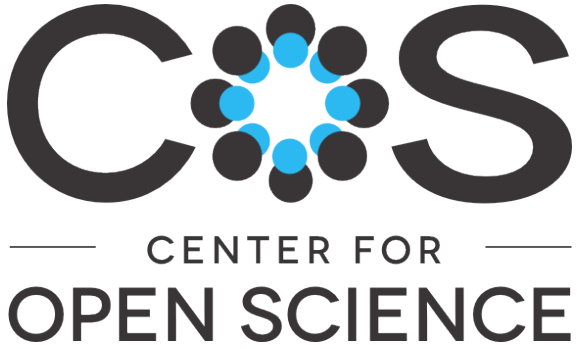

Barriers to replicating preclinical cancer biology research challenges or opportunities?

Tim Errington

Center for Open Science

https://cos.io/

Arnold Ventures
Robert Wood Johnson Foundation
NSF
FLU LAB
JOHN TEMPLETON FOUNDATION
NIH
Templeton Religion Trust
TEMPLETON World Charity Foundation

Mission: Improve openness, integrity, and reproducibility of scientific research

Norms

Communality

Open sharing

Universalism

Evaluate research on own merit

Disinterestedness

Motivated by knowledge and discovery

Organized skepticism

Consider all new evidence, even against one's prior work

Quality

Counternorms

Secrecy

Closed

Particularlism

Evaluate research by reputation

Self-interestedness

Treat science as a competition

Organized dogmatism

Invest career promoting one's own theories, findings

Quantity

Merton, 1942

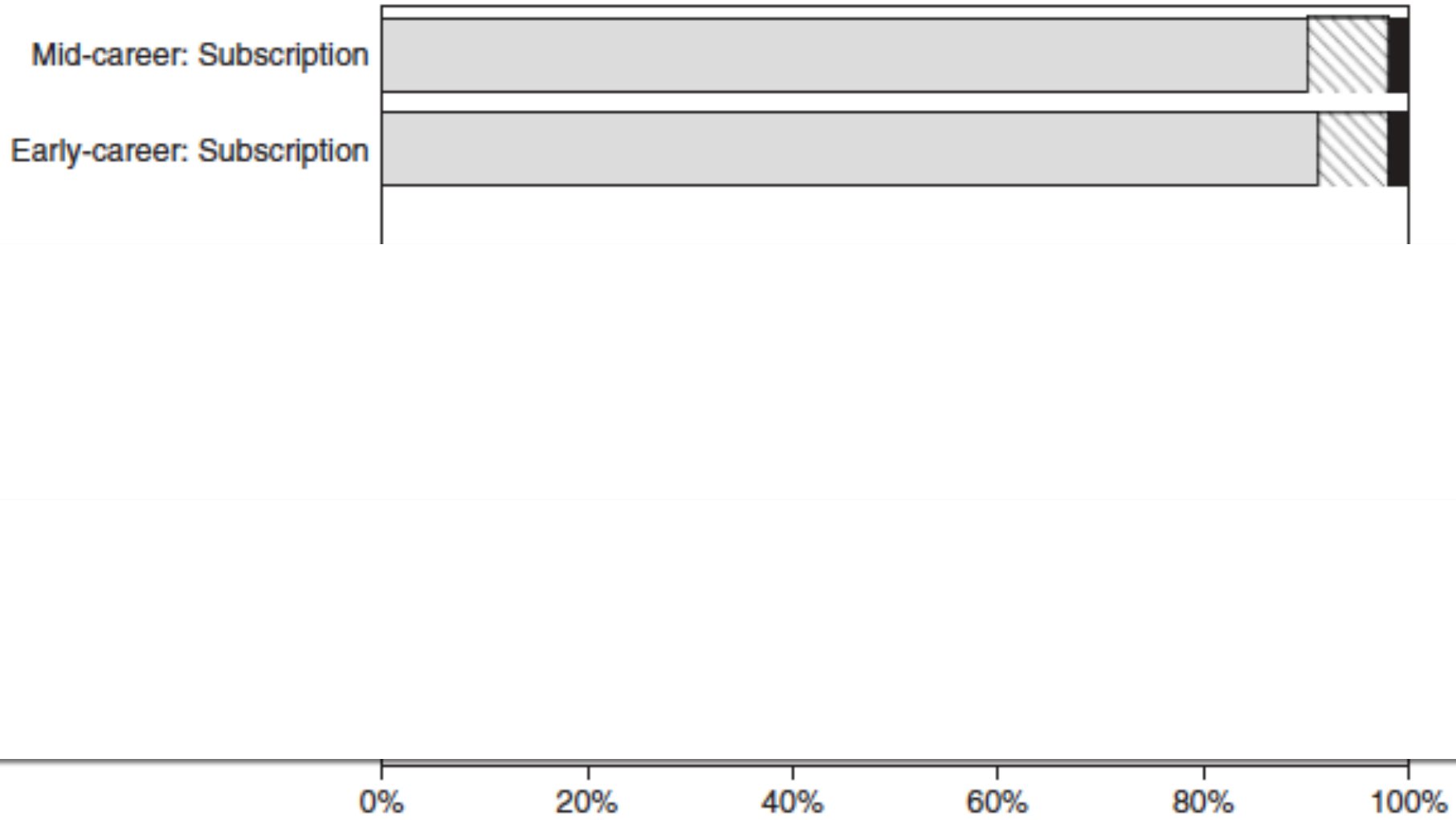

FIG. 3. Norm versus Counternorm Scores: Percent with Norm > Counternorm (dotted), Norm = Counternorm (striped), Norm < Counternorm (solid).

Anderson, Martinson, & DeVries, 2007

Barriers

1. Perceived norms (Anderson, Martinson, & DeVries, 2007)
2. Motivated reasoning (Kunda, 1990)
3. Minimal accountability (Lerner & Tetlock, 1999)
4. Concrete rewards beat abstract principles (Trope & Liberman, 2010)
5. I am busy (Me & You, 2023)
6. Incentives for individual success are focused on getting it published, not getting it right (Nosek, Spies, & Motyl, 2012)

Motivation

REPRODUCIBILITY PROJECT
Cancer Biology

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

Florian Prinz, Thomas Schlange and Khusru Asadullah

Raise standards for preclinical cancer research

C. Glenn Begley and **Lee M. Ellis** propose how methods, publications and incentives must change if patients are to benefit.

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Cancer Biology

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Florian Prinz, Thomas Schlange and Khusru Asadullah

We received input from 23 scientists (heads of laboratories) and collected data from 67 projects, most of them (47) from the field of oncology. This analysis revealed that only in ~20–25% of the projects were the relevant published data completely in line with our in-house findings (FIG. 1c). In almost two-thirds

Raise standards for preclinical cancer research

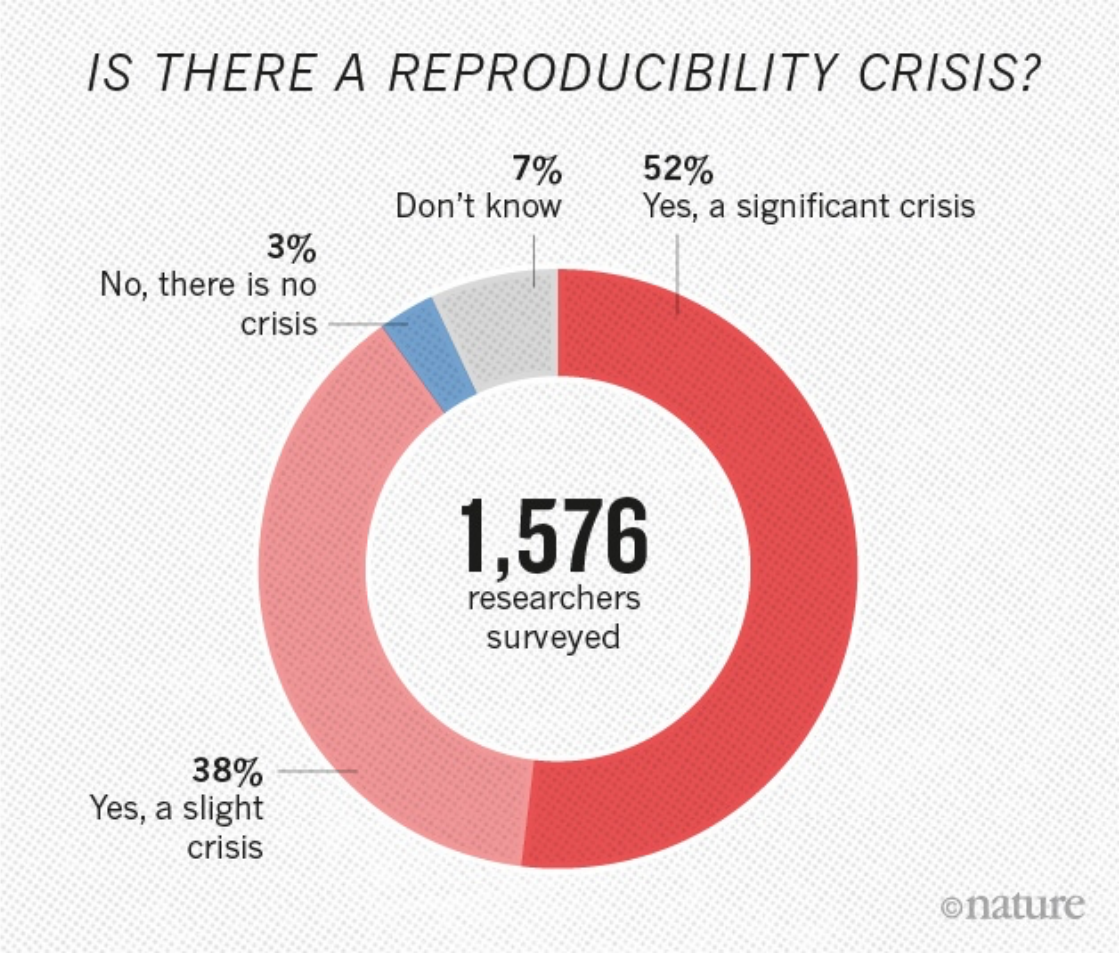
C. Glenn Begley and **Lee M. Ellis** propose how methods, publications and incentives must change if patients are to benefit.

tive clinical uses for existing therapeutics. Nevertheless, scientific findings were confirmed in only 6 (11%) cases. Even knowing the limitations of preclinical research, this was a shocking result.

