

Enhancing the Reproducibility and Transparency of Research Findings

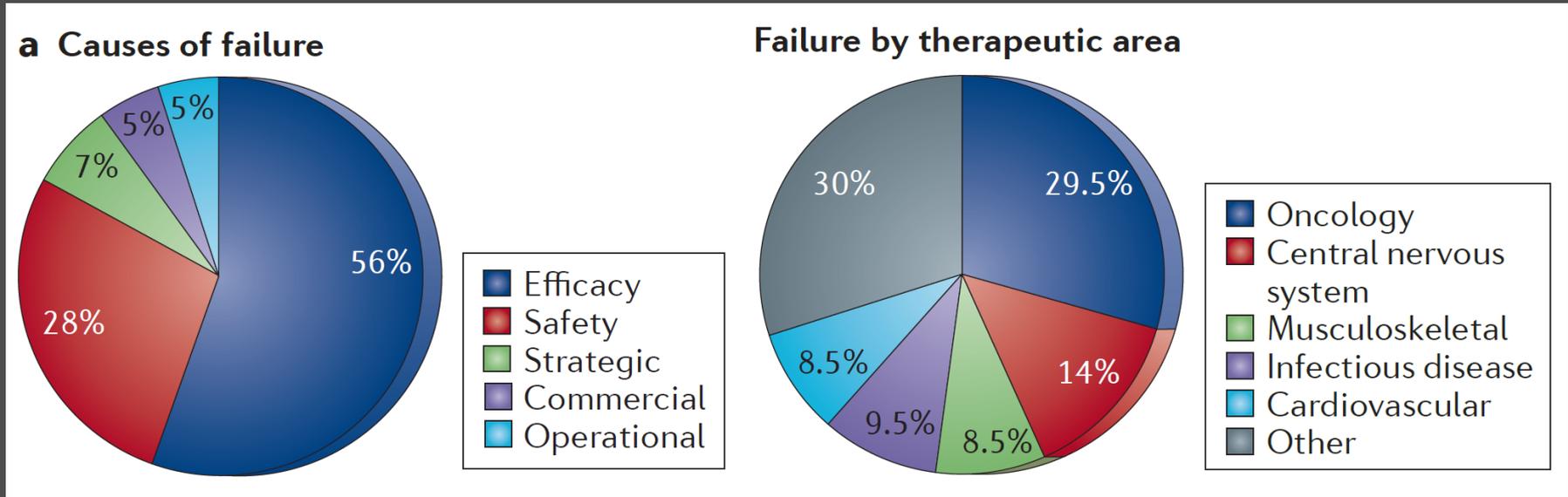
Disclaimer

Opinions I will voice are
NOT official opinions of NIH

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National Institutes of Health

Trial Watch: Phase II and Phase III attrition rates 2011–2012



Arrowsmith & Miller, *Nature Reviews Drug Discovery*, 2013; 12:569

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

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

When Mice Mislead

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

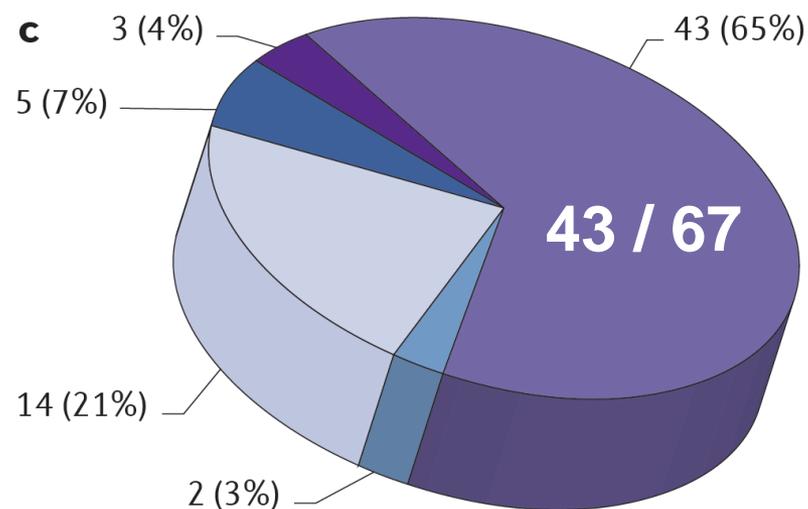
Translating animal research into clinical benefit

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

Prinz, Schlange and Asadullah

Bayer HealthCare

Nature Reviews Drug Discovery
2011; 10:712-713

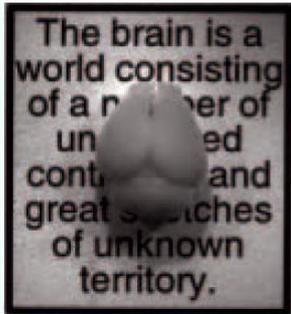


- Inconsistencies
- Not applicable
- Literature data are in line with in-house data
- Main data set was reproducible
- Some results were reproducible

Causes for low reproducibility

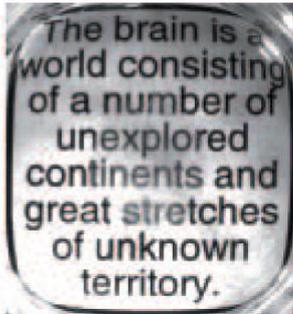
Complex innovative techniques

Before



The brain is a world consisting of a number of unexplored continents and great stretches of unknown territory.

After CLARITY



The brain is a world consisting of a number of unexplored continents and great stretches of unknown territory.

