenstein<sup>5</sup>, Eileen W. Bradley<sup>6</sup>, Ronald G. Crystal<sup>7</sup>, Robert B. Darnell<sup>8</sup>, Robert J. Ferrante<sup>9</sup>, Howard Fillit<sup>10</sup>, Robert Finkelstein<sup>1</sup>, Marc Fisher<sup>11</sup>, Howard E. Gendelman<sup>12</sup>, Robert M. Golub<sup>13</sup>, John L. Goudreau<sup>14</sup>, Robert A. Gross<sup>15</sup>, Amelie K. Gubitzi<sup>1</sup>, Sharon E. Hesterlee<sup>16</sup>, David W. Howells<sup>17</sup>, John Huguenard<sup>18</sup>, Katrina Kelner<sup>19</sup>, Walter Koroshetz<sup>1</sup>, Dimitri Krainc<sup>20</sup>, Stanley E. Lazic<sup>21</sup>, Michael S. Levine<sup>22</sup>, Malcolm R. Macleod<sup>23</sup>, John M. McCall<sup>24</sup>, Richard T. Moxley III<sup>25</sup>, Kalyani Narasimhan<sup>26</sup>, Linda J. Noble<sup>27</sup>, Steve Perrin<sup>28</sup>, John D. Porter<sup>1</sup>, Oswald Steward<sup>29</sup>, Ellis Unger<sup>30</sup>, Ursula Utz<sup>1</sup> & Shai D. Silberberg<sup>1</sup>

The US National Institute of Neurological Disorders and Stroke convened major stakeholders in June 2012 to discuss how to improve the methodological reporting of animal studies in grant applications and publications. The main workshop recommendation is that at a minimum studies should report on sample-size estimation, whether and how animals were randomized, whether investigators were blind to the treatment, and the handling of data. We recognize that achieving a meaningful improvement in the quality of reporting will require a concerted effort by investigators, reviewers, funding agencies and journal editors. Requiring better reporting of animal studies will raise awareness of the importance of rigorous study design to accelerate scientific progress.

**nature**

ANNOUNCEMENT

# Reducing our irreproducibility

*“...we will more systematically ensure that key methodological details are reported, and we will give more space to methods sections. We will examine statistics more closely and encourage authors to be transparent, for example by including their raw data.”*