Motivation

REPRODUCIBILITY PROJECT Cancer Biology

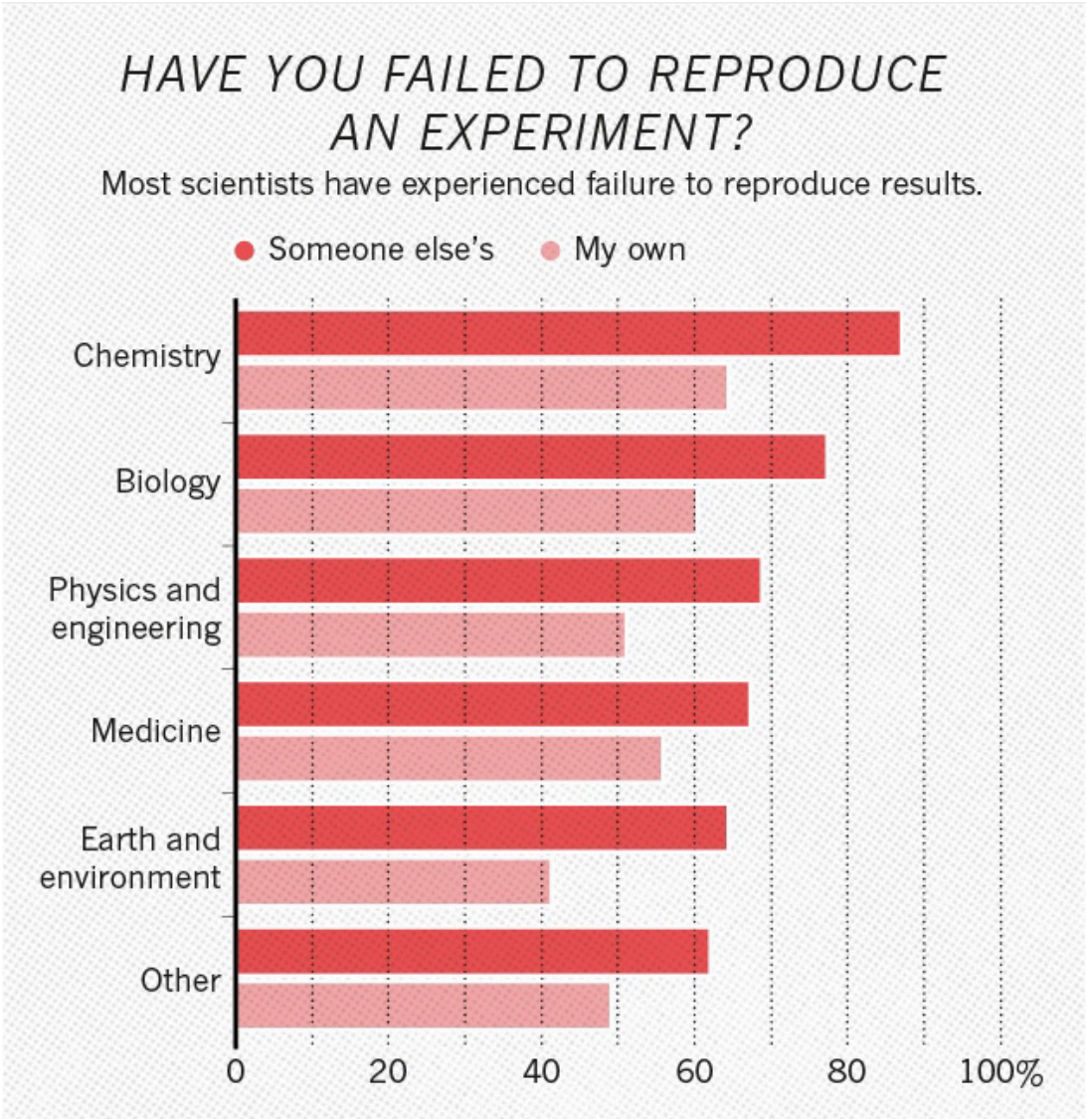
- Nature survey of 1,576 researchers



Baker, 2016

Motivation

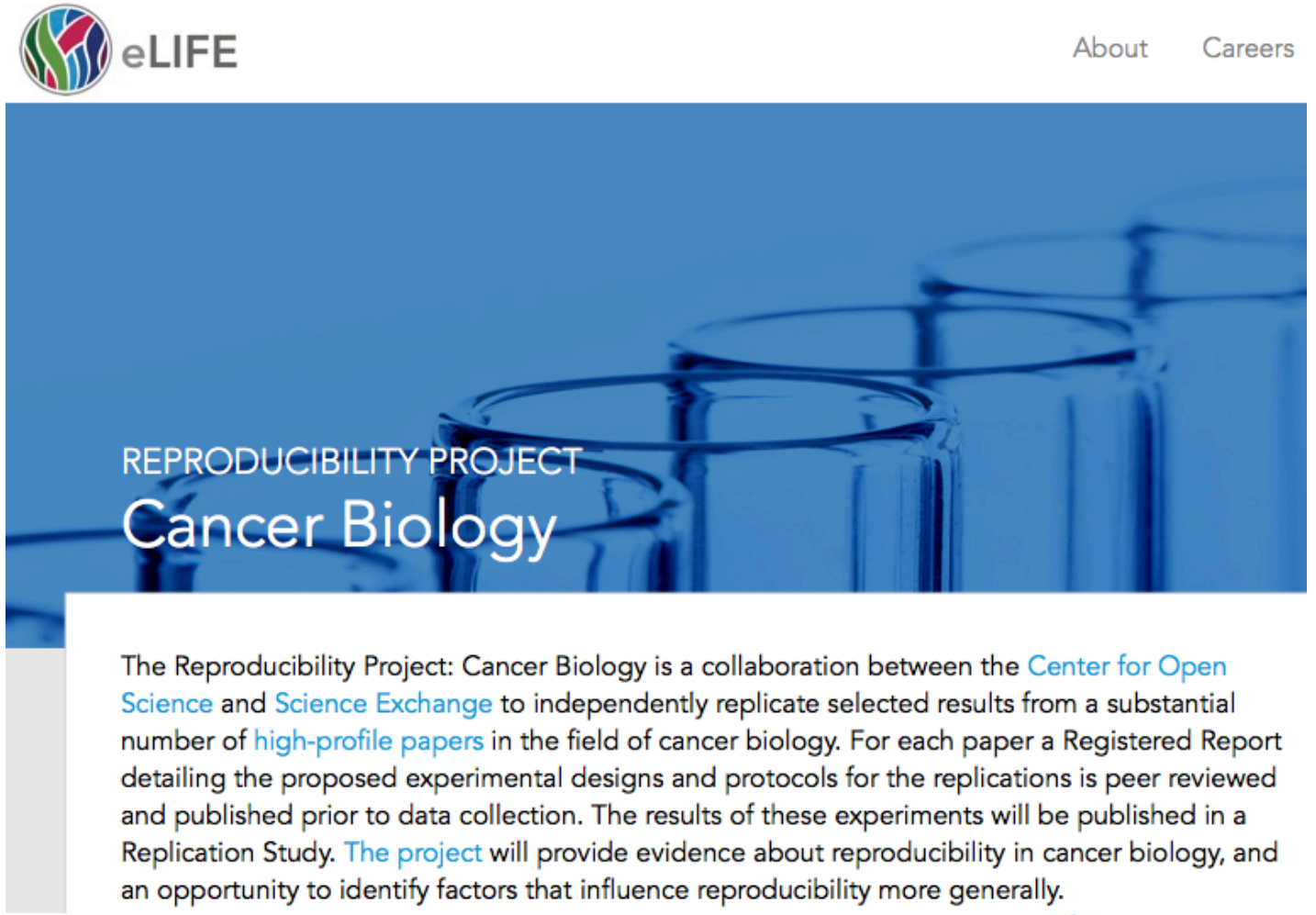
REPRODUCIBILITY PROJECT
Cancer Biology



Baker, 2016

Approach

REPRODUCIBILITY PROJECT
Cancer Biology



laura and john arnold foundation®

CENTER FOR OPEN SCIENCE

Science EXCHANGE

Approach

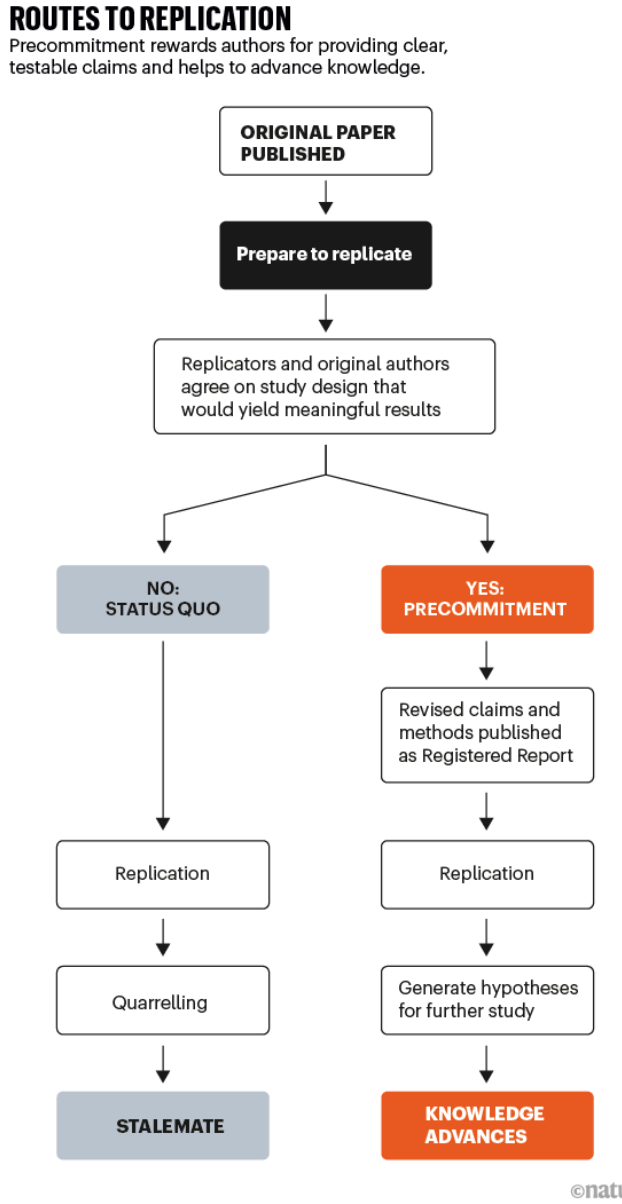
REPRODUCIBILITY PROJECT Cancer Biology

Systematic sampling of 53 high-impact preclinical cancer biology papers

- Papers from 2010-2012
- Excluded genomics, proteomics, high-throughput assays

Primary Outcomes

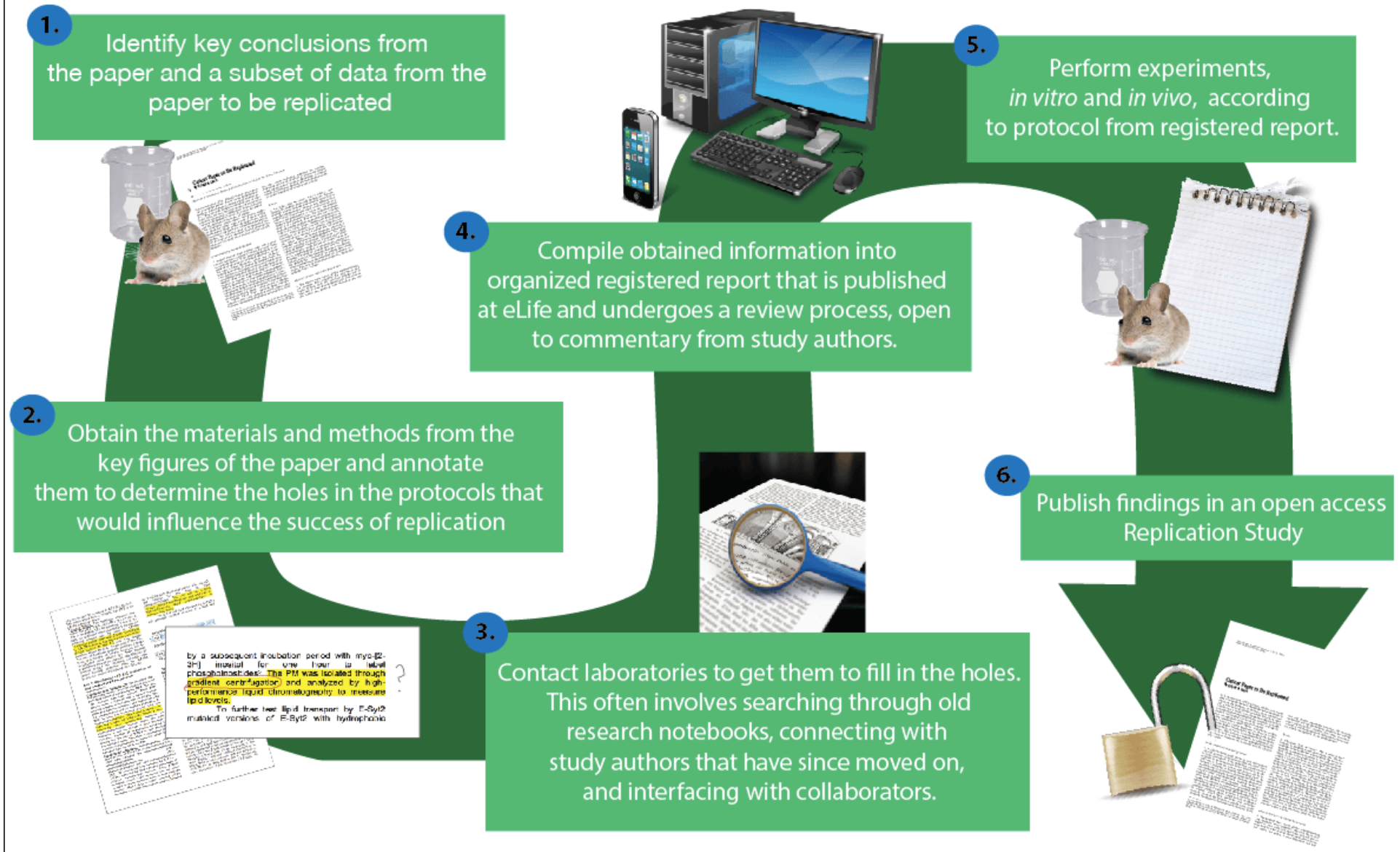
- Summary of process challenges for testing replicability
- Meta-analytic summary of statistical outcomes



Nosek & Errington, 2020

Approach

REPRODUCIBILITY PROJECT
Cancer Biology



Guerra & Lyon, 2015

Challenges & Outcomes

REPRODUCIBILITY PROJECT
Cancer Biology

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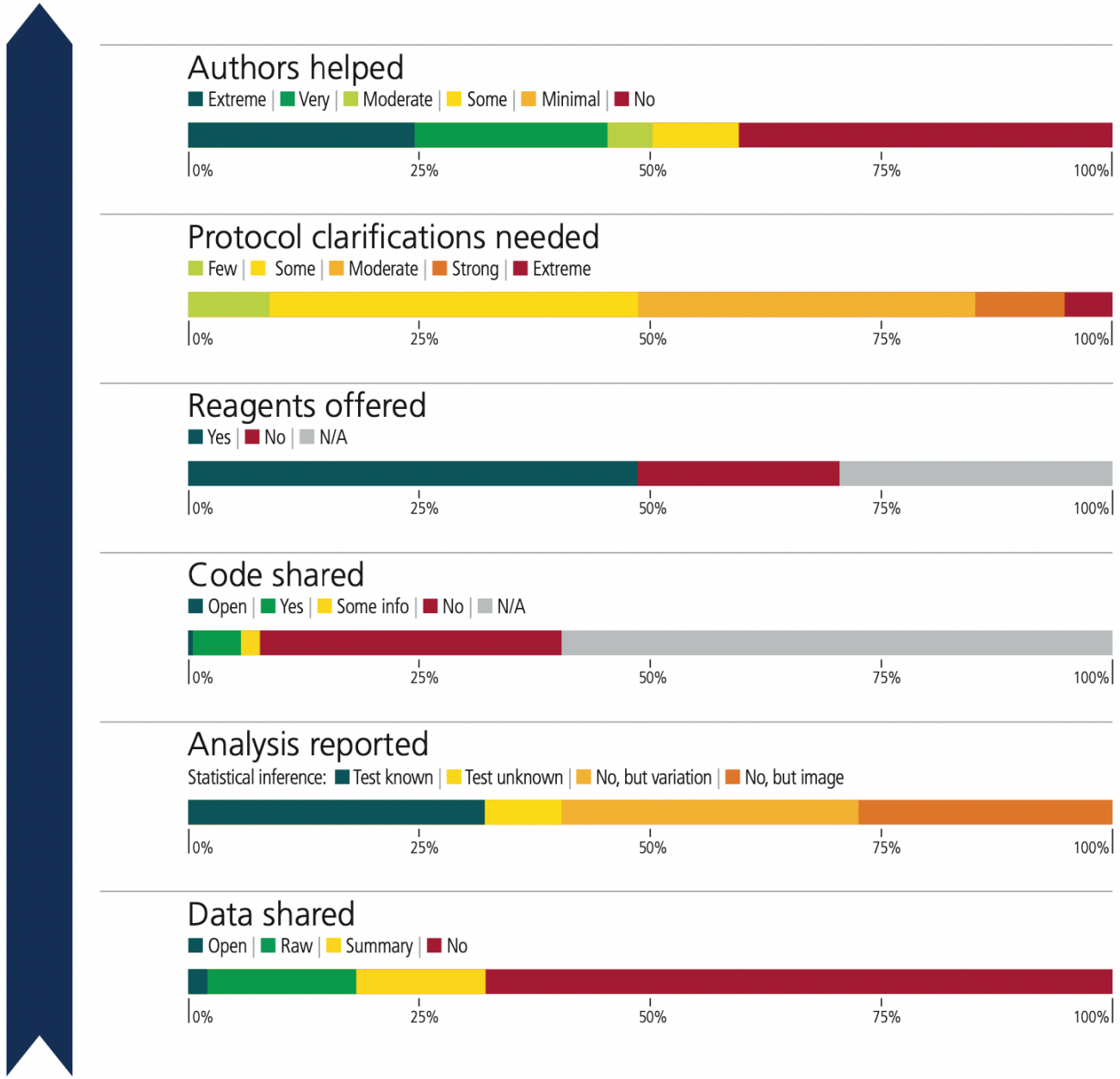
Challenges

REPRODUCIBILITY PROJECT
Cancer Biology

DESIGNED
193 experiments



Challenges

REPRODUCIBILITY PROJECT
Cancer Biology

DESIGNED
193 experiments

2% had open data; after requests 16% shared raw data

Challenges

REPRODUCIBILITY PROJECT Cancer Biology

DESIGNED
193 experiments

21% had unclear statistical tests

Challenges

REPRODUCIBILITY PROJECT
Cancer Biology

DESIGNED
193 experiments

1% had open code; after requests 13% shared code

Challenges

REPRODUCIBILITY PROJECT
Cancer Biology

DESIGNED
193 experiments