Confounding variables



“Unknown unknowns”

Problems with resources



- ❑ Transparency in the reporting of experimental design, conduct, and analysis
- ❑ **Experimental bias** (Human nature)
- ❑ **Chance and publication bias**

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

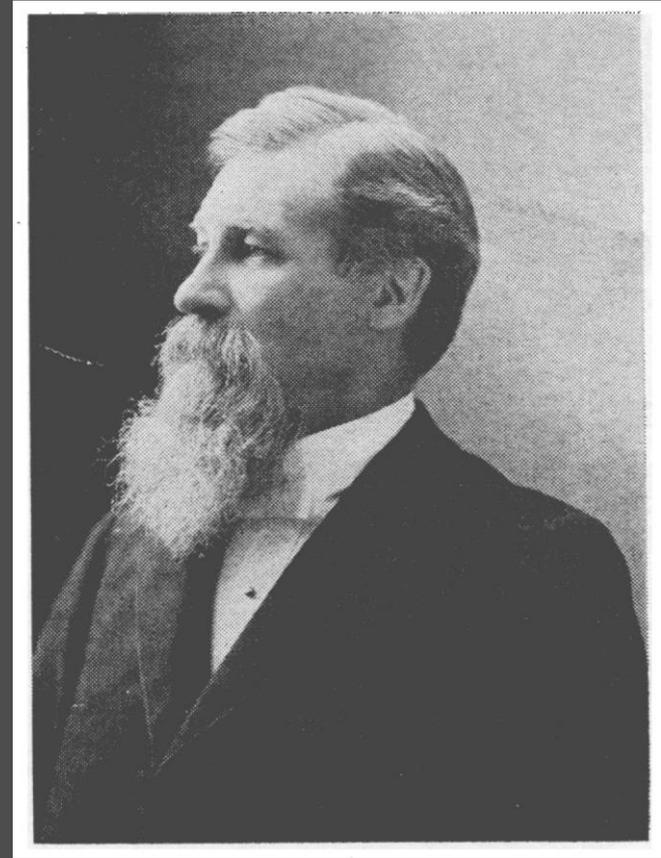


FRANCIS BACON

The Method of Multiple Working Hypotheses

“The moment one has offered an original explanation for a phenomenon which seems satisfactory, that moment affection for his intellectual child springs into existence”

Journal of Geology, 1897



Thomas Chrowder
Chamberlin

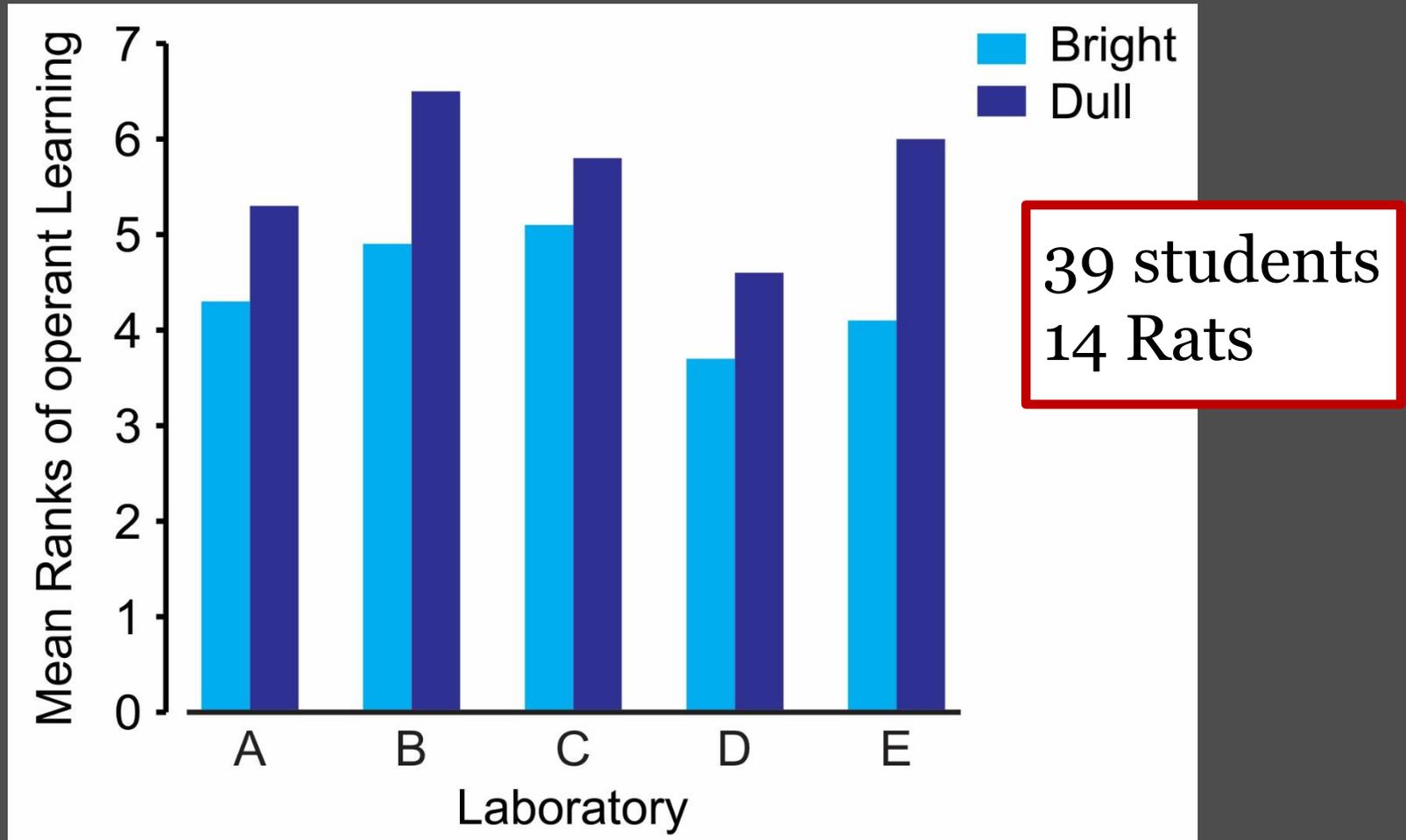
The definition of experimental bias

“The reliability of a study is determined by the investigator’s choices about critical details of research design and conduct”

