Responsible Conduct of Research Workshop Series, 2016-2017

Rigor and Reproducibility

-- February 9, 2017-

Rigour or **rigor** (see spelling differences) describes a condition of stiffness or strictness. Rigour frequently refers to a process of adhering absolutely to certain constraints, or the practice of maintaining strict consistency with certain predefined parameters.

Webster's Dictionary accessed 2016 December

Rigor

Allende, J.. Rigor – The essence of scientific work. **Electronic Journal of Biotechnology**, North America, 724 07 2012.

Electronic Journal of Biotechnology

EDITORIAL

ELECTRONIC JOURNAL OF BIOTECHNOLOGY

....MOVING FROM SCIENCE TO DEVELOPMENT...

Rigor – The essence of scientific work

Some months ago, I read a new biography of Leonardo da Vinci and one of the facts that interested me most about this Renaissance giant was that one of his favourite mottos was "Ostinato Rigore".

Undoubtedly, that idea of unrelenting rigor marked the life of this brilliant artist, scientist, hydraulic and military engineer. Leonardo looked for perfection and beauty with such obstinacy that it caused him great suffering and limited the number of his incredible works.

We could propose a definition for rigor saying that it consists in the disciplined application of reason to subjects related to knowledge and or communication.

Rigor is many things. It is dissatisfaction with uncertainty, with inaccurate answers, with unprecise measurements, with the spread between the plus and the minus.

Rigor is also being methodical commitment to experimental procedure, to the need of controlling all parameters that can affect the results of our tests.

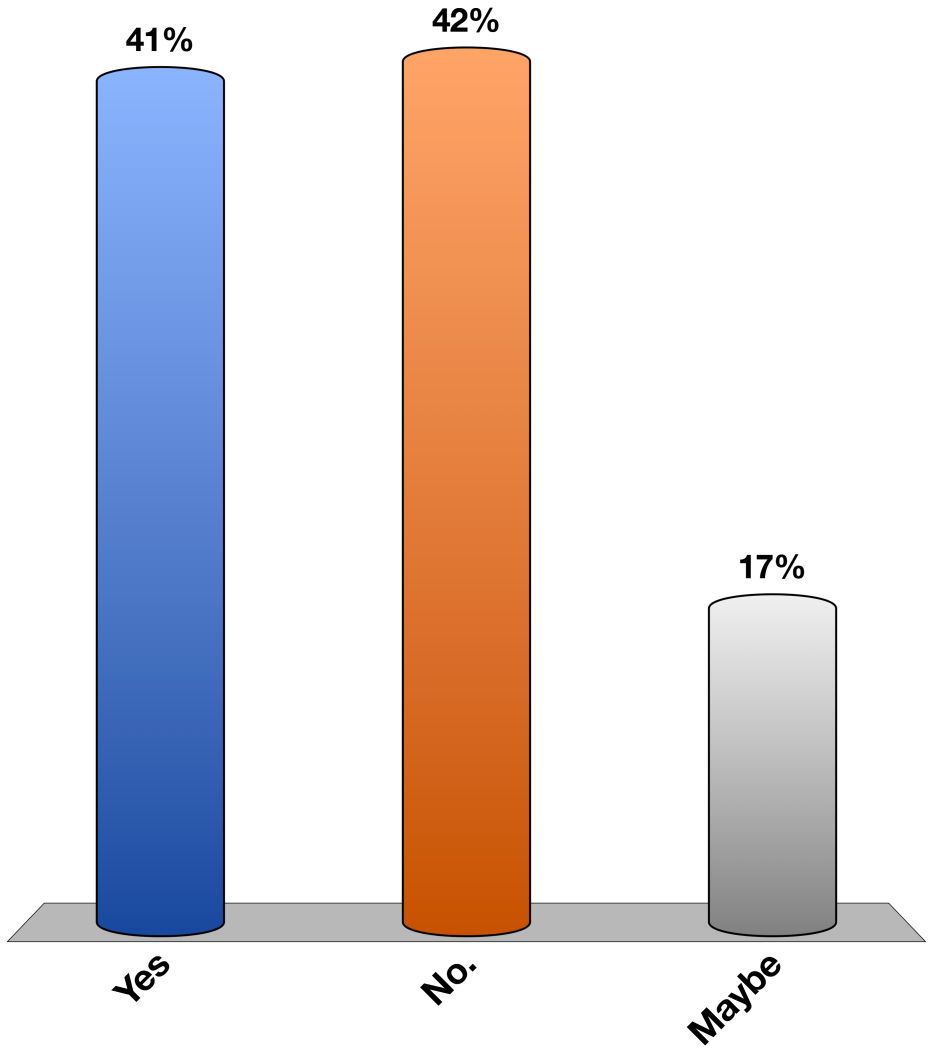
But rigor is also strict adherence to the truth, it is to disrobe ourselves of our prejudices and enthusiasm when we interpret our results, it is to search for all possible explanations of what we observe, it is accepting a result that demonstrates the fallacy of our most precious hypothesis

Rigor is an attitude that contrasts with the weaknesses of human nature, does not allow laziness, the lack of attention, the acceptance of inexact methods, the adoption of groundless conclusions, accepting the predominant opinion despite the lack of data which sustain it. A famous biochemist, Dr. Efraim Racker, once said "there's nothing sadder that an ugly fact destroying a beautiful idea". Rigor demands us to accept the destruction of that beautiful idea by facts.

Rigor is in the essence of scientific work, in each one of the stages of the research work. Rigor implies a structured and controlled way of planning, developing, analyzing and evaluating our research and a special care in adapting the presentation of the results to the demands of the audience we communicate the results of our investigations.

Have you talked about rigor in your research group?

1. Yes
2. No.
3. Maybe



Reproducibility is the ability of an entire experiment or study to be duplicated, either by the same researcher or by someone else working independently. Reproducing an experiment is called **replicating** it. Reproducibility is one of the main principles of the scientific method.

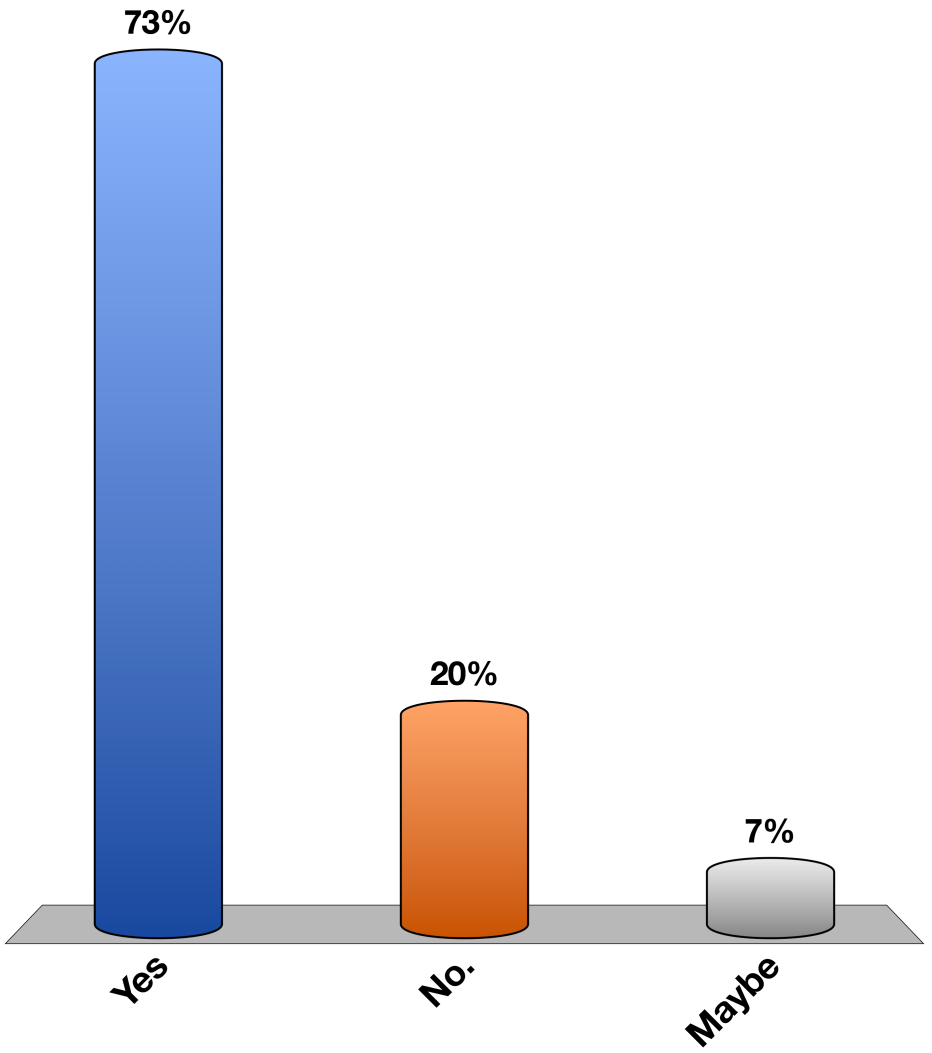
But a new paper in Science Translational Medicine argues that the current movement to replicate results is crippled by a lack of agreement about the very nature of the word “replication” and its synonyms.

https://en.wikipedia.org/wiki/Reproducibility

https://www.statnews.com/2016/06/01/reproducibility-science/

Have you talked about reproducibility in your research group?