70% required asking for key reagents;
69% willing to share

Challenges

REPRODUCIBILITY PROJECT
Cancer Biology

DESIGNED
193 experiments

All needed clarifications with 49% few/some; 20% strong/extreme

Challenges

REPRODUCIBILITY PROJECT Cancer Biology

DESIGNED
193 experiments

41% extremely/very helpful, 32% not at all helpful/no response

Challenges

REPRODUCIBILITY PROJECT Cancer Biology

From the publication

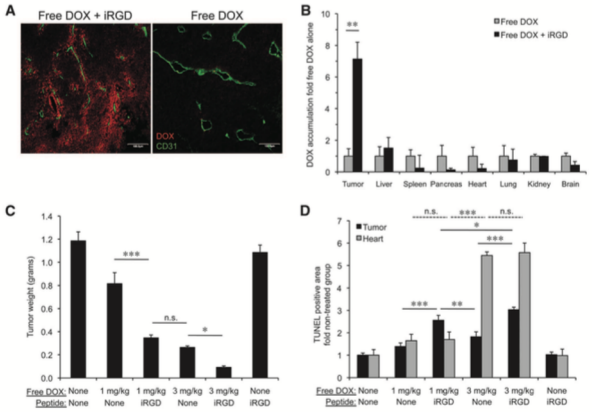


Fig. 2. Enhanced antitumor effect of free DOX co-injected with iRGD. (**A** and **B**) Mice bearing orthotopic 22Rv1 human prostate tumors were intravenously injected with a mixture of DOX (10 mg/kg) and 4 μmol/kg of iRGD or PBS. Tumors and tissues were collected 1 hour later. $n = 3$ per group. In (A), the tumors were sectioned and stained for blood vessels with anti-CD31, and the native fluorescence was used to detect DOX. Scale bars, 100 μm. In (B), DOX in the tissues was quantified. (**C**) Mice bearing orthotopic 22Rv1 tumors implanted 2 weeks earlier received intravenous injections of DOX (1 or 3 mg/kg) or PBS, combined with 4 μmol/kg of iRGD or PBS, every other day. The tumors were harvested and weighed after 24 days of treatment. $n = 10$ per group. (**D**) TUNEL staining was performed on tumors and hearts from the treatment study and was quantified for positive staining. Statistical analyses were performed with Student's *t* test (B) and ANOVA (C and D). Error bars denote mean ± SEM. n.s., not significant; $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Materials and Methods