“**Bias is unintentional and unconscious.** It is defined broadly as the systematic erroneous association of some characteristic with a group in a way that distorts a comparison with another group.....”

“.....The process of addressing bias involves **making everything equal during the design, conduct and interpretation of a study,** and reporting those steps in an explicit and **transparent** way.”

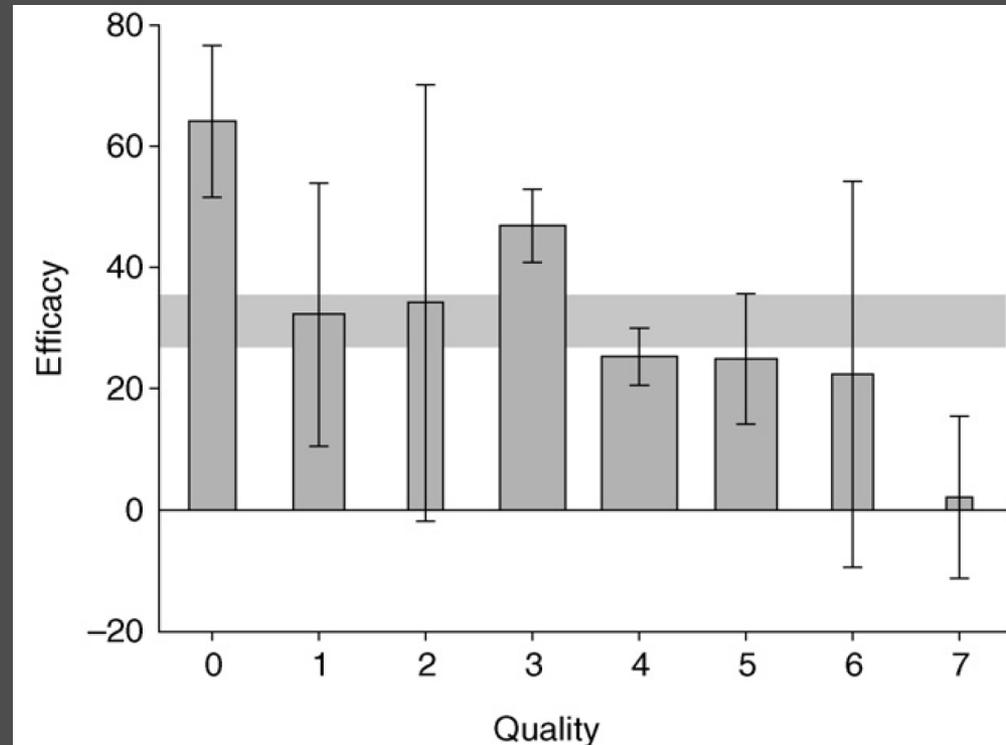
A LONGITUDINAL STUDY OF THE EFFECTS OF
EXPERIMENTER BIAS ON THE OPERANT LEARNING OF
LABORATORY RATS*



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

	<i>Number of publications</i>	<i>Masked assessment of outcome (%)</i>	<i>Random allocation to group (%)</i>	<i>Sample size calculation (%)</i>
Alzheimer's disease ³⁰	428	95 (22)	67 (16)	0 (0)
Multiple sclerosis ¹¹	1,117	178 (16)	106 (9)	2 (< 1)
Parkinson's disease ³¹	252	38 (15)	40 (16)	1 (< 1)
Intracerebral hemorrhage ³²	88	43 (49)	27 (31)	0 (0)