**nature  
immunology**

Raising standards

**nature  
structural &  
molecular biology**

Raising standards

**nature  
cell biology**

Raising reporting standards

**nature  
neuroscience**

Raising standards

**EDITORIAL**

**NATURE MEDICINE**

Raising standards

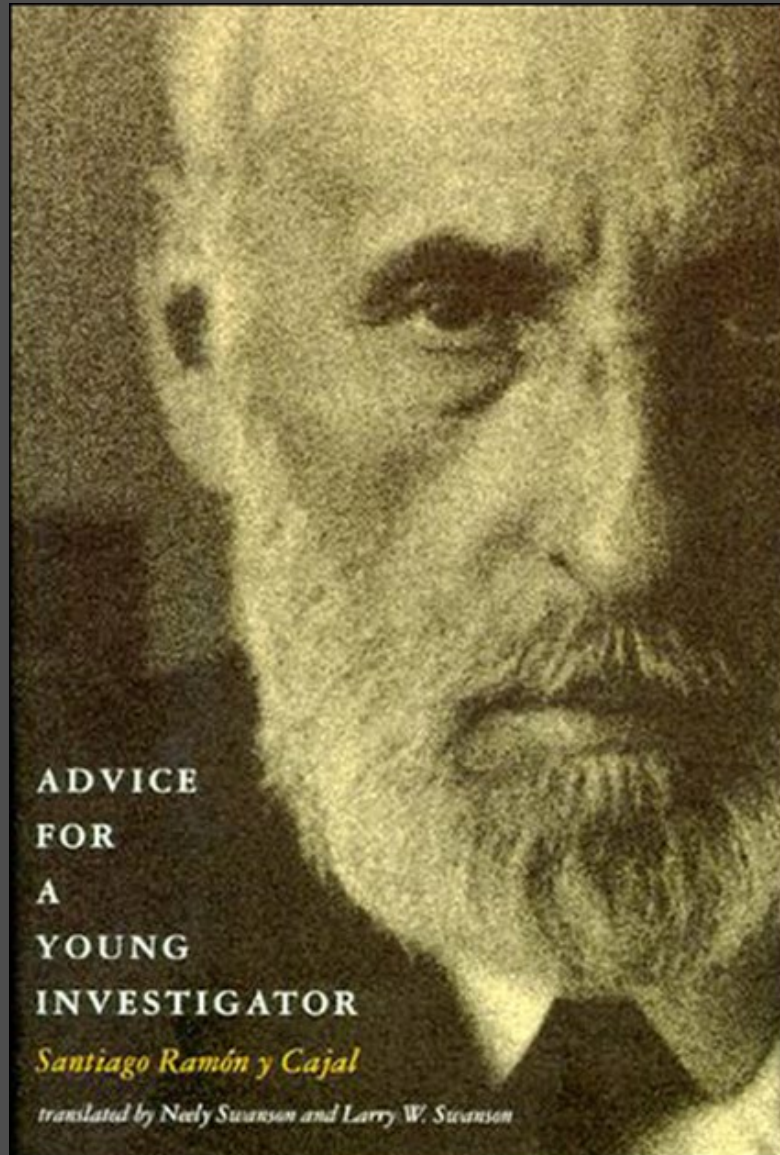
# Implementing Rigor and Transparency in NIH & AHRQ Research Grant Applications



# NIH & AHRQ Announce Upcoming Updates to Application Instructions and Review Criteria for Research Grant Applications

“....replacing the term "scientific premise" with "the rigor of the prior research" and adding instruction and review language so that "the rigor of the prior research" is addressed under Significance and Approach”