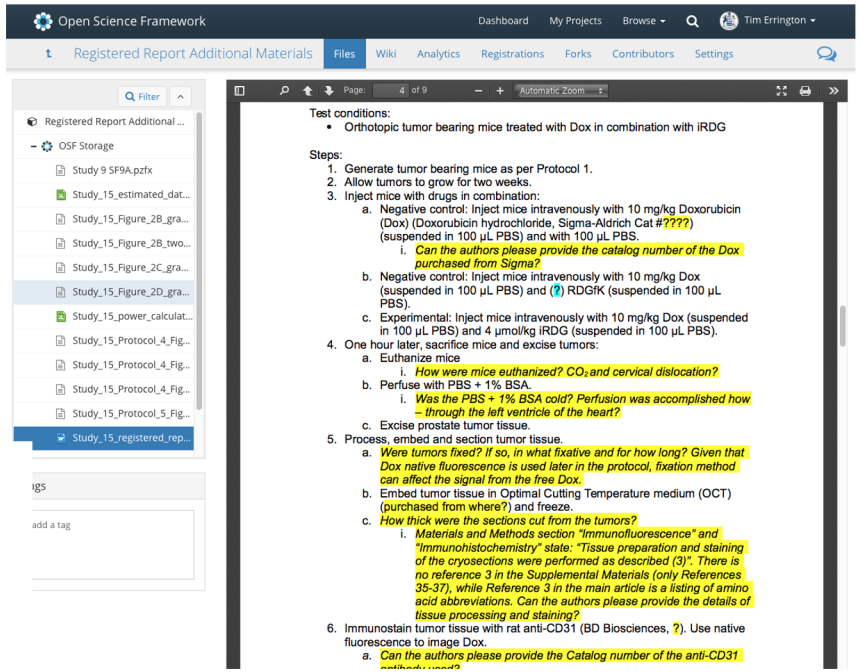
***In vivo* skin permeability assay** was performed as described elsewhere (*6*).

Immunofluorescence. Tissue preparation and staining of the cryosections were performed as described (*3*). The primary antibodies were rat anti-mouse CD31 (BD Biosciences), FITC-labeled HLA-A,B,C (BD Biosciences), and FITC-labeled H-2kd (BD Biosciences) monoclonal, and rabbit anti-T7 phage polyclonal (*6*) antibodies. The secondary antibodies, Alexa Fluor 594 goat anti-rat, 647 goat anti-rat, and 488 donkey anti-rabbit antibodies were from Molecular Probes.

Immunohistochemistry. Tissue preparation and staining of the cryosections were performed as described (*3*). The primary antibodies used were biotinylated rabbit anti-FITC/Oregon green polyclonal (Molecular Probes), and biotinylated mouse anti-dextran monoclonal (Stemcell Technologies, Vancouver, BC, Canada) and biotinylated rat anti-mouse CD31 monoclonal (BD Biosciences) andtibodies. Biotinylated secondary polyclonal antibodies were goat anti-rabbit and rabbit anti-human (both from Pierce Biotechnology, Rockford, IL). In some experiments, tissue sections were stained with a TUNEL assay kit (In Situ Cell Death Detection Kit, POD; Roche Applied Science, Indianapolis, IN), and quantified for the positive areas with a scanner as described elsewhere in this manuscript.

Ex vivo tumor penetration assay. PPC-1 subcutaneous tumors (about 1 cm in diameter) were excised and placed in DMEM containing 1% BSA. The tumors were first incubated with the inhibitors or peptides for 20 min at 4°C. G_7 or iRGD phage were then added to the solution and the tumors were further incubated for 90 min at 37°C or 4°C. The tumors were then washed with cold DMEM containing 1% BSA, fixed in 4% paraformaldehyde, sectioned, immunofluorescently stained, and viewed under a confocal microscope.

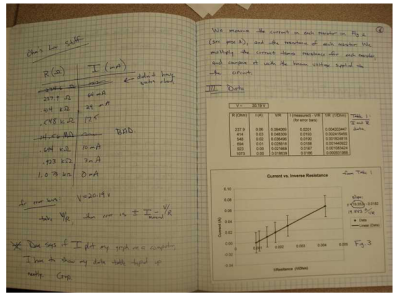
Quantification of ABX in tumors and tissues was performed as described elsewhere (*3*).



From the publication

- What antibodies were used?
- What sex were the mice?
- How long was the treatment period for?
- What instrument/software was used?
- What was the staining protocol used?
- How was positive area defined and measured?
- Can you share the data with us?

From the authors



"I think that nuance was lost trying to edit the text down to size."

"I do not have those data with me and will need to dig a bit in my back-ups"

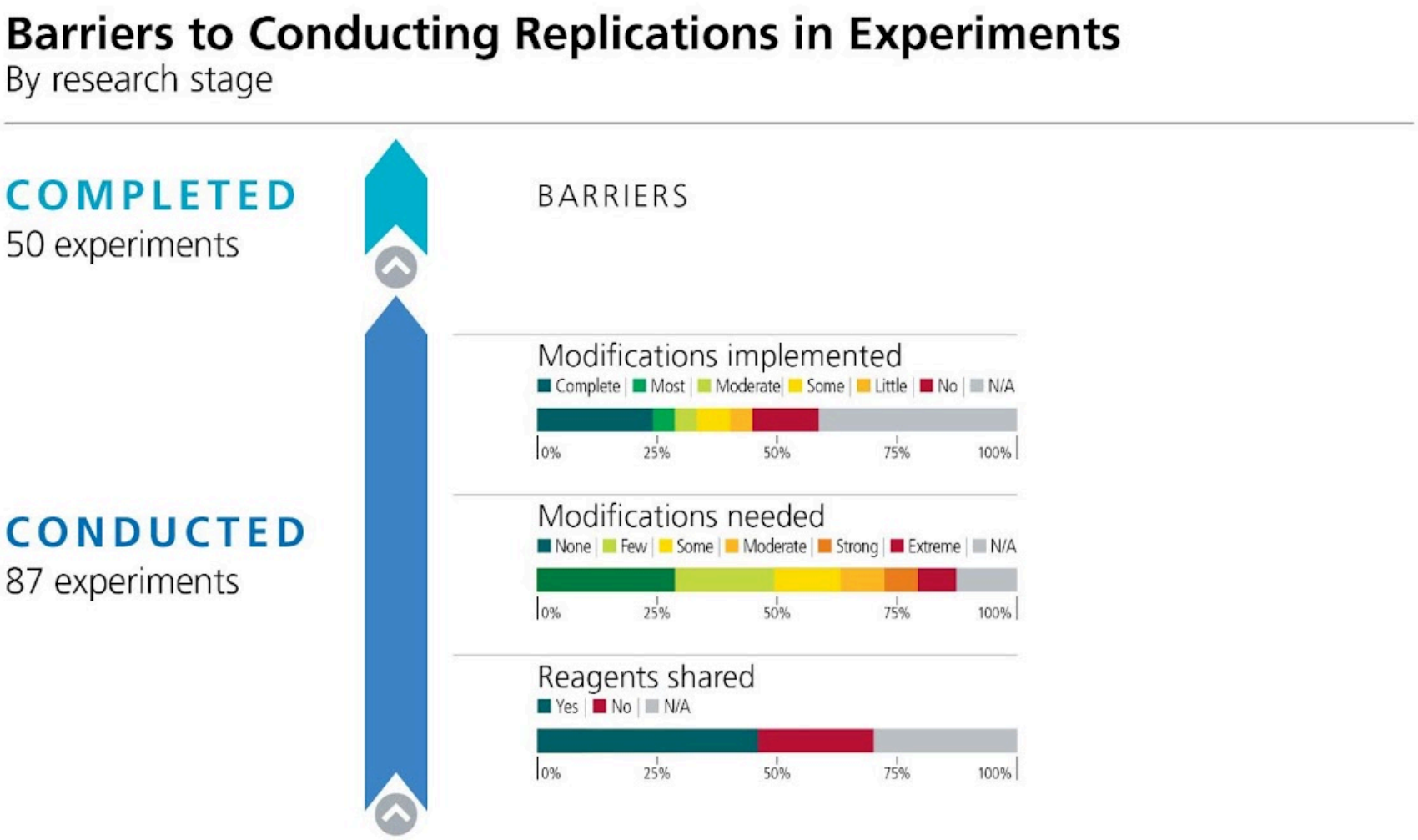
"we have been working with the protocol document. Problem was that different experiments were done by different authors"

"I do not have the raw data anymore"

"some of the details you are seeking are not readily accessible"

Challenges

REPRODUCIBILITY PROJECT
Cancer Biology



Challenges

REPRODUCIBILITY PROJECT Cancer Biology

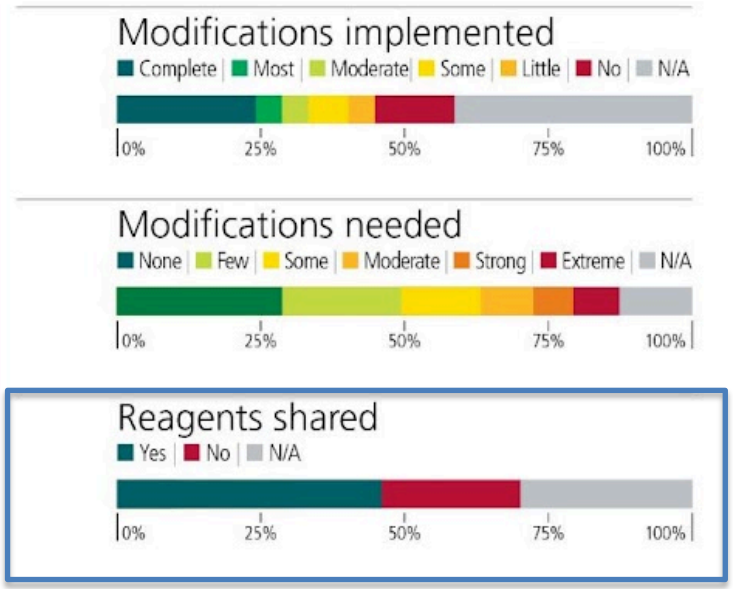
Barriers to Conducting Replications in Experiments