1. Yes
2. No.
3. Maybe



Begley & Ellis *Nature* 483, 531–533, 2012

- "In 2012, Amgen alarmed the scientific world by revealing that it had been able to reproduce the results of only six out of 53 "landmark" cancer studies. This confirmed similar, worrying findings from German drug company Bayer released the previous year."

https://www.timeshighereducation.com/news/amgen-launches-new-platform-help-fix-scientific-reproducibility-crisis

Are you alarmed by this finding?

1. Yes
2. No.
3. Maybe

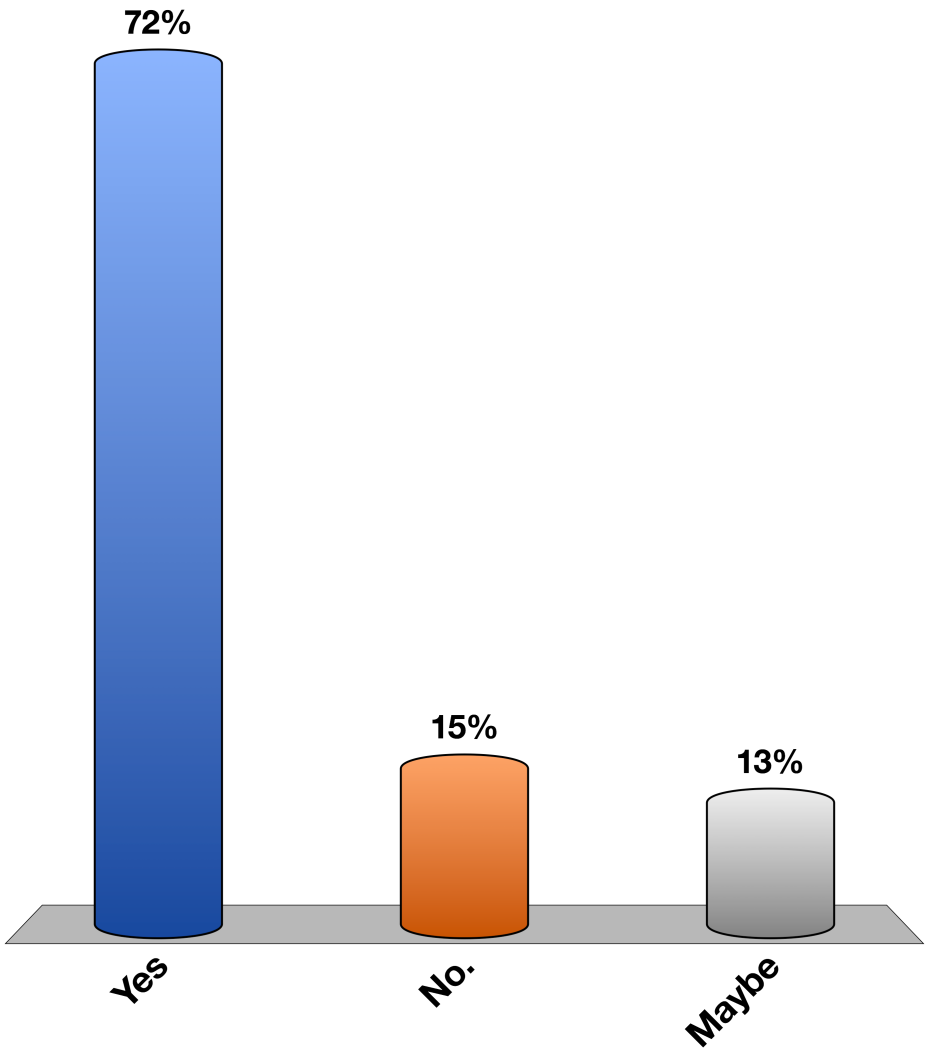


Table 1: Reproducibility of research findings
Preclinical research generates many secondary publications, even when results cannot be reproduced.

From

Drug development: Raise standards for preclinical cancer research

C. Glenn Begley & Lee M. Ellis

Nature **483**, 531–533 (29 March 2012) | doi:10.1038/483531a

back to article

Table 1: Reproducibility of research findings

Preclinical research generates many secondary publications, even when results cannot be reproduced.

Journal impact factor	Number of articles	Mean number of citations of non-reproduced articles*	Mean number of citations of reproduced articles
>20	21	248 (range 3–800)	231 (range 82–519)
5–19	32	169 (range 6–1,909)	13 (range 3–24)

Results from ten-year retrospective analysis of experiments performed prospectively. The term 'non-reproduced' was assigned on the basis of findings not being sufficiently robust to drive a drug-development programme.

*Source of citations: Google Scholar, May 2011.

"Begley's Rules"

1) Were studies blinded?
2) Were all results shown?
3) Were experiments repeated?
4) Were positive and negative controls shown?
5) Were reagents validated?
6) Were the statistical tests appropriate?

http://www.forbes.com/sites/brucebooth/2012/09/26/scientific-reproducibility-begleys-six-rules/#5642ede57c30

Reproducibility Project

From Wikipedia, the free encyclopedia

The **Reproducibility Project: Psychology** was a collaboration completed by 270 contributing authors to repeat 100 published experimental and correlational psychological studies to see if they could get the same results a second time.[1] The project was set up in 2011 by Brian Nosek and his collaborators.[2] It showed that only 39 percent of replications obtained statistically significant results.[3][4] While the authors emphasize that the findings reflect the reality of doing science and there is room to improve reproducibility in psychology, they have been interpreted as part of a growing problem of "failed" reproducibility in science.[5][6][7] There was no evidence of fraud and no evidence that any original study was definitely false. The conclusion of the collaboration was that evidence for frequently published findings in psychological science was not as strong as originally claimed. This may be a result of pressure to publish and a hypercompetitive culture across the sciences that favor novel findings and provide little incentive for replicating findings.[8]

One earlier study found that around $28 billion worth of research per year in medical fields is non-reproducible.[9]