# Education & Culture



ADVICE  
FOR  
A  
YOUNG  
INVESTIGATOR

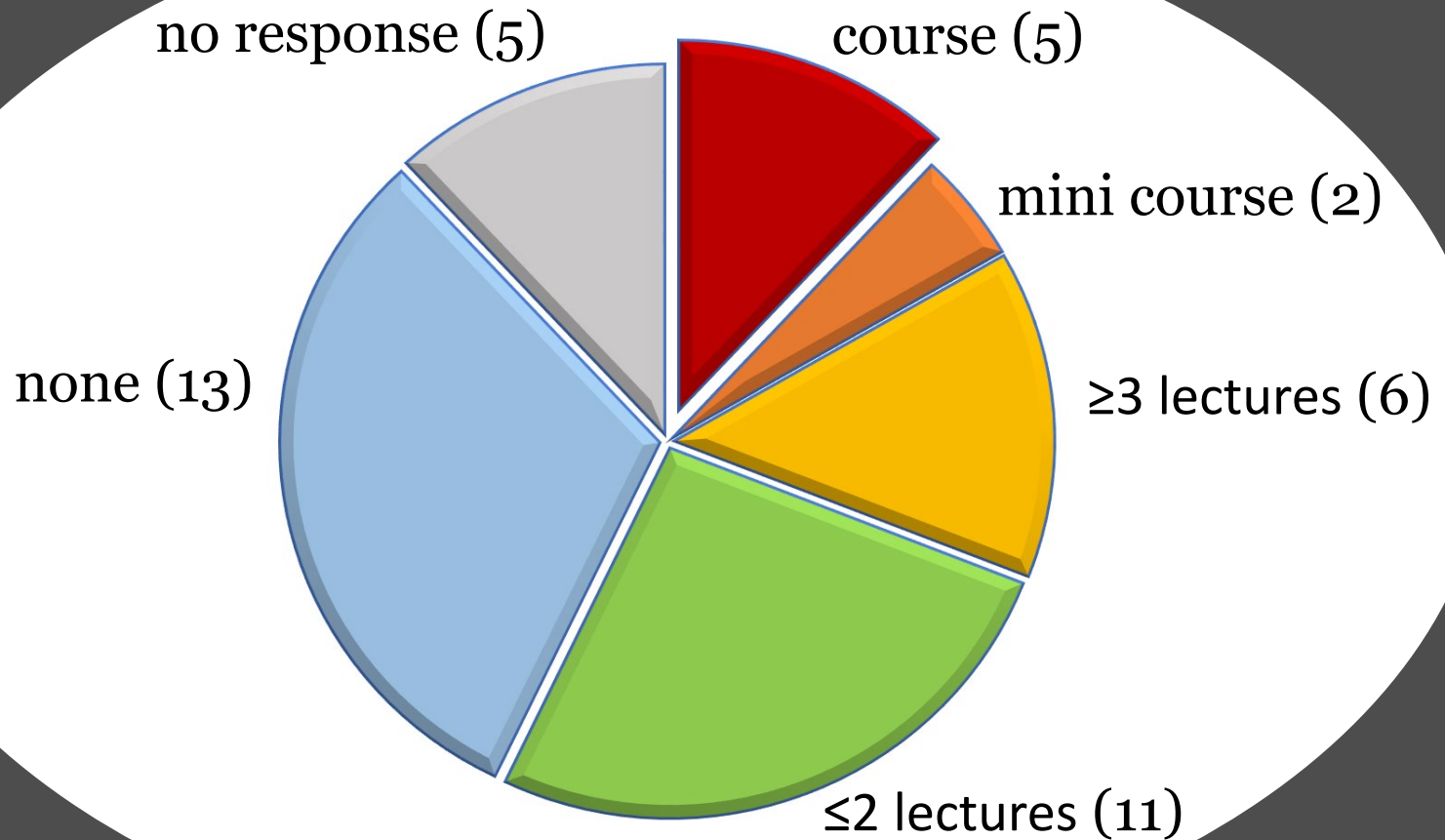
*Santiago Ramón y Cajal*

*translated by Neely Swanson and Larry W. Swanson*

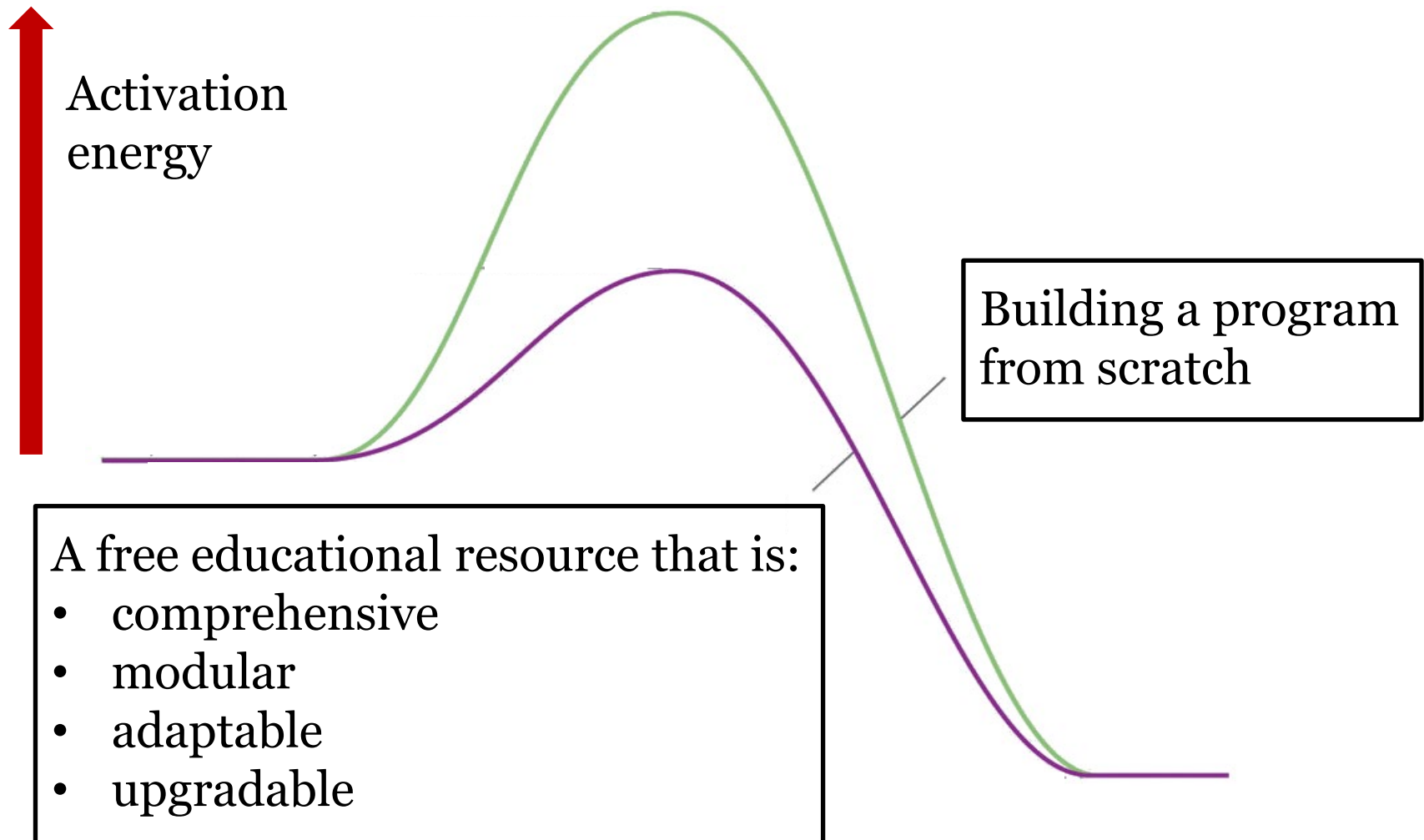
# Jointly Sponsored Ruth L. Kirschstein National Research Service Award Institutional Predoctoral Training Program in the Neurosciences (T32)