By research stage

COMPLETED
50 experiments

CONDUCTED
87 experiments

BARRIERS



66% actually shared reagents

Challenges

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Cancer Biology

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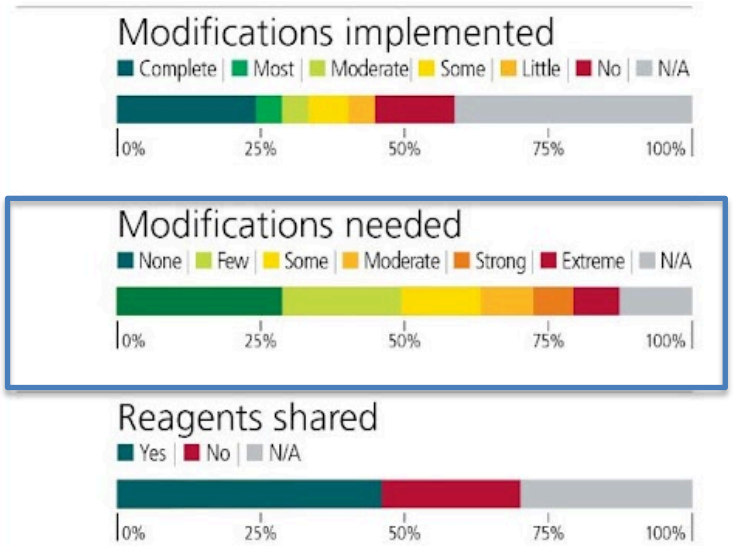

67% required modifications with 39% few/some; 17% strong/extreme

Challenges

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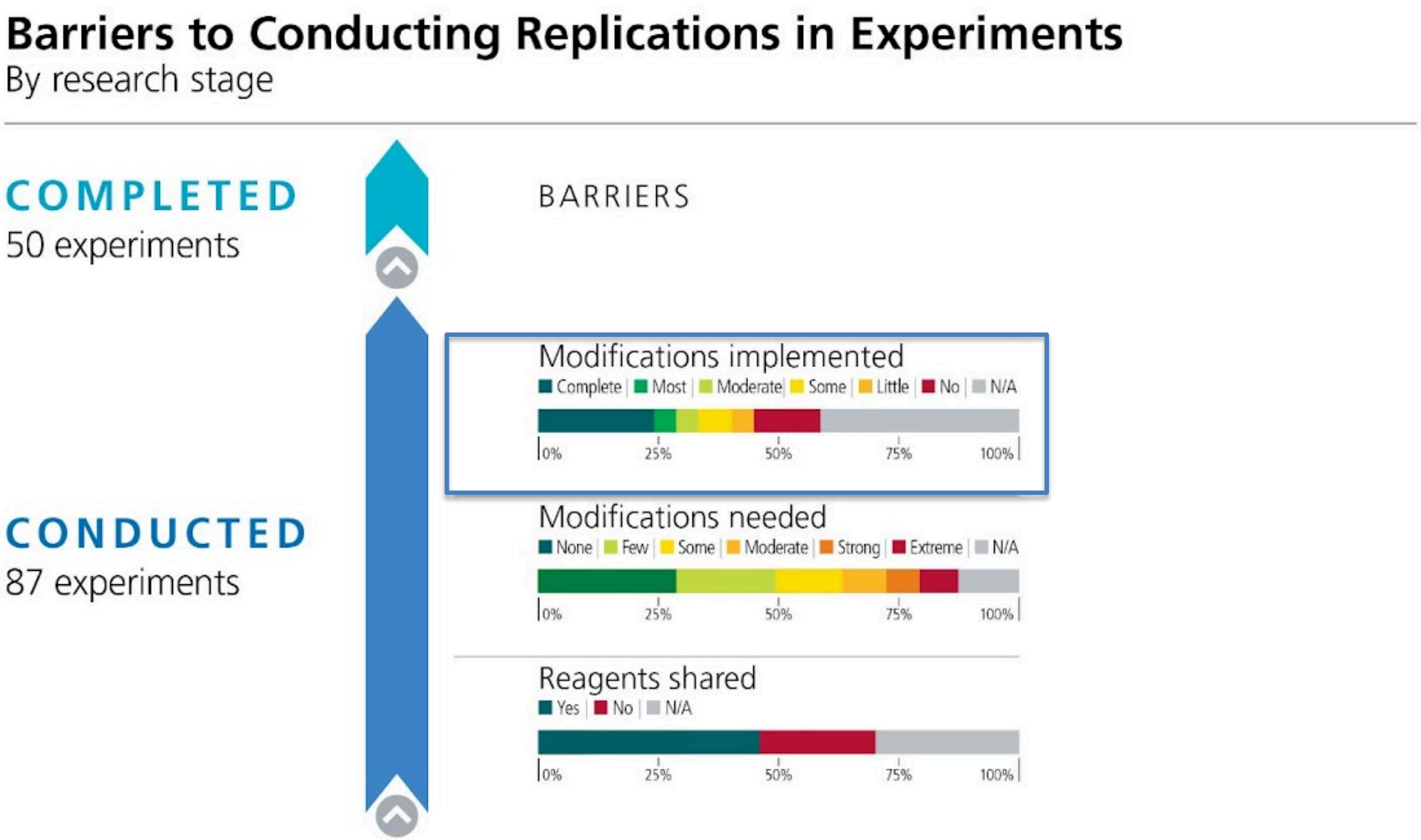

41% completely implemented

Testing replicability impeded by…

- Lack of transparency and accessibility of methodology
- Lack of sharing of original data and reagents
- Lack of communication for obtaining needed information
- Unexpected challenges with protocols during experimentation
- Resource challenges (cost, time, uncertainty) inflated by all the above

Outcomes

REPRODUCIBILITY PROJECT Cancer Biology

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REPRODUCIBILITY PROJECT Cancer Biology

How to assess replicability?

- Same direction

- Same direction and statistically significant

- Original effect size in replication confidence interval

- Replication effect size in original confidence interval

- Replication effect size in prediction interval

- Replication effect size compared to original effect size

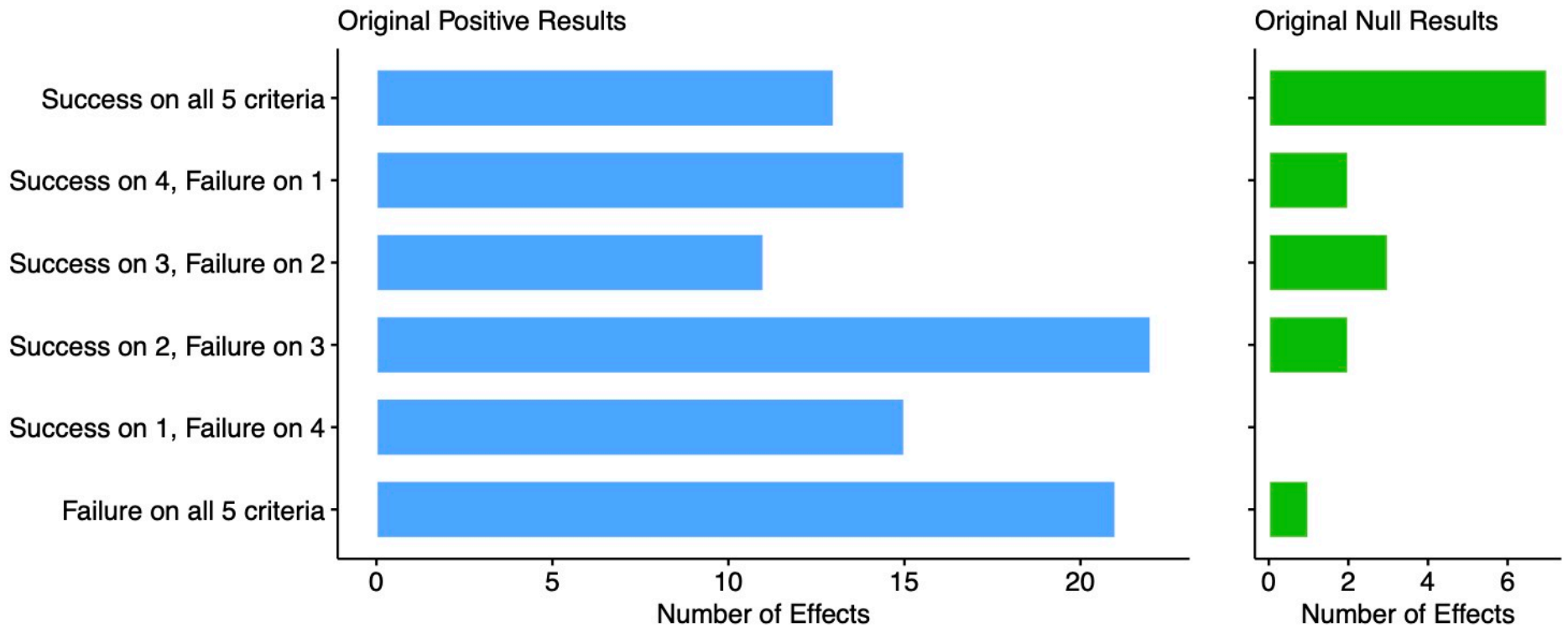
- Direction and statistical significance of meta-analysis

Summarizing across five dichotomous replication success criteria

- 47%: Same direction and statistically significant
- 25%: Original effect size in the replication 95% confidence interval
- 48%: Replication effect size in the original 95% confidence interval
- 61%: Replication effect size in the 95% prediction interval
- 63%: Meta-analysis of original and replication