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



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

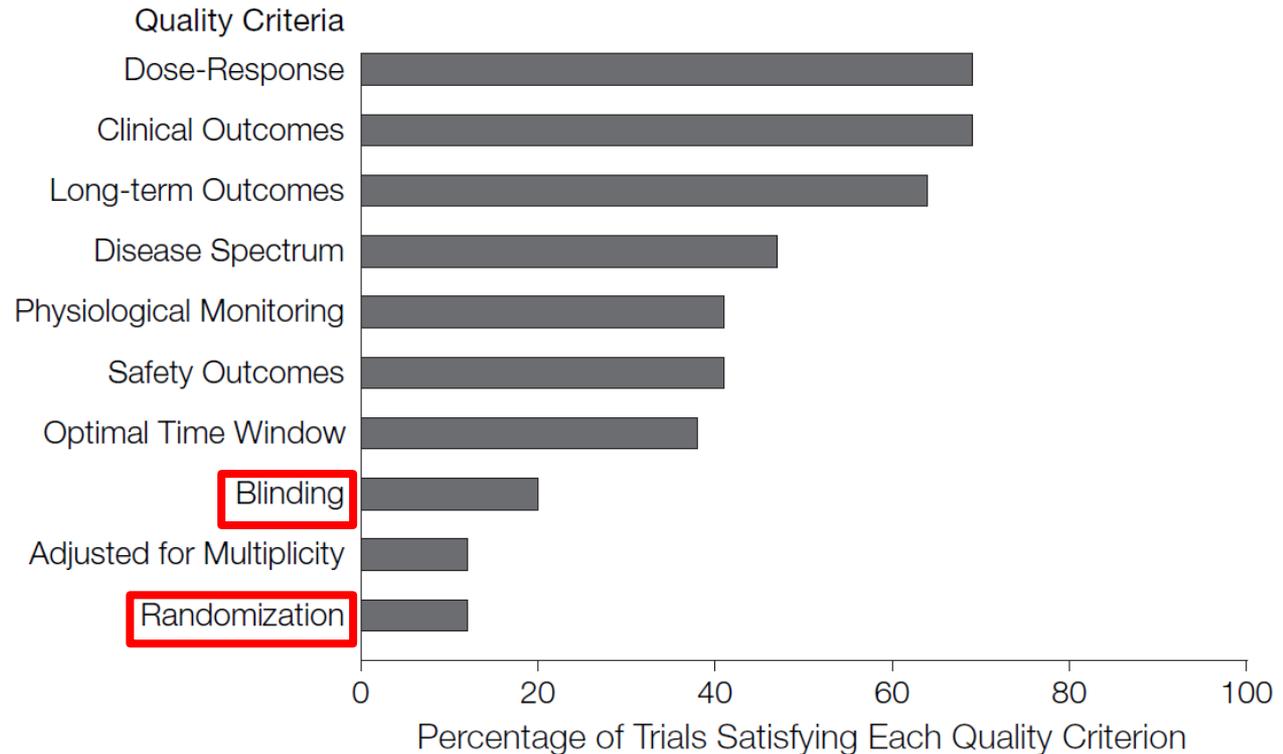
Inadequate reporting is widespread

Journals:

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

>500 citations

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

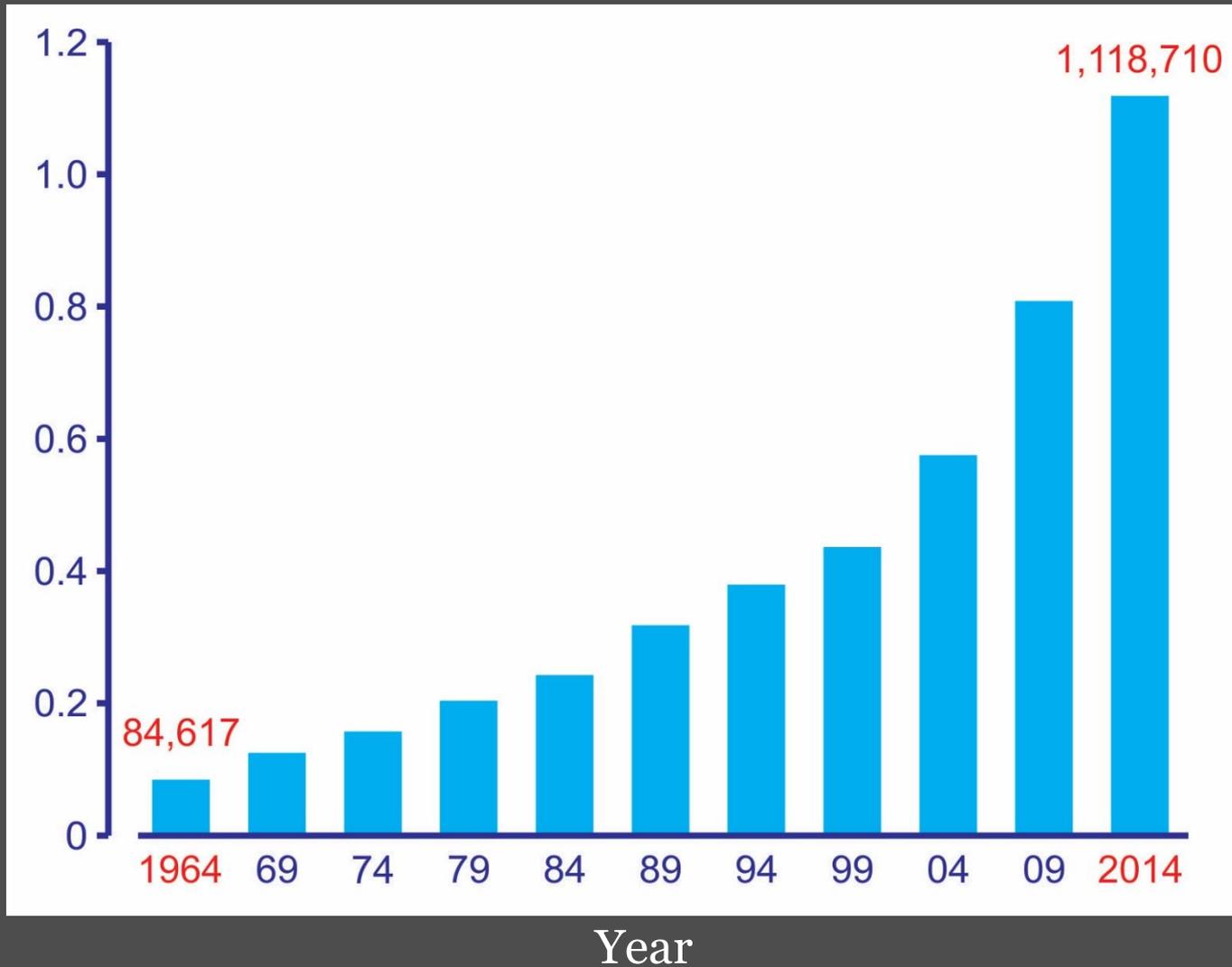


Peer Review

“Peer review is the evaluation of work by one or more people of similar competence to the producers of the work.”