See also

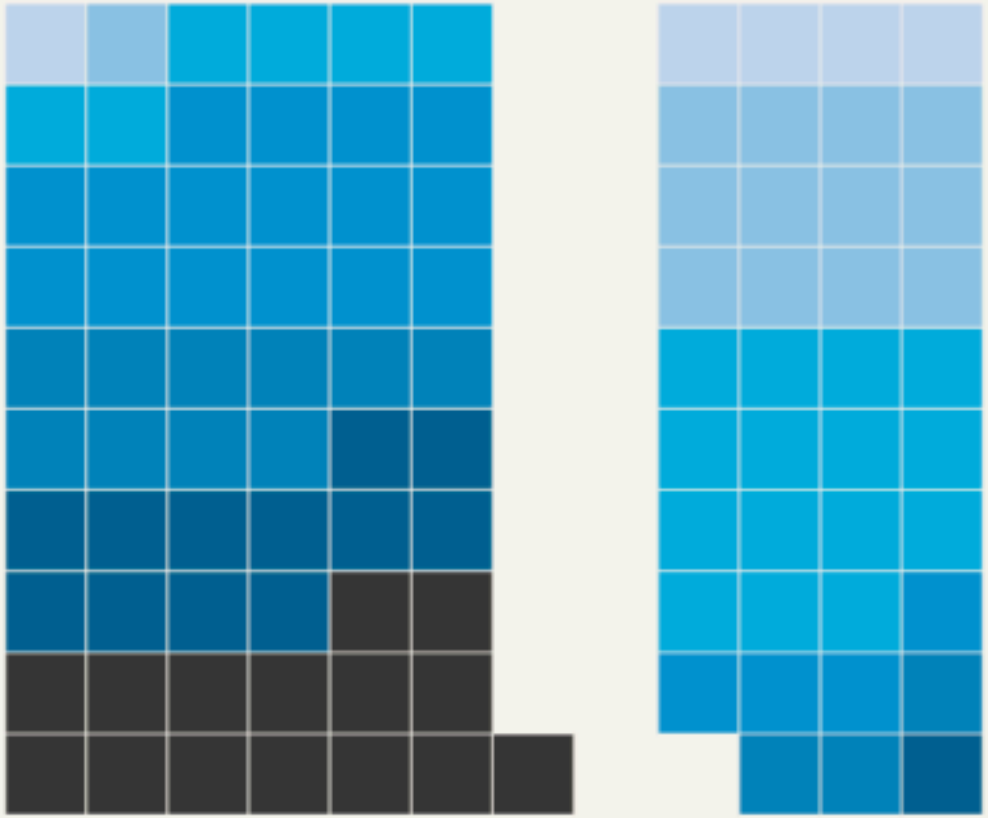
RELIABILITY TEST

An effort to reproduce 100 psychology findings found that only 39 held up.* But some of the 61 non-replications reported similar findings to those of their original papers.

Did replicate match original's results?

NO: 61

YES: 39



Replicator's opinion: How closely did findings resemble the original study:

- Virtually identical
- Extremely similar
- Very similar
- Moderately similar
- Somewhat similar
- Slightly similar
- Not at all similar

* based on criteria set at the start of each study

http://www.nature.com/news/first-results-from-psychology-s-largest-reproducibility-test-1.17433

SO WHAT?!!

We are duty bound to those that support us as scientists

We are duty bound to science and to FACT

Let’s do this right

Simply an awesome paper

Cell Metabolism
Crosstalk

Never Waste a Good Crisis: Confronting Reproducibility in Translational Research

Daniel J. Drucker[1,*]
[1]Department of Medicine, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, ON M5G 1X5, Canada
*Correspondence: drucker@lunenfeld.ca
http://dx.doi.org/10.1016/j.cmet.2016.08.006

The lack of reproducibility of preclinical experimentation has implications for sustaining trust in and ensuring the viability and funding of the academic research enterprise. Here I identify problematic behaviors and practices and suggest solutions to enhance reproducibility in translational research.

Differences in Data reporting for Clinical vs Basic Science

•”Human clinical trials are often carried out using a randomized double-blinded design, and outliers, or suboptimal responders, are not discarded from the analysis. It is expected that clinical researchers will ideally account for and report on every single study subject screened, and ultimately enrolled in a clinical trial, even if subjects drop out or move away. Non-responders are not simply discarded from the trial results, and there are statistical methods employed to account for study subjects who may not complete the entire study”

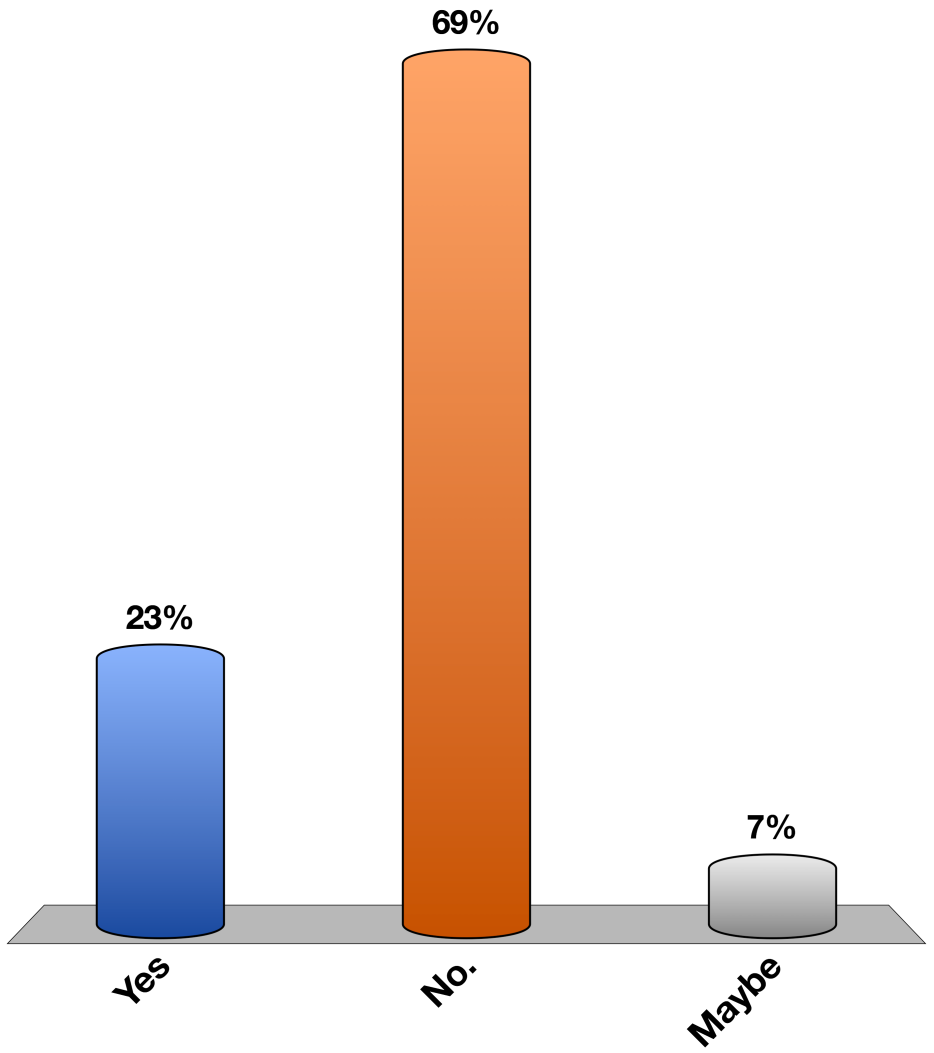
•”Moreover, many large clinical trials study large numbers of genetically diverse subjects, from different regions of the world, both male and female, often including a wide range of ages”

Contrast this situation with current norms and expectations for preclinical studies and research in animals

Cell Metabolism 24, September 13, 2016 349

Do you/will you use cell lines in your research?