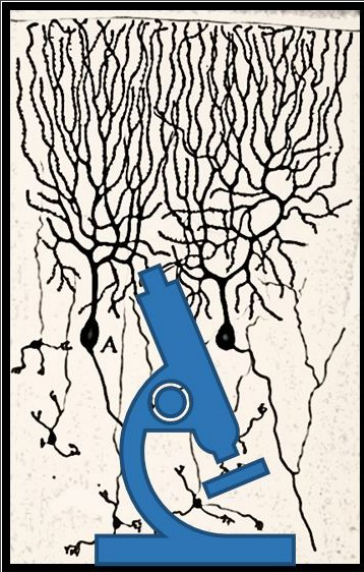
“The training supported by the JSPTPN must be grounded in principles of rigorous experimental design, an understanding of the critical need for, and proper use of, statistics, and quantitative literacy.”

# Survey of formal training in the principles of rigorous research at Institutions with neuroscience training grants (n=42)



# The value of a visionary educational resource to instill the principles of rigorous research





# A Visionary Resource for Instilling Fundamental Principles of Rigorous Neuroscience Research Workshop

Natcher Conference Center  
NIH Campus  
Bethesda, MD

October 22-23, 2018

<https://meetings.ninds.nih.gov/meetings/RigorResource/>

# Agenda

- ❖ Keynote address: Prof. Malcolm Macleod
- ❖ Session 1: What are the fundamental principles of rigorous neuroscience research?
- ❖ Session 2: How best to instill the principles of rigorous research in traditional settings such as the lab and classroom?
- ❖ Session 3: How best to instill the principles of rigorous research using non-traditional educational tools