Outcomes

REPRODUCIBILITY PROJECT Cancer Biology



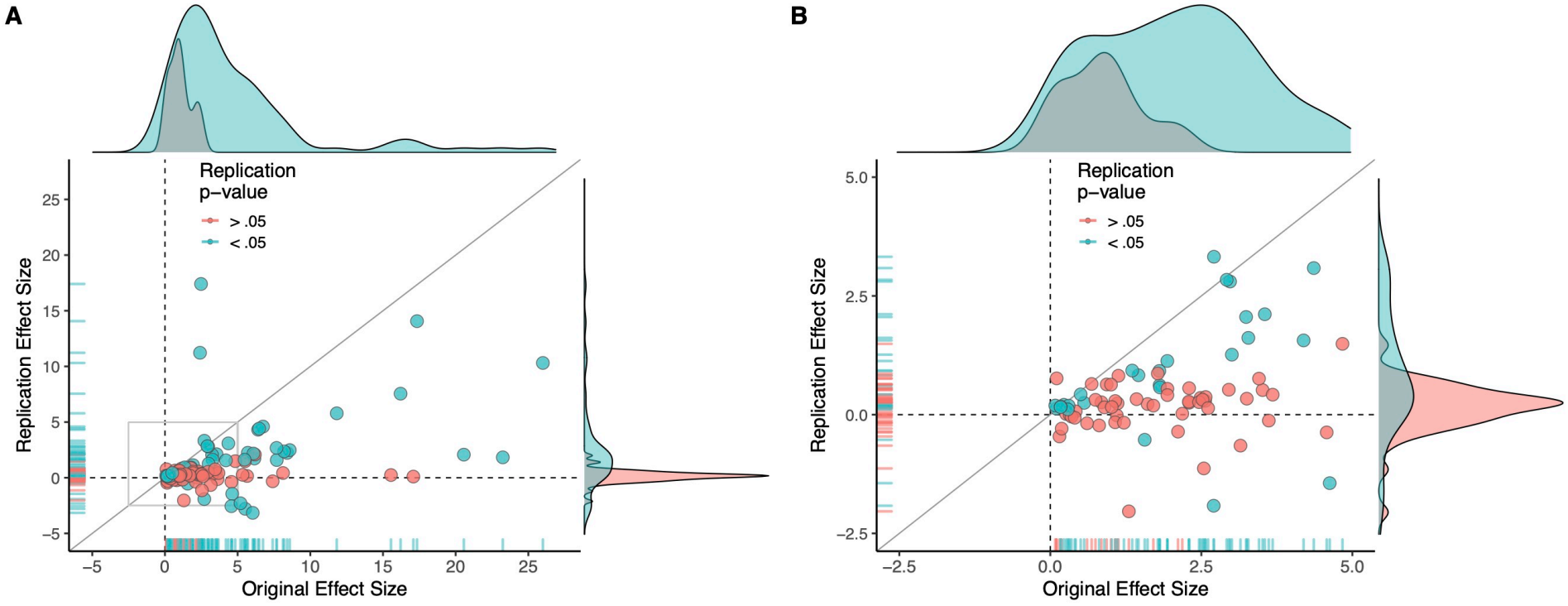
46% succeeded on most criteria, 54% failed on most criteria

80% of original null effects succeeded on most criteria

40% of original positive effects succeeded on most criteria

REPRODUCIBILITY PROJECT Cancer Biology

Replication effects compared with original effects

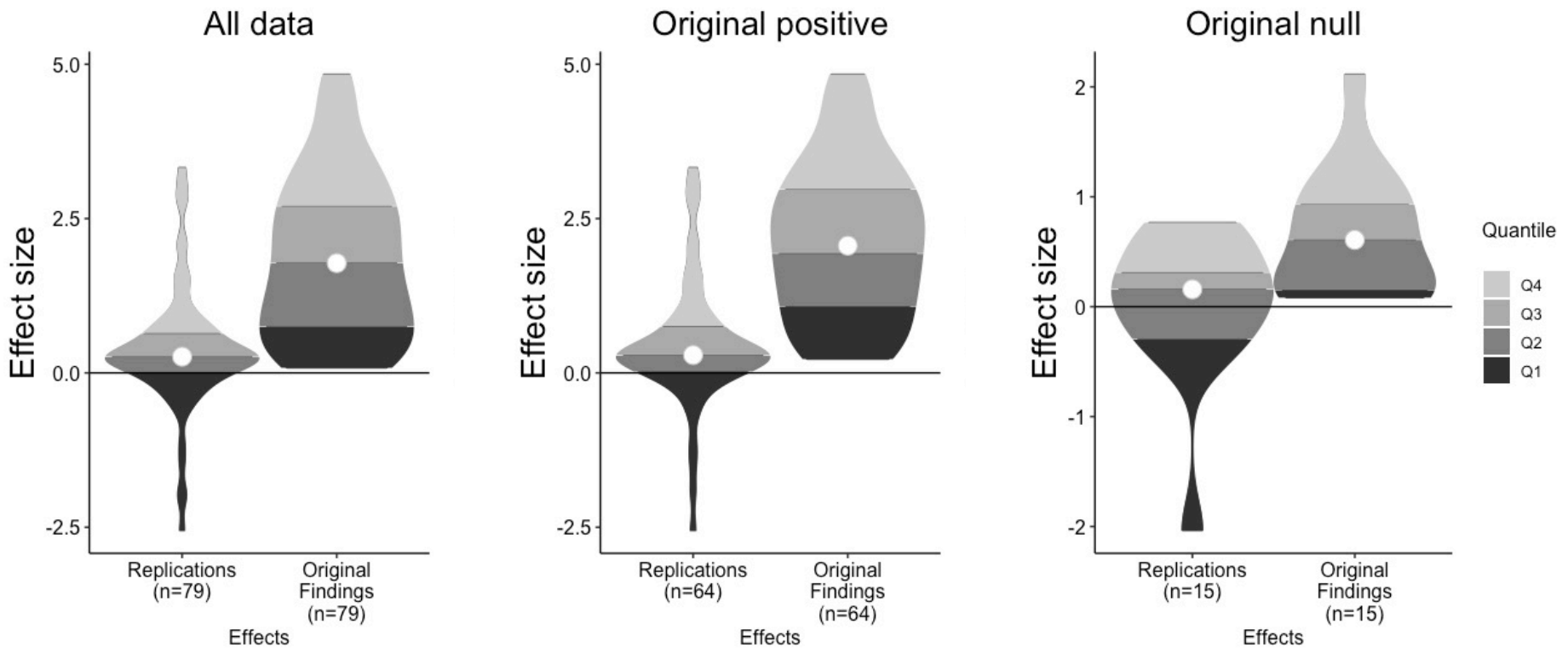


Replications 85% smaller on average

Zoomed in on effect sizes <5

REPRODUCIBILITY PROJECT Cancer Biology

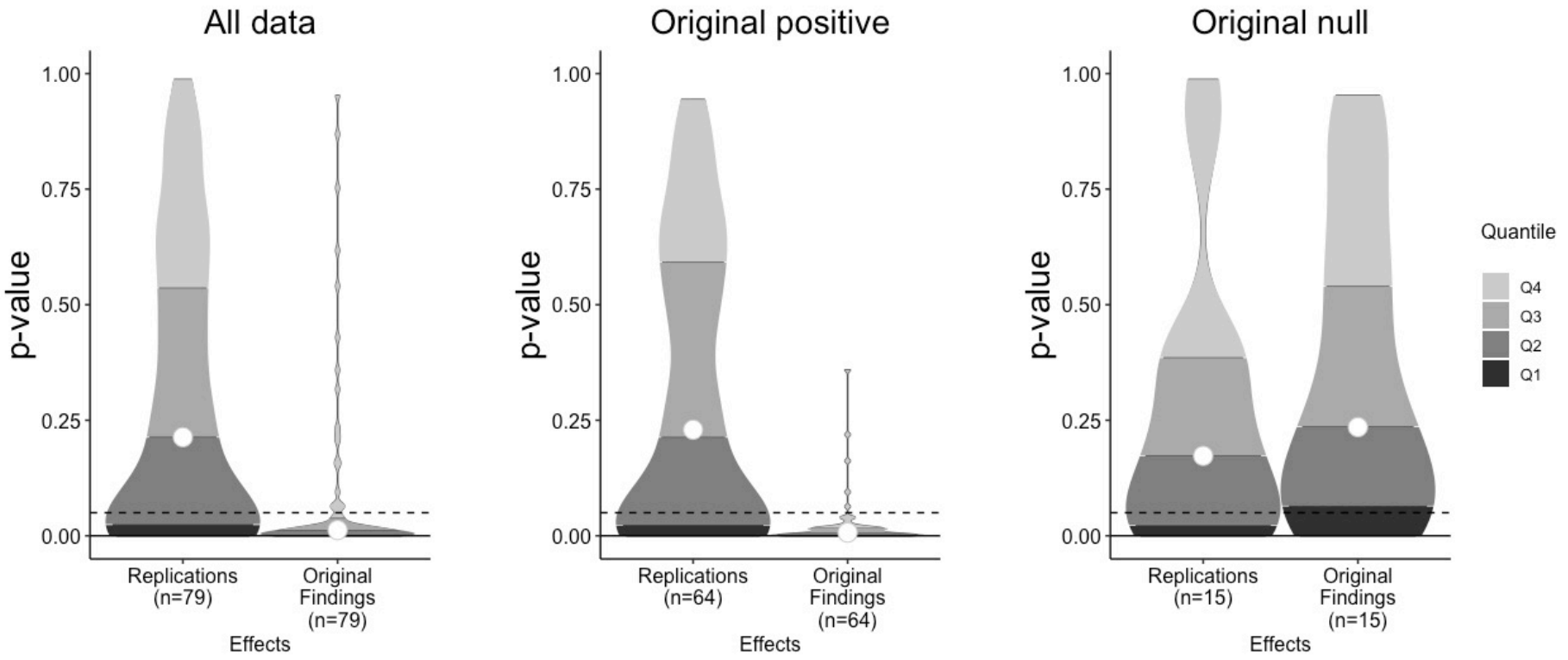
Replication effects compared with original effects