1. Yes
2. No.
3. Maybe

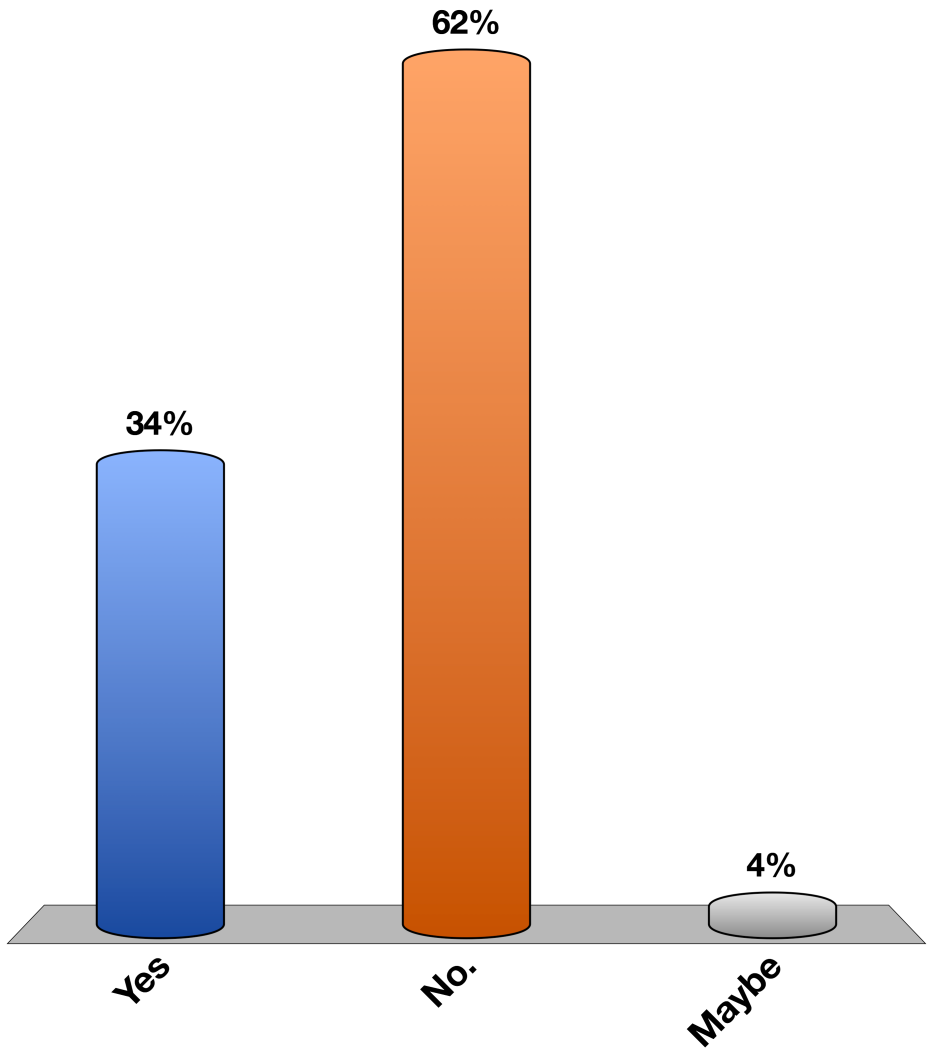


Cell Lines

“Considerable debate has focused on the identification and reliability of cell lines and, while progress has been made in this area, the problem continues to fester. As a postdoctoral fellow in the mid-1980s, I was excited to have isolated, with colleagues, a new human glucagon-producing cell line. We were convinced this would be an invaluable reagent for study of human glucagon biosynthesis and secretion, and we had assembled a good many figures for our envisioned paper. Like many things in life, what seemed too good to be true actually was; analysis of genomic DNA from my ‘‘human cells’’ revealed the presence of repeated DNA sequences from both human and rat DNA. It turned out that our ‘‘human glucagonoma’’ cell line was likely a mixture of HeLa cells and our new RIN1056A glucagon-producing cell line, and the party was over. Several years later, **we also discovered mycoplasma contamination of our hamster glucagon-producing cell line** and wasted several valuable months redoing key experiments after re-deriving ‘‘mycoplasma-free’’ InR1G9 hamster glucagonoma cells. In hindsight, it was a valuable learning experience to identify, early on, the pitfalls of using incompletely characterized or infected cell lines for basic science studies.”

Do you/will you use antibodies in your research?

1. Yes
2. No.
3. Maybe



Antibodies (I love you, I hate you)

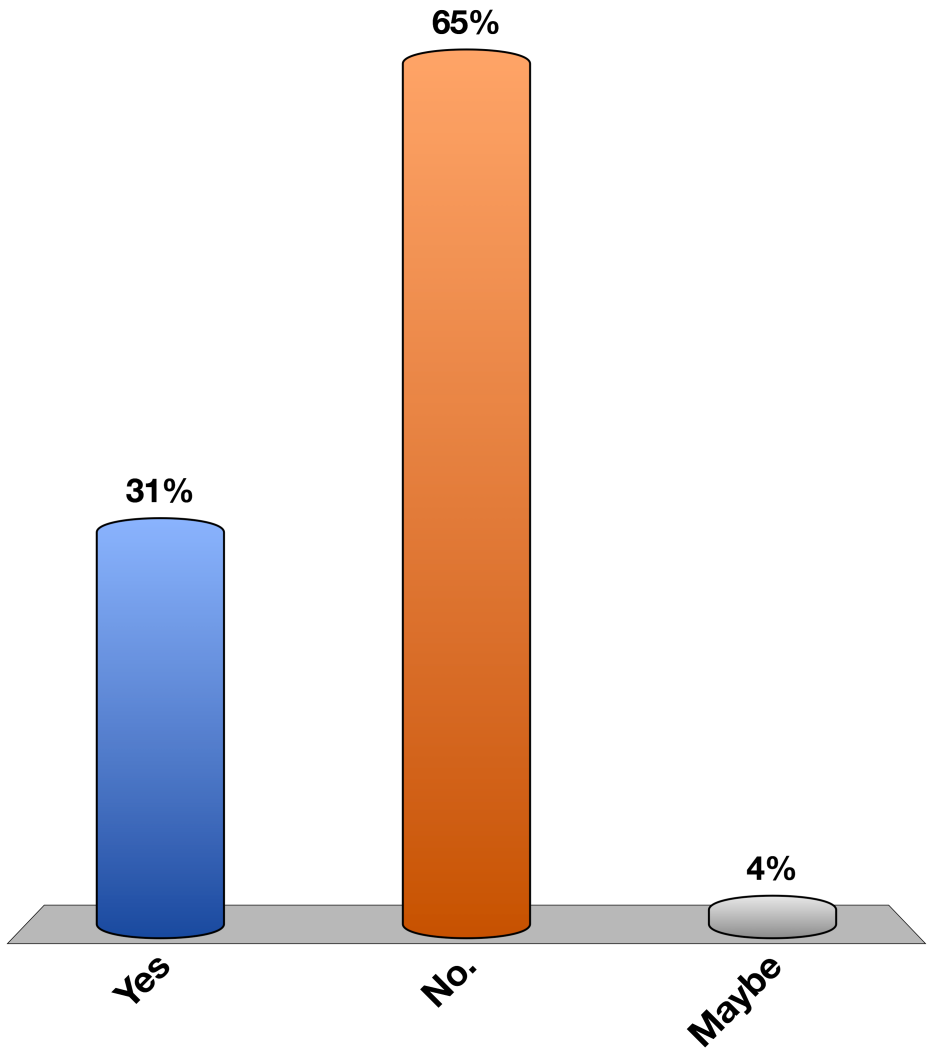
•”Equally vexatious is the ongoing crisis promulgated by use of antibodies that have not been properly validated and, as a result, generate irreproducible or incorrect data due to lack of sensitivity and/or problems with specificity. This challenge extends to all fields of research that use antibodies, and every researcher has their own story with ‘‘problematic antibodies.’’ In the incretin field, there are dozens of published papers using commercial antibodies employed to detect the GLP-1 receptor; our own laboratory experience, regrettably, is that most of these antibodies do not detect the GLP-1 receptor.”

•”Sadly, although our paper describing problems with the sensitivity and specificity of GLP-1R antisera appeared online in November 2012, I estimate that about every other week I still read another new publication reporting data using suspect or incompletely characterized GLP-1R antibody”

Cell Metabolism 24, September 13, 2016 349

Do you/will you use genetically modified organisms in your research?