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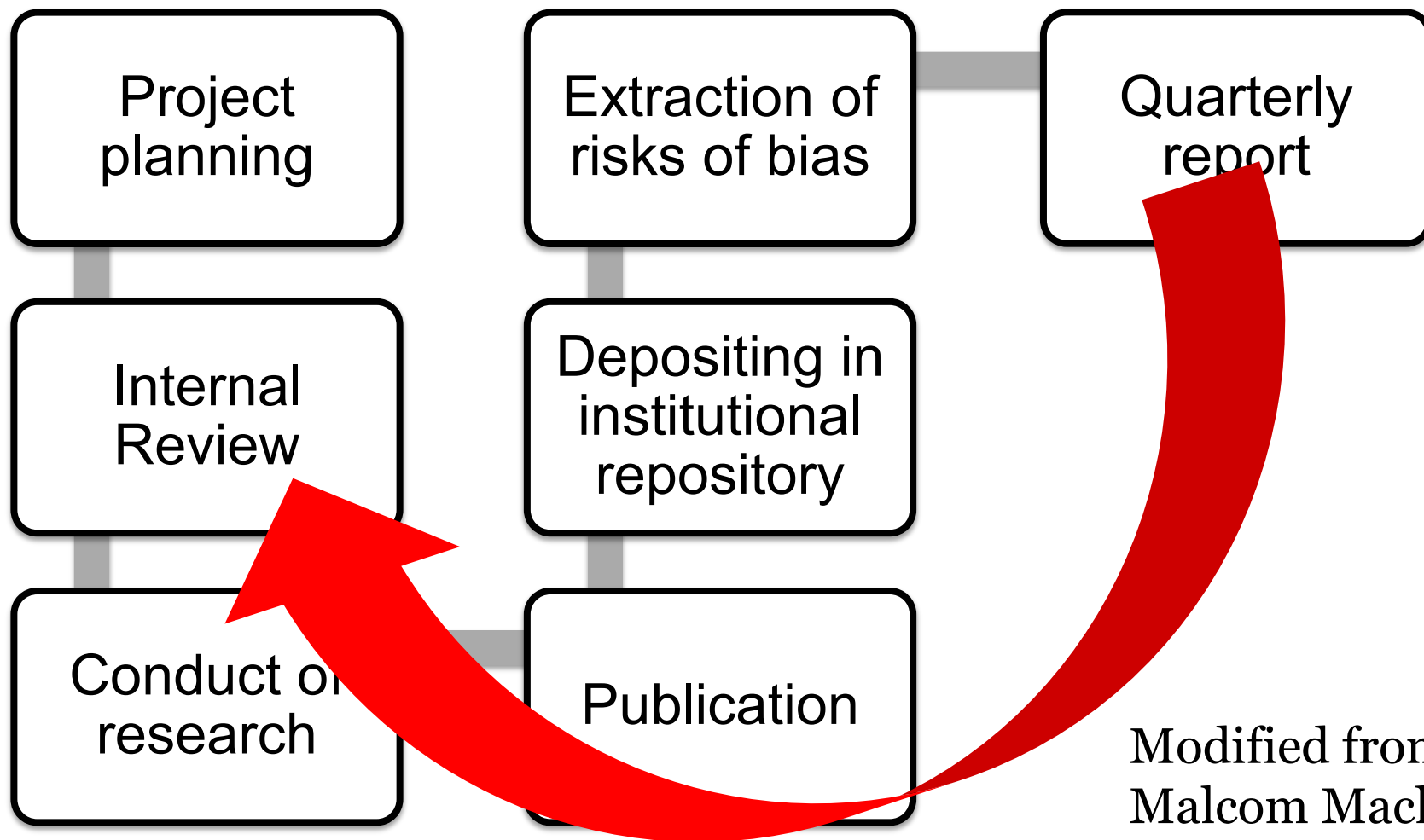
- ❖ Session 4: Vision of a living educational resource for students, educators, and scientists
- ❖ Session 5: Recommendations

# Major recommendations

- ✓ Most important principles of rigorous research agreed upon
  - May take different forms in different settings
- ✓ Culture change is required at all levels
  - From undergraduates to senior faculty
  - Embrace failures
- ✓ The resource should be targeted to all career stages
- ✓ Evaluations must include assessment of behavioral change
- ✓ Community needs to champion efforts and share resources
- ✓ Institutions need to step up!