The Escalation in Scientific Reporting (Annual PubMed Publications in English)

Publications
(x10⁶)



Publish or perish!

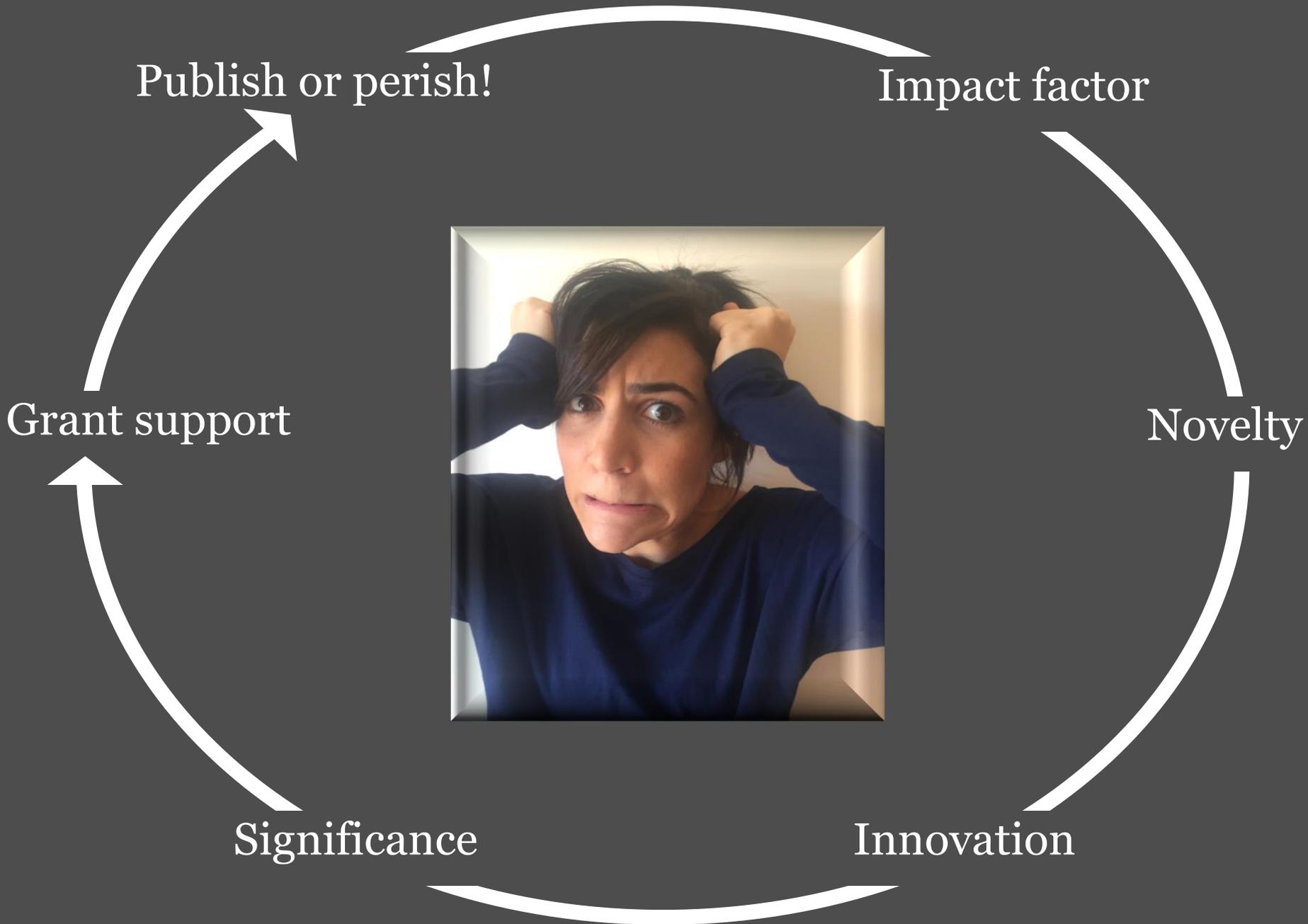
Impact factor

Novelty

Innovation

Significance

Grant support



Publication Bias

Research Question



hypothesis



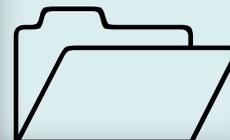
Experiments
to test the hypothesis



Publish!



File



“Publication bias in reports of animal stroke studies leads to overstatement of efficacy”

“We identified 16 systematic reviews of interventions tested in animal studies of acute ischaemic stroke involving **525** unique publications.

Only ten publications (2%) reported no significant effects on infarct volume.”