1. Yes
2. No.
3. Maybe



Use of Genetically modified **Anything**

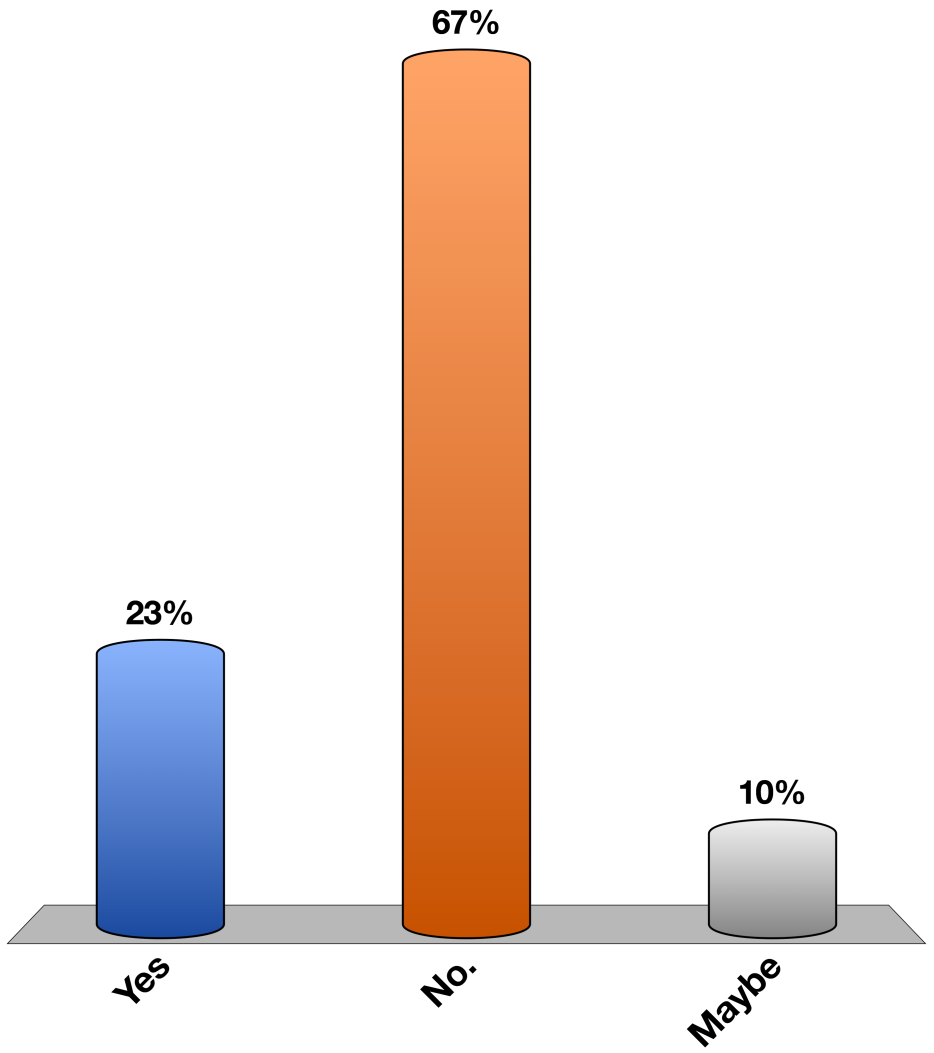
•”We experienced these reproducibility challenges when we moved our laboratory across the street from the Toronto General Hospital to the Mount Sinai Hospital about 10 years ago. After re-deriving mouse lines and reanalyzing several of our most exciting gut phenotypes, we were stunned and disappointed to note that **a few of our most exciting observations made in one mouse facility had simply failed to transfer and were no longer evident** when we moved to a new animal facility across the street”

•”Cre toxicity and ensuing DNA damage may also become more evident in proliferating or apoptotic cells, conditions common in studies of β cell biology (Schmidt-Supprian and Rajewsky, 2007). Hence, the β cell field is faced with the disquieting realization that **some of the observations contained within dozens of papers published using elegant genetic technology to produce β cell knockouts may in fact contribute to results and interpretations that may be incorrect**.”

Cell Metabolism 24, September 13, 2016 349

Is your lab model age-specific?

1. Yes
2. No.
3. Maybe



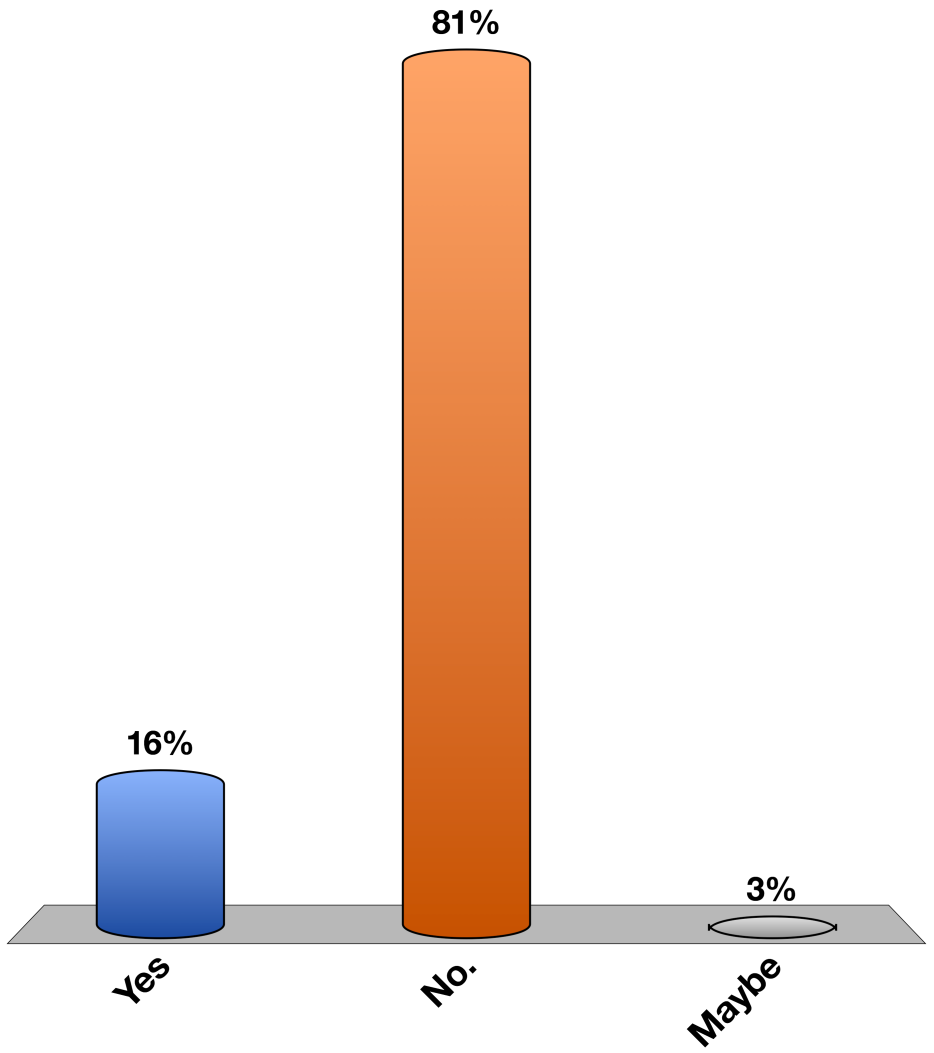
Young vs Old: model choice

•”Many older human subjects have experienced years of low-grade tissue inflammation and fibrosis, dyslipidemia, weight gain, and hypertension, associated with a gradual progression from impaired glucose tolerance to frank dysglycemia and T2D. The suitability of using young mice, often predominantly only one strain (C57BL/6J), for assessing the translational potential of new therapeutic mechanisms is questionable. Younger animals are far more likely to exhibit a greater potential for organ repair, cellular plasticity, and cell proliferation, compared to older animals.”

Cell Metabolism 24, September 13, 2016
349

Do you/will you use mice in your research?

1. Yes
2. No.
3. Maybe



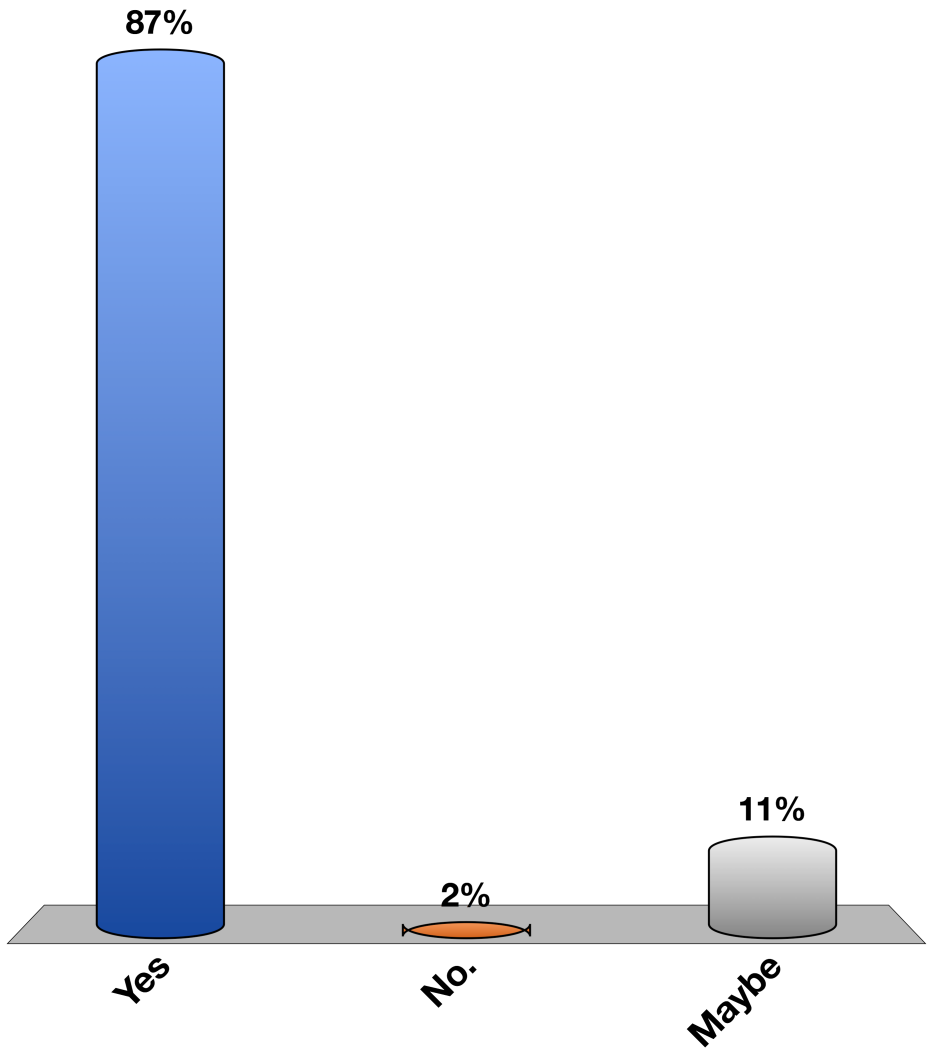
Mice Are Not Always Good Models for Studying Disease Pathophysiology Relevant to Humans