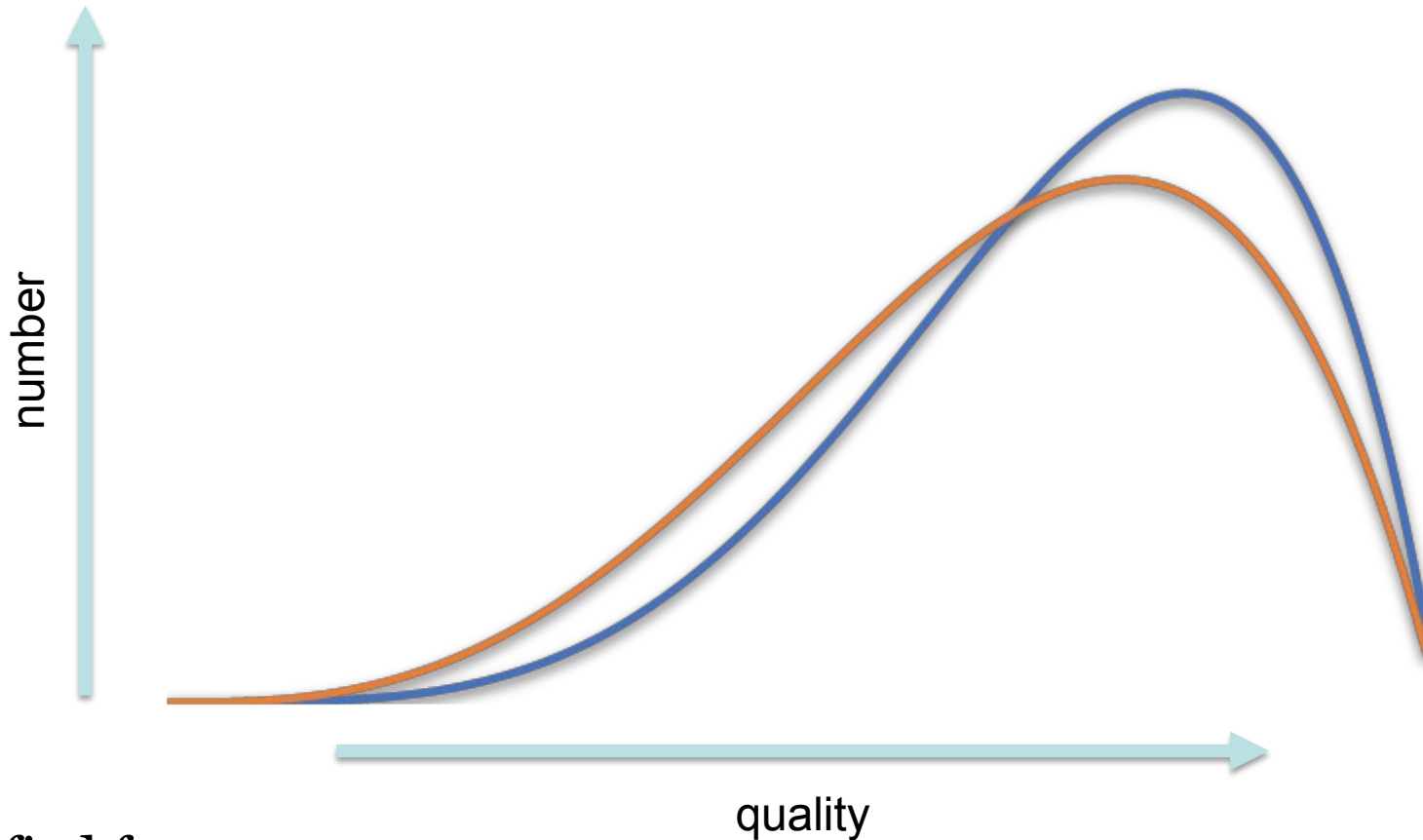
# Would you fund an institution that did not have a research improvement strategy?



Modified from  
Malcom Macleod



# Research Improvement Strategy



on

Modified from  
Malcom Macleod

“Action is the foundational  
key to all success”

Pablo Picasso