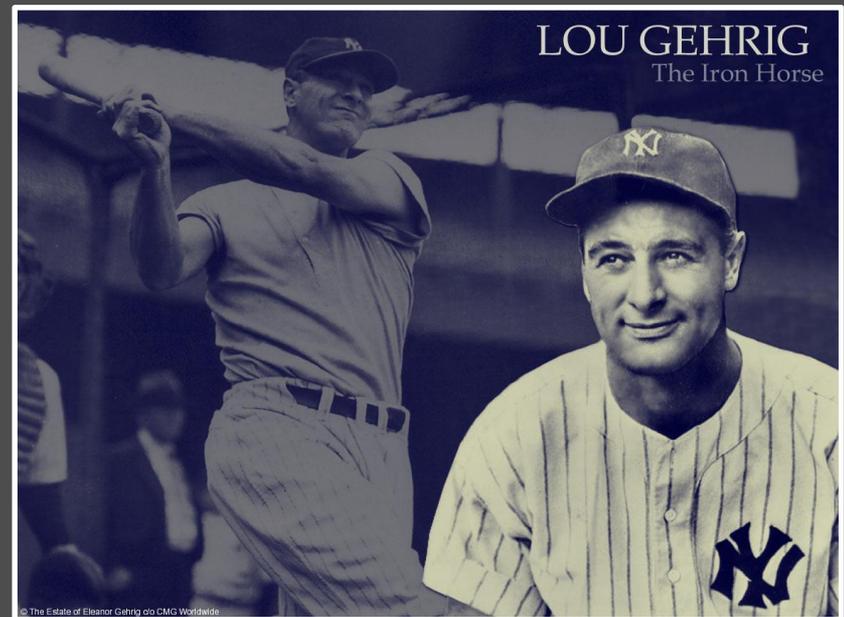
Amyotrophic lateral sclerosis (ALS)

- Death within 5 years of diagnosis
- Central pathological finding is motor neuron death
- 3% of cases from gain of function mutations in SOD1
- Rodents over-expressing SOD1 recapitulate ALS

2002: **Minocycline** reported to extend survival of SOD1 mice

2003: Randomized placebo controlled trial (412 patients treated for 9 months)

2007: Results of the trial are published - **minocycline** found to have a harmful effect on patients with ALS



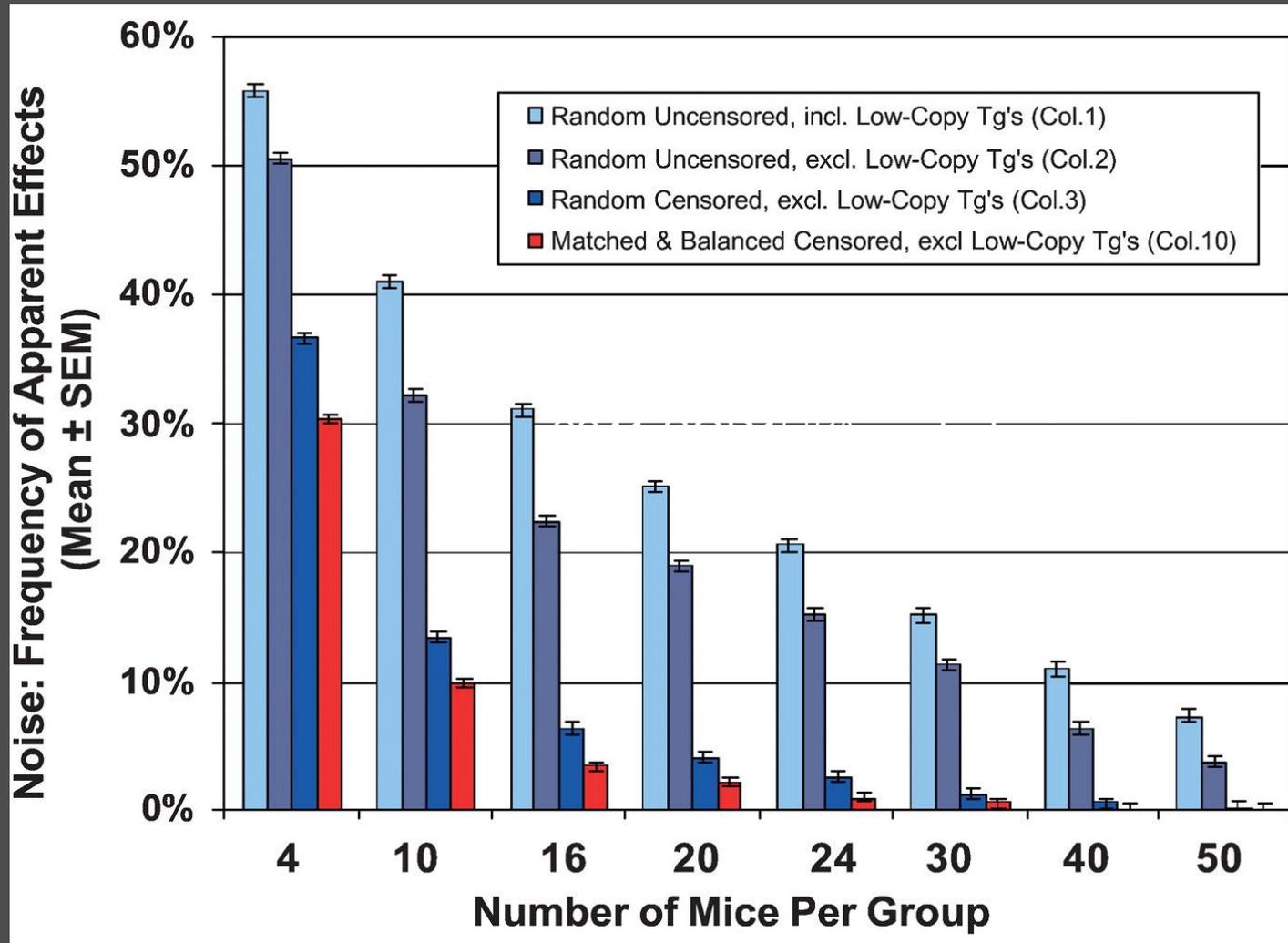
Design, power, and interpretation of studies in the standard murine model of ALS

ALS Therapy Development Institute (ALS TDI)