•”Tremendous differences in metabolic rate, basal cardiovascular function, feeding behavior, hepatic lipid metabolism, and other species-specific physiological differences may also contribute to difficulties in translation of preclinical research findings across Species”

Cell Metabolism 24, September 13, 2016 349

Will you publish your research?

1. Yes
2. No.
3. Maybe



Journals, Editors, Public Relations Staff, and the Media

•”The media itself has an extraordinary appetite for scientific and medical information, especially stories with a hint of therapeutic relevance. The media beast is insatiable, although even my mother has now learned that most “medical breakthrough stories” featured on the television, radio, in print, or disseminated via the internet and social media are almost always exaggerated and often frankly incorrect.

How did we arrive at this state of affairs?

Cell Metabolism 24, September 13, 2016 349

Journals, Editors, Public Relations Staff, and the Media

•"Competition for faculty positions and resources in the best academic institutions is fierce, and the most valuable currency continues to be a mixture of publications in "the best journals," ideally coupled with already secured independent funding. To obtain these valuable prestigious publications, one must meet the standards and expectations of journal editors, who similarly prize research that is spectacular, highly novel, and ideally accompanied by wellvdefined reductionist mechanisms and immediate obvious translational relevance"

"Hence, despite a paucity of high-impact papers in the best journals, it seems clear that careful incremental, solid science, although rarely flashy, may, brick by brick, help build a field of science that is reproducible within and across many species, ultimately enabling successful drug development programs"

Cell Metabolism 24, September 13, 2016
349

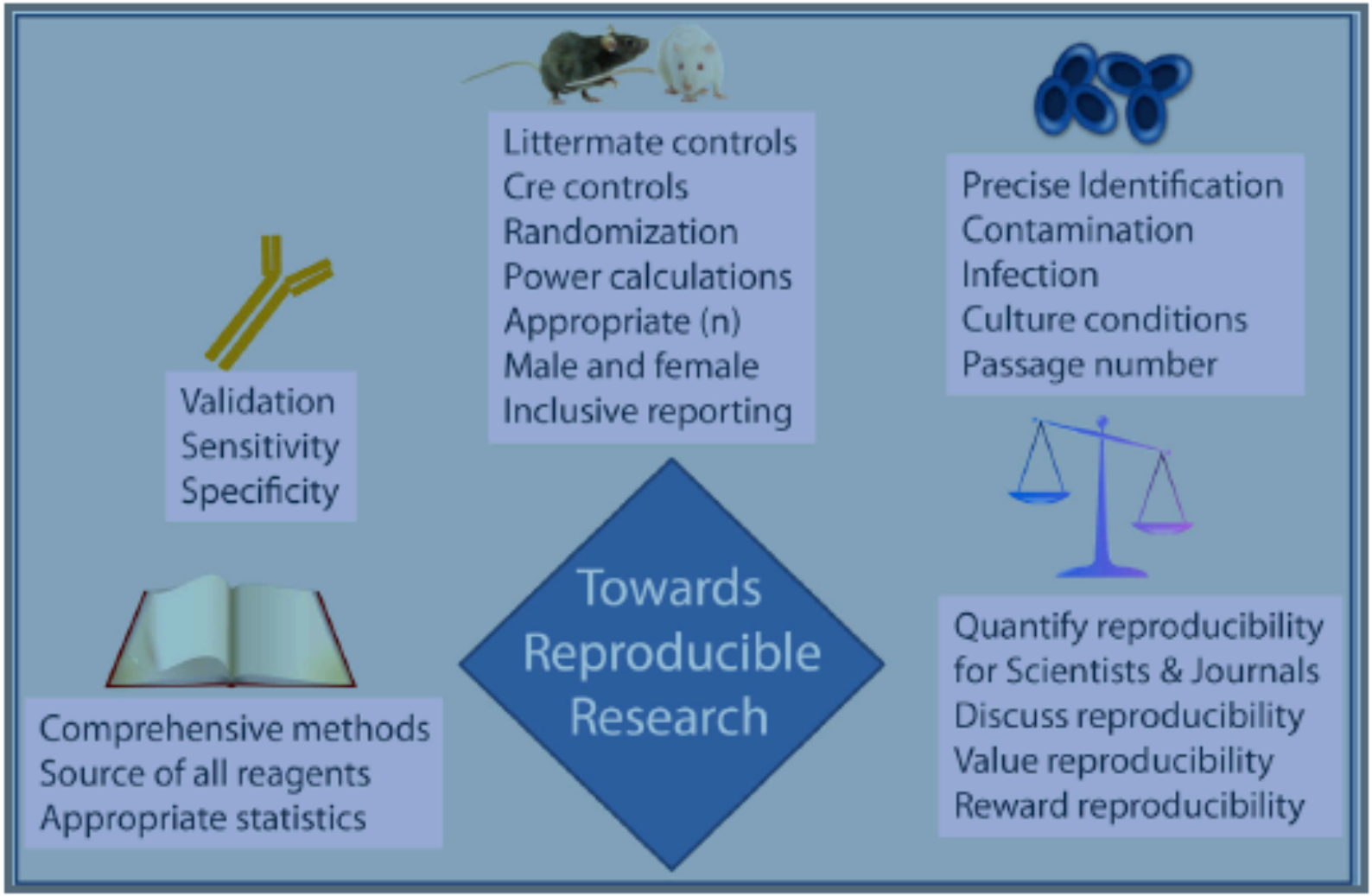


Figure 2. Issues Contributing to Suboptimal Reproducibility of Preclinical Research Are Highlighted

Strategies to enhance research reproducibility are outlined.

WHAT NIH IS ASKING OF US

Moving beyond the Status Quo toward Highly Reproducible Research

Rigor and Transparency in Research

- To support the **highest quality science, public accountability, and social responsibility in the conduct of science**.

- Intended to clarify expectations and highlight attention to four areas that may need more explicit attention by applicants and reviewers:
  - **Scientific premise**
  - **Scientific rigor**
  - **Consideration of relevant biological variables, such as sex**
  - ***Authentication of key biological and/or chemical resources**

- **For Reviewer:**

  Assess the scientific merit of each application according to the review criteria which now includes scientific premise, rigor, and consideration of relevant biological variables. *The adequacy of the authentication of key biological and/or chemicals is an administrative issue.

Reviewing Rigor and Transparency

	Where will I find it in the application?	Where do I include it in my critique?	Addition to review criteria	Affect overall impact score?
Scientific Premise	Research Strategy (Significance)	Significance	Is there a strong scientific premise for the project?	Yes
Scientific Rigor	Research Strategy (Approach)	Approach	Are there strategies to ensure a robust and unbiased approach?	Yes
Consideration of Relevant Biological Variables, Such as Sex	Research Strategy (Approach)	Approach	Are adequate plans to address relevant biological variables, such as sex, included for studies in vertebrate animals or human subjects?	Yes
Authentication of Key Biological and/or Chemical Resources	New Attachment	Additional review considerations	Comment on plans for identifying and ensuring validity of resources.	No

Scientific Premise (I)

Ensure that the underlying **scientific foundation** of the project – concepts, previous work, and data (when relevant) – is sound.