effect sizes <5

REPRODUCIBILITY PROJECT Cancer Biology

Replication p-values compared with original p-values

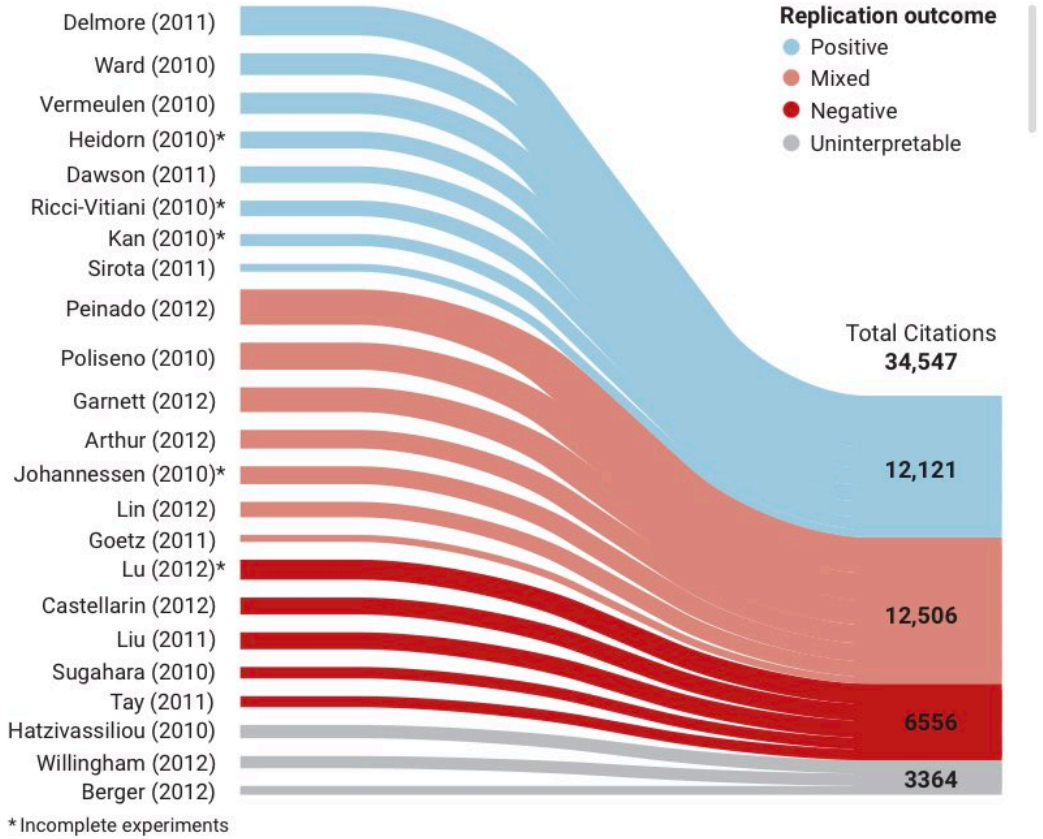


effect sizes <5

Outcomes

REPRODUCIBILITY PROJECT Cancer Biology

Subjective assessment



GRAPHIC: K. FRANKLIN/*SCIENCE*; DATA: REPRODUCIBILITY PROJECT: CANCER BIOLOGY

Kaiser, 2022

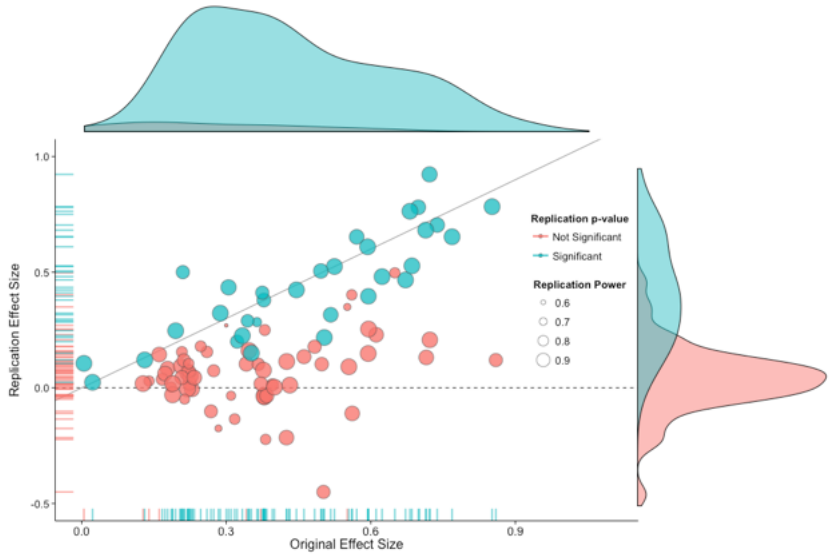
Meta-analysis conclusions

- Replication effects were much weaker than originals
- “Success” was low across replication criteria with variability due, in part to liberalness of the test
- Positive results were half as likely to replicate as null results
- Animal and non-animal declines similar magnitudes - animal effects lower success rate because small original effect sizes
- There is room for improvement

REPRODUCIBILITY PROJECT Cancer Biology

Replication in…

Psychology



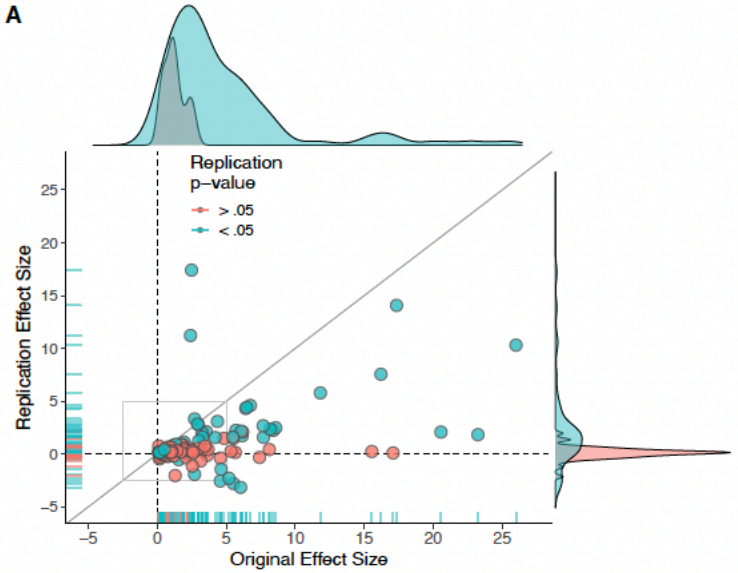
Open Science Collaboration, 2015 *Science*

<u>Replications</u>

36% significant, same direction as original

50% smaller than original on average

Cancer Biology



Errington et al., 2021 *eLife*

<u>Replications</u>

43% significant, same direction as original

85% smaller than original on average

Interpreting failures to replicate

- A failure to replicate could mean:
  - The original finding was a false positive
  - The replication was a false negative
  - Both are “true” and key conditions in the experimental design differ

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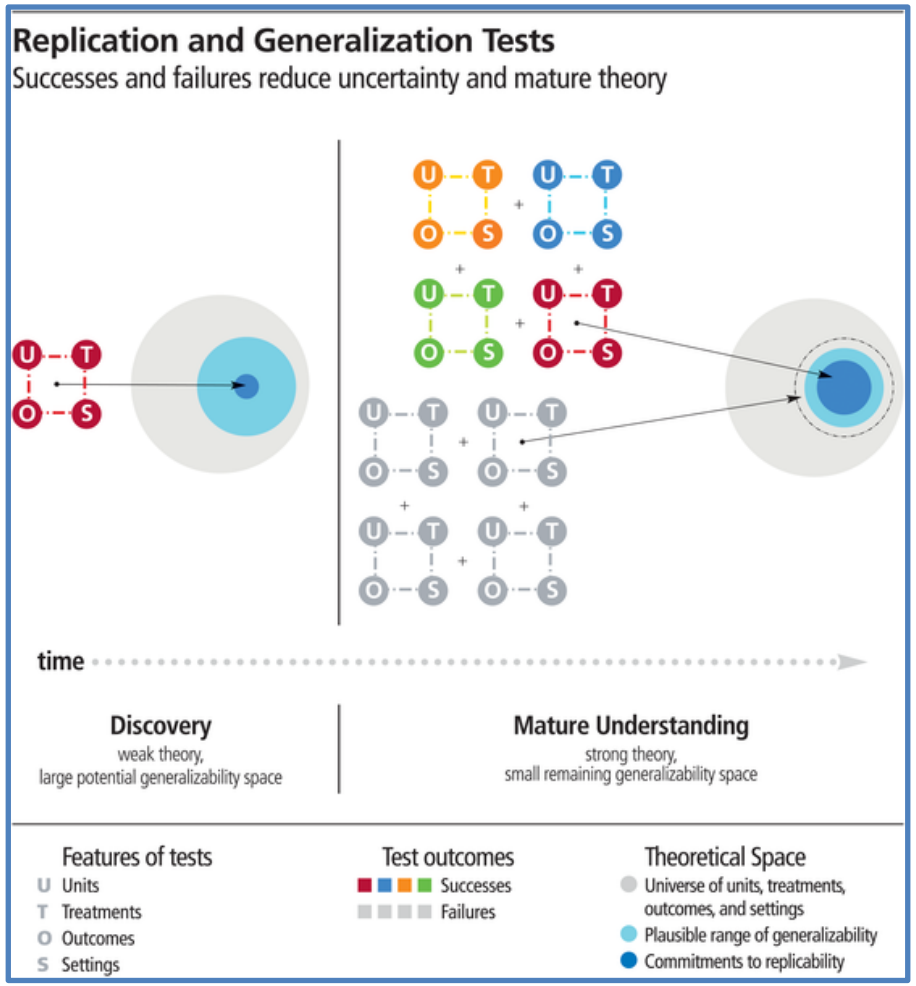
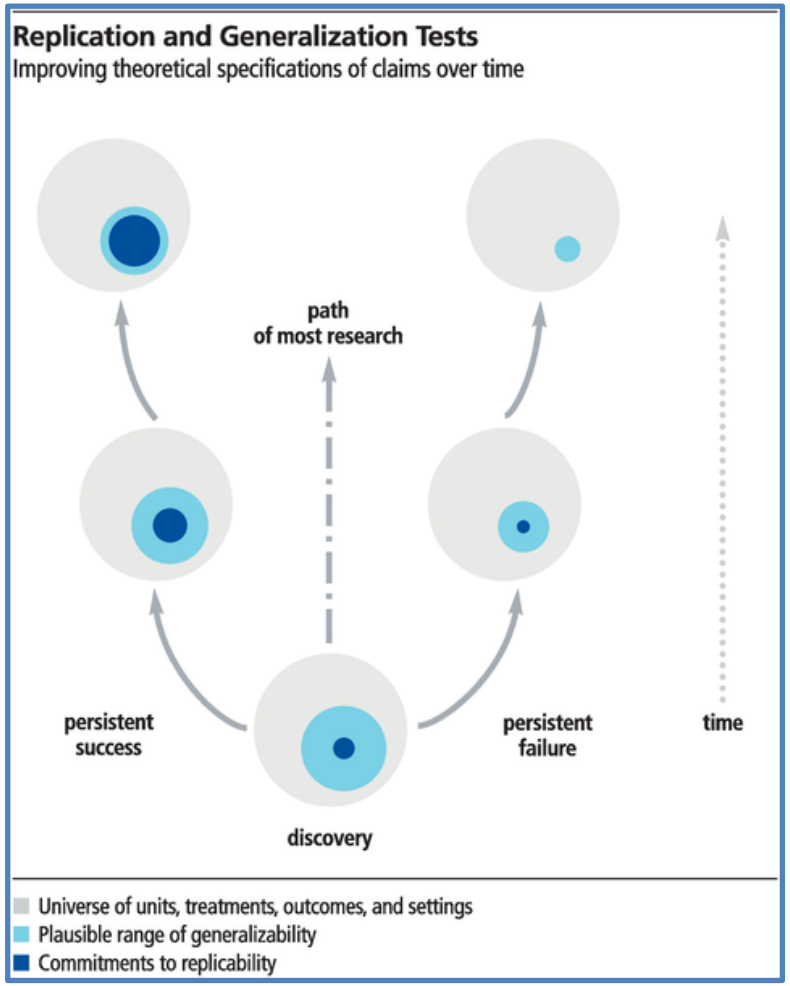
Do we know the conditions necessary to observe a finding?