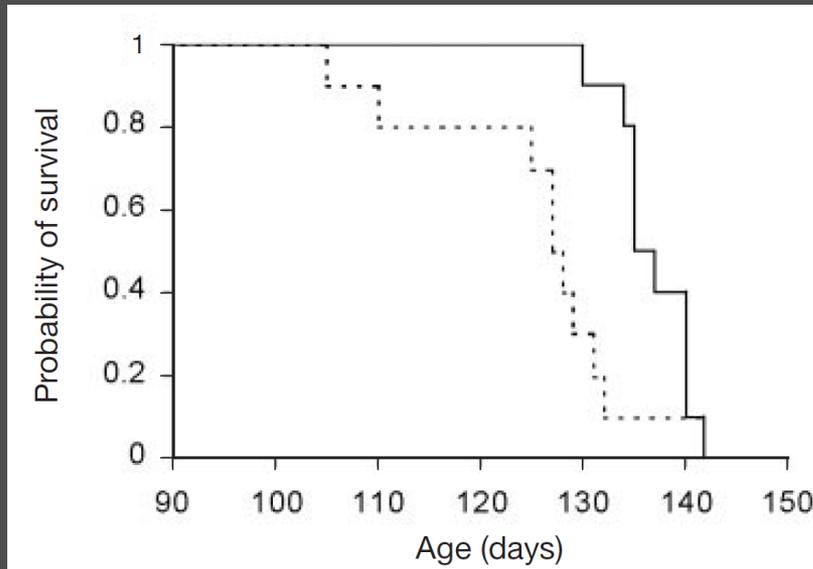
- Screened more than 70 drugs in 18000 mice across 221 studies
- Used rigorous and appropriate statistical methodologies
- measured a significant difference in survival between males and females with great sensitivity
- **No statistically significant positive (or negative) effects for any of the compounds tested, including several previously reported as efficacious.**

“...the majority of published effects are most likely measurements of **noise in the distribution of survival means** as opposed to actual drug effect.”

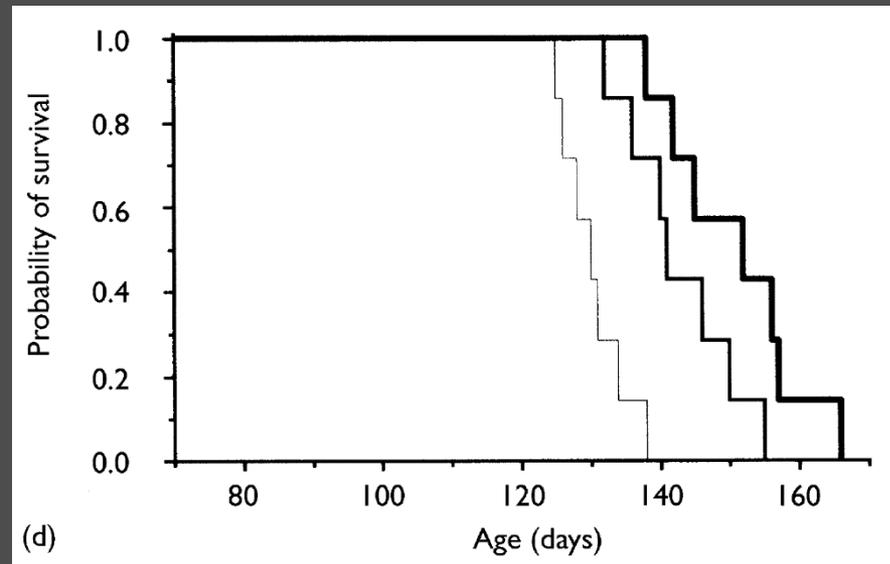
The probability of seeing an apparent effect by chance is significant even with 10 animals per group



The survival benefit of minocycline in the SOD1^{G93A} mouse model of ALS might be due to small sample size and/or Bias



- SOD1^{G93A} transgenic mice
- Started at 5 weeks of age
- i.p. 10mg/kg/day
- **10** animals / group (sex?)
- **Not randomized**
- **Not blinded**



- SOD1^{G93A} transgenic mice
- Started at 10 weeks of age
- i.p. 25 and 50 mg/kg/day
- **7** animals / group (females)
- **Not randomized**
- **“The experimenter was blinded to the treatment protocol.”**

How to improve reproducibility?

Lack of transparency
in reporting

Review



Transparency
in reporting

Unconscious bias;
Deficient experimental
procedures

Chance and
Publication bias

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
structural &
molecular biology**

Raising standards

**nature
cell biology**

Raising reporting standards

**nature
neuroscience**

Raising standards

**nature
immunology**

Raising standards

EDITORIAL

NATURE MEDICINE

Raising standards

Scientific Premise of Proposed Research

The scientific premise for an application is the research that is used to form the basis for the proposed research question.

NIH expects applicants to describe the general strengths and weaknesses of the prior research being cited by the investigator as crucial to support the application.



Rigorous Experimental Design

NIH expects applicants to describe how they will achieve robust and unbiased results when describing the experimental design and proposed methods.