- Address in the **Significance** criterion
- Pertains to the **underlying evidence/supporting data**
- **Significance** review criteria:
  - Does the project address an important problem or a critical barrier in the field?
  - **Is there a strong scientific premise for the project?**
  - If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?
  - How will successful completion of the aims change the concepts, methods, methodologies treatments, services, or preventative interventions that drive the field?

Scientific Premise (II)

- Addition to the review criteria: “Is there a strong scientific premise?” Specifically, has the applicant:
  - Provided sufficient justification for the proposed work
  - Cited appropriate work and/or preliminary data
  - Appropriately identified strengths/weaknesses in prior work in the field
  - Proposed to fill a significant gap in the field
  - **OR** has the applicant explained why this is not possible

Scientific Rigor (I)

Ensure a strict application of scientific methods that supports **robust and unbiased design**, analysis, interpretation, and reporting of results, and sufficient information for the study to be assessed and reproduced. Give careful consideration to the methods and issues that matter in your field.

- Address in the **Approach** criterion
- Pertains to the **proposed research**
- **Approach** review criteria:
  - Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?
  - **Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?**
  - Are the potential problems, alternative strategies, and benchmarks for success presented?
  - If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?
  - Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

Scientific Rigor (II)

- Addition to the review criteria: “Are there strategies to ensure a robust and unbiased approach, as appropriate for the proposed work?”
  - Determining group sizes
  - Analyzing anticipated results
  - Reducing bias
  - Ensuring independent and blinded measurements
  - Improving precision and reducing variability
  - Including or excluding research subjects
  - Managing missing data

Relevant Biological Variables (I)

Ensure that the research accounts for sex and other relevant biological variables in developing research questions and study designs.

- Address in the **Approach** criterion
- Applies to studies in vertebrate animals and/or human subjects
- Pertains to the **proposed research**
- **Approach** review criteria:
  - Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?
  - Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?
  - Are the potential problems, alternative strategies, and benchmarks for success presented?
  - If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?
  - **Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?**

Relevant Biological Variables (II)

- Addition to the review criteria: “Are there adequate plans to address relevant biological variables for studies in vertebrate animals or human subjects?”
  - Applies broadly to all biological variables relevant to the research such as sex, age, source, weight, or genetic strain
  - Has the applicant considered biological variables, such as sex, that are relevant to the experimental design
  - Will relevant biological variables be controlled or factored into the study design

Resource Authentication

Ensure processes are in place to identify and regularly validate key resources used in their research and avoid unreliable research as a result of misidentified or contaminated resources.

New additional review consideration:

- Reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.
- Rate as acceptable/unacceptable (provide brief explanation if unacceptable).
- Does not affect criterion scores or overall impact score.

RIGOR AND REPRODUCIBILITY

Rigor and Reproducibility

Updated Application Instructions to Enhance Rigor and Reproducibility

Request for Information (RFI): Effects of Extrinsic Environmental Factors on Animal Research: Rigor and Reproducibility

Through this Request for Information (RFI), NIH wants your input on the significance of standard environmental conditions for the scientific rigor of animal model experiments and the effects of such conditions on the reproducibility of outcomes. Deadline for response is December 18, 2016.

Two of the cornerstones of science advancement are rigor in designing and performing scientific research and the ability to reproduce biomedical research findings. The application of rigor ensures robust and unbiased experimental design, methodology, analysis, interpretation, and reporting of results. When a result can be reproduced by multiple scientists, it validates the original results and readiness to progress to the next phase of research. This is especially important for clinical trials in humans, which are built on studies that have demonstrated a particular effect or outcome.

Johns Hopkins University students in a laboratory. *Johns Hopkins University*

In recent years, however, there has been a growing awareness of the need for rigorously designed published preclinical studies, to ensure that such studies can be reproduced. This webpage provides information about the efforts underway by NIH to enhance rigor and reproducibility in scientific research.

Email Updates

Sign up to receive email updates about rigor and reproducibility.

Sign up for updates

Related Links

Letter from Dr. Stephen I. Katz: An Update on the NIH Initiative to Enhance Research Rigor and Reproducibility

Contact Us

Please send email to NIHReprodEfforts@od.nih.gov.

https://www.nih.gov/research-training/rigor-reproducibility

https://www.nih.gov/research-training/rigor-reproducibility/training

Do Module 1 and Module 2

RIGOR AND REPRODUCIBILITY

Rigor and Reproducibility

Principles and Guidelines

Expanded Guidelines

Application Instructions

Training

Funding Opportunities

Meetings and Workshops

Publications

Publications

The following is a list of publications from NIH authors on the issue of reproducibility and NIH's actions to enhance reproducibility.

NIAID scientists studying the human immune response to HIV. *NIAID*

- Becker, JB, Koob, GF. Sex Differences in Animal Models: Focus on Addiction. *Pharmacological Reviews*. 68(2), 242-63. (April 2016).
- Arrowsmith, CH, Audia, JE, Austin, C, Baell, J, Bennett, JB, Bountra, C, et al. The promise and peril of chemical probes. *Nat. Chem Biol.* 11, 536541 (21 July 2015).
- Lorsch, JR, Collins, FS, Lippincott-Schwartz, J. Fixing problems with cell lines. *Science*. 346, 1452-1453. (19 December 2014).
- Clayton, JA, Collins, FS. Policy: NIH to balance sex in cell and animal studies. *Nature*. 509, 282-283. (15 May 2014). Link to full article.
- Collins, FS, Tabak, LA. Policy: NIH plans to enhance reproducibility. *Nature*. 505, 612–613. (30 January 2014). Link to full article.
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Reproducibility Project: Psychology

Contributors: Alexander A. Aarts, Christopher Jon Anderson, Joanna Anderson, Marcel A.L.M. van Assen, Peter Raymond Attridge, Angela Attwood, Jordan Axt, Molly Babel, Štěpán Bahník, Erica Baranski, Michael Barnett-Cowan, Elizabeth Bartmess, Jennifer Beer, Raoul Bell, Heather Bentley, Don van den Bergh, Leah Beyan, Bobby den Bezemer, Denny Borsboom, Annick Bosch, Frank Bosco, Sara Bowman, Mark Brandt, Erin Braswell, Hilmar Brohmer, Benjamin T. Brown, Kristina Brown, Jovita Brüning, Ann Calhoun-Sauls, Shannon Callahan, Elizabeth Chagnon, Jesse J. Chandler, Christopher R. Chartier, Felix Cheung, Phuonguyen Chu, Linda Cillessen, Russ Clay, Hayley Cleary, Mark Cloud, Michael Cohn, Johanna Cohoon, Simon Columbus, Giulio Costantini, Leslie Cramblet Alvarez, Edward Cremata, Jan Crusius, Jamie DeCoster, Michelle DeGaetano, Nicolás Della Penna, Marie Deserno, Olivia Devitt, Laura Dewitte, Philip DiGiacomo, David Dobolyi, Geneva T. Dodson, Brent Donnellan, Ryan Donohue, Roel van Dooren, Johnny van Doorn, Rebecca A. Dore, Angela Rachael Dorrough, Anniek te Dorsthorst, Anna Dreber Almenberg, Michelle Dugas, Elizabeth Dunn, Kayleigh Easey, Sylvia Eboigbe, Casey Eggleston, Jo Embley, Sacha Epskamp, Tim Errington, Vivien Estel, Frank J. Farach, Jenelle Feather, Anna Fedor, Belén Fernández-Castilla, Susann Fiedler, James G. Field, Stanka Fitneva, Taru Flagan, Amanda Forest, Eskil Forsell, Joshua Foster, Michael C. Frank, Rebecca S. Frazier, Heather Fuchs, Philip Gable, Jeff Galak, Elisa Maria Galliani, Anup Gampa, Sara Garcia, Douglas Gazarian, Elizabeth Gilbert, Roger Giner-Sorolla, Andreas Glöckner, Lars Goellner, Jin X. Goh, Rebecca M. Goldberg, Stephen D Goldinger, Patrick T. Goodbourn, Shauna Gordon-McKeon, Bryan Gorges, Jessie Gorges, Justin Goss, Jesse Graham, Jeremy R. Gray, C.H.J. Hartgerink, Fred Hasselman, Timothy B. Hayes, Emma Heikensten, Felix Henninger, Grace Hicks, John Hodsoll, Taylor Holubar, Gea Hoogendoorn, Marije van der Hulst, Denise Humphries, Cathy O. Y. Hung, Nathali Immelman, Vanessa C. Irsik, Georg Jahn, Frank Jäkel, Marc Jekel, Magnus Johannesson, David J. Johnson, Kate Johnson, Larissa Johnson, William Johnston, Kai Jonas, Jennifer Joy-Gaba, Heather Kappes, Kim Kelso, Mallory C. Kidwell, Seung Kyung Kim, Matthew Kirkhart, Bennett Kleinberg, Goran Knezevic, Franziska Maria Kolorz, Robert Wilhelm Krause, Job Krijnen, Tim Kuhlmann, Yoram Kevin Kunkels, Megan Kyc, Calvin Lai, Aamir Laique, Daniel Lakens, Kristin Lane, Bethany Lassetter, Lili Lazarevic, Etienne P. LeBel, Key Jung Lee, Minha Lee, Kristi Lemm, Carmel Levitan, Melissa Lewis, Lin Lin, Stephanie Lin, Matthias Lippold, Darren Loureiro, Daniel Lumian, Ilse Luteijn, Sean Mackinnon, Heather N. Mainard, Denise Marigold, Dan Martin, Tylar Martinez, E.J. Masicampo, Josh Matacotta, Psy.D., Maya Mathur, Michael May, Kateri McRae, Todd McElroy, Nicole Mechin, Pranjal Mehta, Johannes Meixner, Alissa Melinger, Jeremy K. Miller, Mallorie Miller-Smith, Katherine Moore, Marcus Möschl, Matt Motyl, Stephanie Muller, Marcus Munafo, Alisa Raquel Muñoz, Koen Ilja Neijenhuijs, Taylor Nervi, Gandalf Nicolas, Gustav Nilsonne, Brian A. Nosek, Catherine Olsson, Colleen Osborne, Lutz Ostkamp, Misha Pavel, Olivia Kathleen Perna, Dr Cyril Pernet, Marco Perugini, R Nathan Pipitone, Michael Pitts, Franziska Plessow, Jason M. Prenoveau, Kate Ratliff, David Reinhard, Frank Renkewitz, Daan van Renswoude, Ashley A. Ricker, Anastasia Rigney, Hedderik van Rijn, Andrew M Rivers, Mark Roebke, Abraham M. Rutchick, Robert S. Ryan, Onur Sahin, Anondah Saide, Gillian Sandstrom, David Santos, Rebecca Saxe, René Schlegelmilch, Kathleen Schmidt, Sabine Scholz, Larissa Seibel, Dylan Selterman, Samuel Shaki, William B Simpson, H. Colleen Sinclair, Jeanine Skorinko, Agnieszka Slowik, Joel S. Snyder, Courtney Soderberg, Carina Sonnleitner, Nicholas Brant Spencer, Jeffrey R. Spies, Angela D. Staples, sara steegen, Mia Steinberg, Stefan Stieger, Nina Strohminger, Gavin Brent Sullivan, Thomas Talhelm, Megan Tapia, Manuela Thomae, Sarah Thomas, Helen Tibboel, Pia Tio, Frits Traets, Steve Tsang, Francis Tuerlinckx, Alexa Tullett, Paul Turchan, wolf vanpaemel, Alejandro Vásquez Echeverría, Anna van 't Veer, Natalia Vélez, Mathijs van de Ven, Marieke Vermue, Mark Verschoor, Michelangelo Vianello, Martin Voracek, Gina Vuu, Eric-Jan Wagenmakers, Joanneke Weerdmeester, Ashlee Welsh, Erin Westgate, Joeri Wissink, Michael Wood, Andy, Emily Wright, Sining Wu, Marcel Zeelenberg, Kellylynn Zuni, Joshua Hartshorne, James A. Grange

Affiliated institutions: Center For Open Science, University of Virginia

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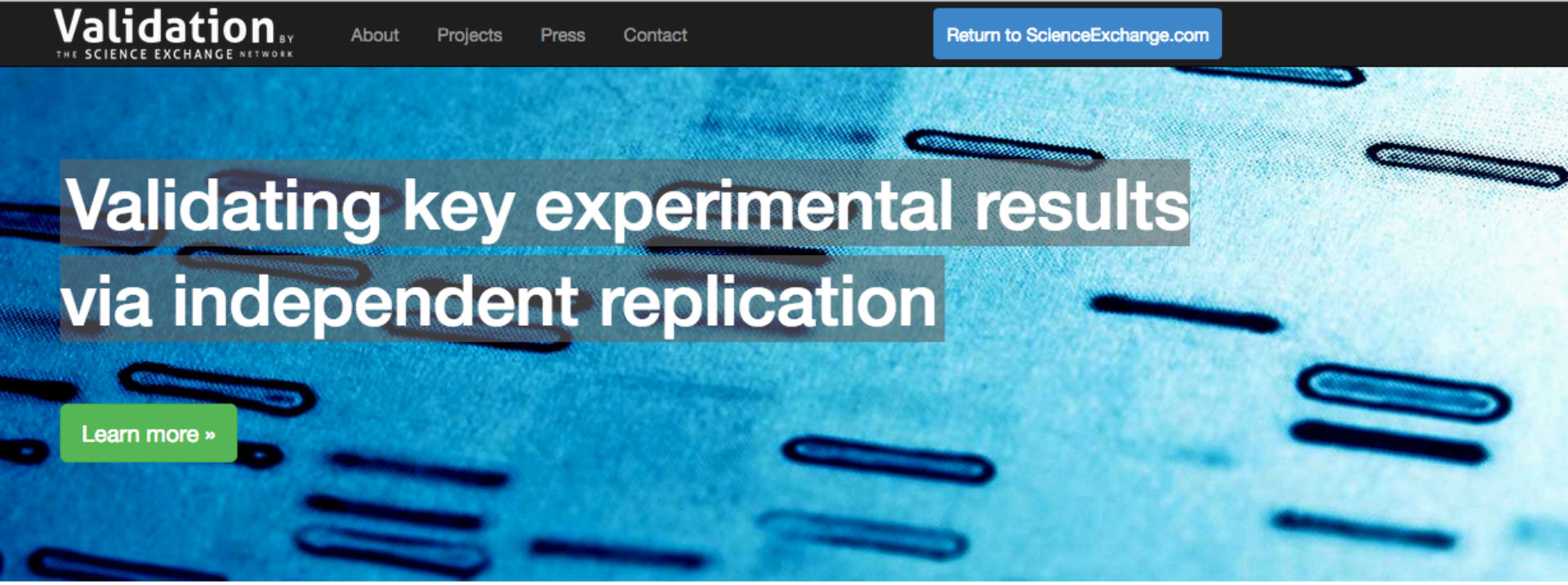

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Elizabeth Iorns, Ph.D.

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PLOS BIOLOGY

META-RESEARCH ARTICLE

Authorization of Animal Experiments Is Based on Confidence Rather than Evidence of Scientific Rigor

Lucile Vogt[1☯], Thomas S. Reichlin[1☯], Christina Nathues[2], Hanno Würbel[1]*

1 Division of Animal Welfare, Veterinary Public Health Institute, Vetsuisse Faculty, University of Bern, Bern, Switzerland, **2** Division of VPH-Epidemiology, Veterinary Public Health Institute, Vetsuisse Faculty, University of Bern, Liebefeld, Switzerland

Author Summary

Scientific validity of research findings depends on scientific rigor, including measures to avoid bias, such as random allocation of animals to treatment groups (randomization) and assessing outcome measures without knowing to which treatment groups the animals belong (blinding). However, measures against bias are rarely reported in publications, and systematic reviews found that poor reporting was associated with larger treatment effects, suggesting bias. Here we studied whether risk of bias could be predicted from study protocols submitted for ethical review. We assessed mention of seven basic measures against bias in study protocols submitted for approval in Switzerland and in publications resulting from these studies. Measures against bias were mentioned at very low rates both in study protocols (2%–19%) and in publications (0%–34%). However, we found a weak positive correlation, indicating that the rates at which measures against bias were mentioned in study protocols predicted the rates at which they were reported in publications. Our results indicate that animal experiments are often licensed based on confidence rather than evidence of scientific rigor, which may compromise scientific validity and induce unnecessary harm to animals caused by inconclusive research.

What you can do

- Think about your own research
  - -where could you improve rigor
  - -how to show reproducibility?
- Talk AS A GROUP
- Keep this discussion going

Last Workshop of the Semester

- Peer Review March 2, 2017