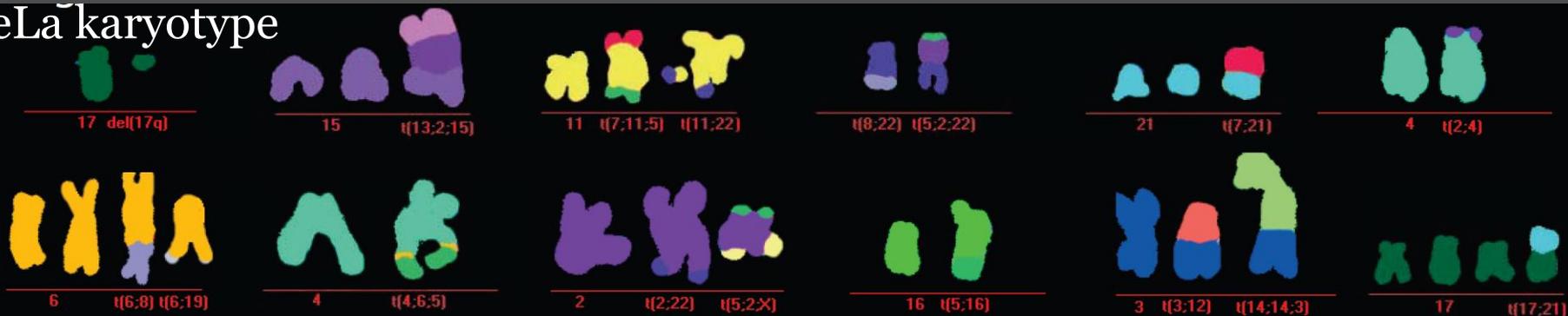
The Flight of Icarus (by Jacob Peter Gowdy)

Authentication of Key Biological and/or Chemical Resources

NIH expects that key biological and/or chemical resources will be regularly authenticated to ensure their identity and validity for use in the proposed studies.

Researchers should transparently report on what they have done to authenticate key resources, so that consensus can emerge.

HeLa karyotype



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Education

Attentiveness to bias;
Good experimental
design

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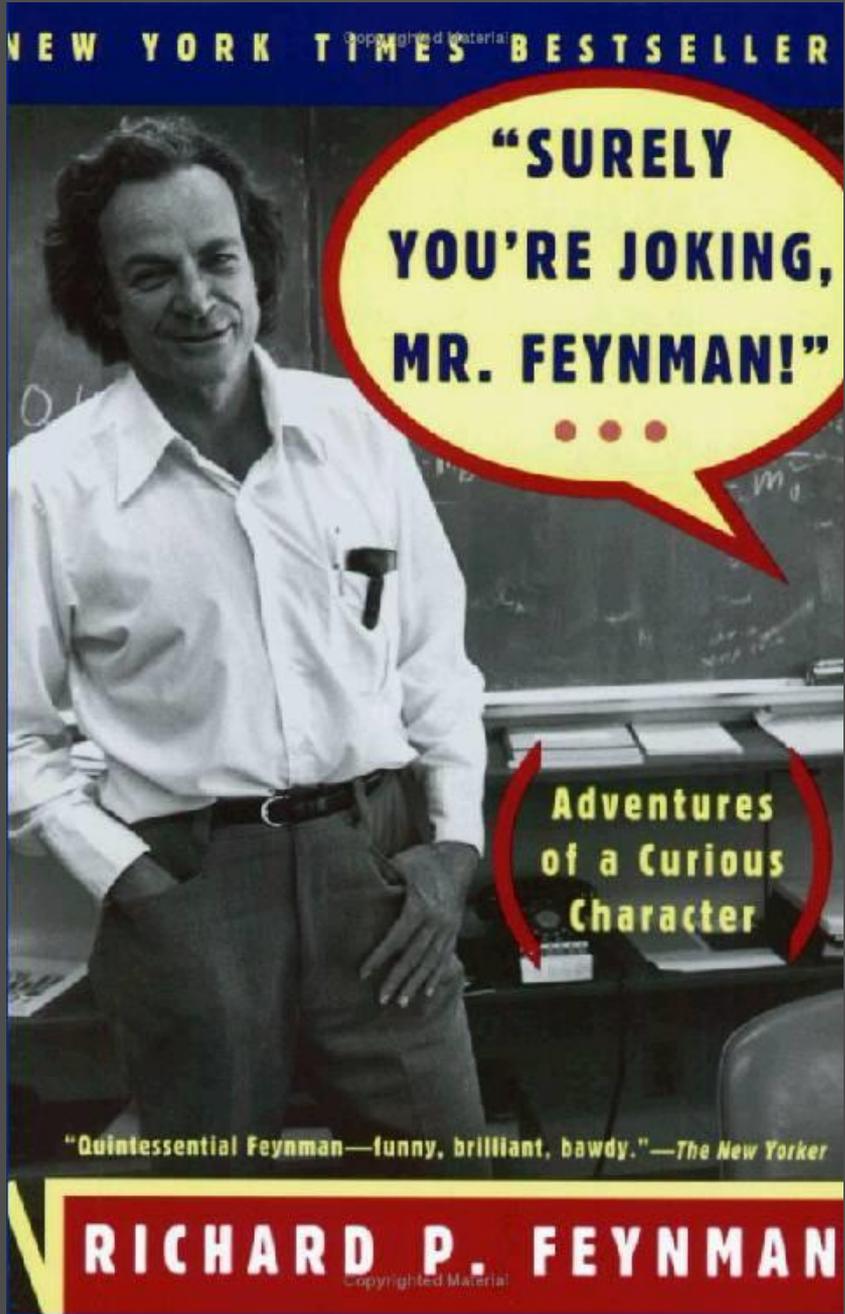
Culture

Focus on rigor not
glitter

We are all prone to bias!

- ❑ Critically assess results/publications
- ❑ Rigorously design, execute, and analyze experiments
- ❑ Plan experiments to disprove the hypothesis
- ❑ Favor robust findings, but....
if it appears to be too good to be true, it probably is!





“If you’re doing an experiment, you should report everything that you think might make it invalid – not only what you think is right about it....