Nosek & Errington, 2020a

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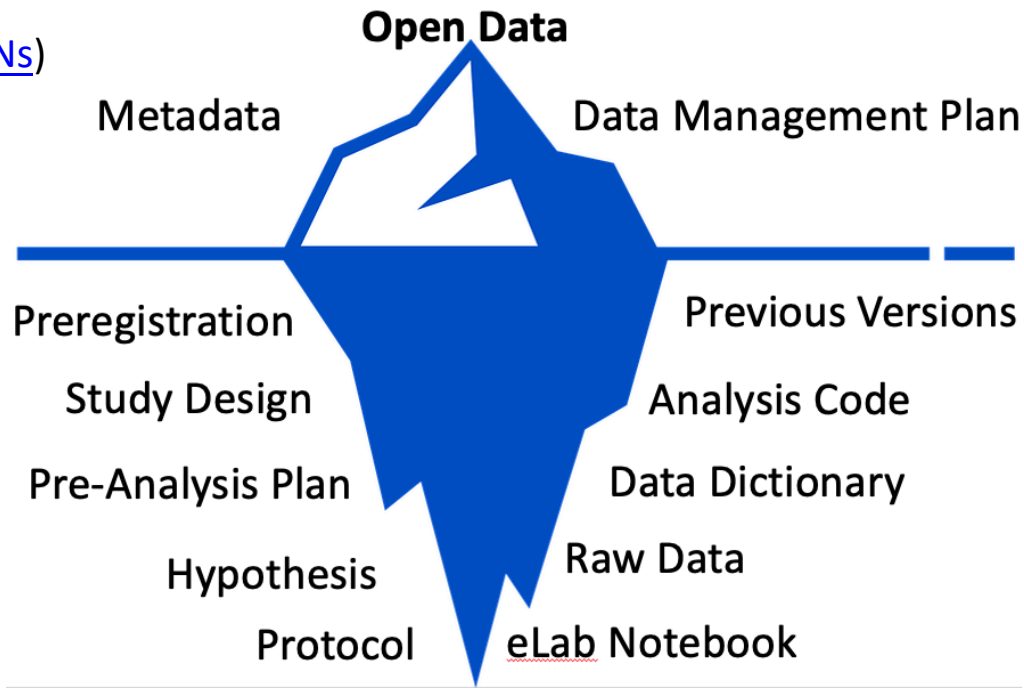
What can we do?

- Incentivize open science practices in your community
  - Aligning institutional policies with open science practices (e.g., NASEM Roundtable)
  - Journal polices that incentivize open practices (e.g., TOP Guidelines)
  - Assessment of researchers and scholarly research (e.g., DORA)
  - Training on reproducible and open science practices

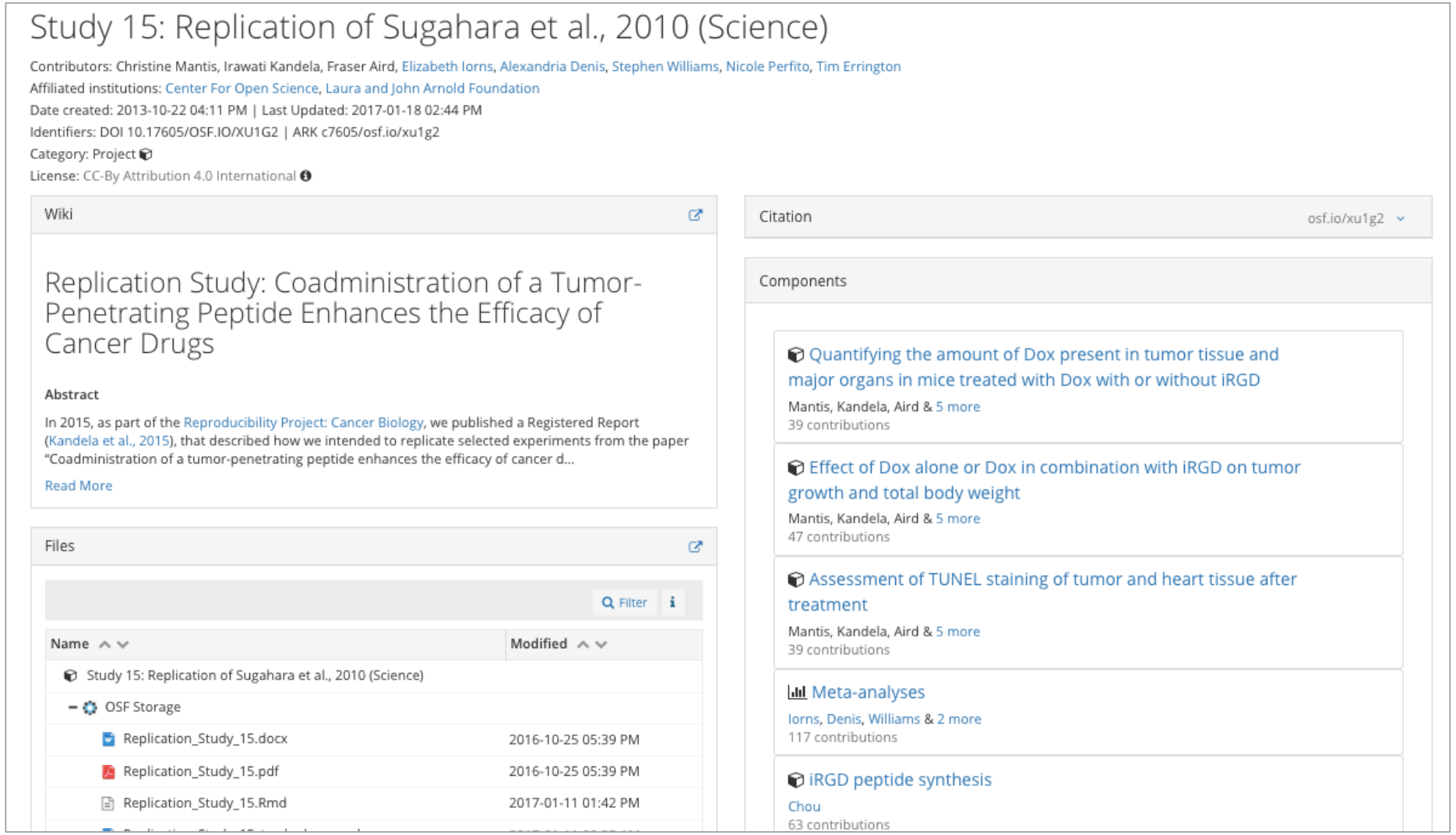
What can we do?

- Incorporate open science practices in your research
  - Share data/code/etc using repositories (e.g., NIH GREI Repositories)
  - Deposit reagents in repositories (e.g., addgene)
  - Make detailed protocols open (e.g., ELNs)
  - Try preregistration/Registered Reports



Conclusions

REPRODUCIBILITY PROJECT
Cancer Biology



Study 15: Replication of Sugahara et al., 2010 (Science)

Contributors: Christine Mantis, Irawati Kandela, Fraser Aird, Elizabeth Iorns, Alexandria Denis, Stephen Williams, Nicole Perfito, Tim Errington
Affiliated institutions: Center For Open Science, Laura and John Arnold Foundation
Date created: 2013-10-22 04:11 PM | Last Updated: 2017-01-18 02:44 PM
Identifiers: DOI 10.17605/OSF.IO/XU1G2 | ARK c7605/osf.io/xu1g2
Category: Project
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Wiki

Replication Study: Coadministration of a Tumor-Penetrating Peptide Enhances the Efficacy of Cancer Drugs

Abstract

In 2015, as part of the Reproducibility Project: Cancer Biology, we published a Registered Report (Kandela et al., 2015), that described how we intended to replicate selected experiments from the paper "Coadministration of a tumor-penetrating peptide enhances the efficacy of cancer d...

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Citation osf.io/xu1g2

Components

Quantifying the amount of Dox present in tumor tissue and major organs in mice treated with Dox with or without iRGD
Mantis, Kandela, Aird & 5 more
39 contributions

Effect of Dox alone or Dox in combination with iRGD on tumor growth and total body weight
Mantis, Kandela, Aird & 5 more
47 contributions

Assessment of TUNEL staining of tumor and heart tissue after treatment
Mantis, Kandela, Aird & 5 more
39 contributions

Meta-analyses
Iorns, Denis, Williams & 2 more
117 contributions

iRGD peptide synthesis
Chou
63 contributions

Conclusions

REPRODUCIBILITY PROJECT
Cancer Biology

Dose administration

Mice were intravenously injected (IV) by tail vein, based on body weight on injection day. For tumor and organ penetrance analysis, Figure 1, mice were anesthetized, perfused, and sacrificed 1 hr after drug administration. For multi-day experiments mice were injected by IV every other day for 24 days based on body weight on injection day. On the last day, mice were anesthetized, perfused, and sacrificed 1 hr after drug administration. Further details of these methods are available at (https://osf.io/bkhnp/).

Conclusions

REPRODUCIBILITY PROJECT
Cancer Biology

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Conclusions

REPRODUCIBILITY PROJECT
Cancer Biology

Dose administration

Mice were intravenously injected (IV) by tail vein, based on body weight on injection day. For tumor and organ penetrance analysis, Figure 1, mice were anes
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TUNEL analysis

TUNEL (EMD Millipore, cat # S7100) stained slides were evaluated by Dr. Gennadiy Bondarenko and Dr. Andrey Ugolkov. Images were captured using a Carl Zeiss Axial Lab A1 microscope and a 40x objective, by Dr. Ugolkov, or a Olympus BX45 microscope and a 40x objective, by Dr. Bondarenko (images available at: https://osf.io/3fs27/). Drs. Bondarenko and Ugolkov were blinded to group allocation, only receiving the animal ID with H or P designation to indicate heart or prostate tumor. The frequency of apoptosis was calculated as an apoptotic index, in which the proportion of cells undergoing apoptosis was expressed as a percentage of all cells observed. The apoptotic index of each tissue sample was calculated as the number of TUNEL-positive cells and bodies per 500 cells/microscopic view or 2500 cells/slide (5 slides/tissue), counted in five randomly selected microscopic fields in each tissue sample. Percent apoptotic index was calculated with the following formulation: (i/500) X100%. i = cell undergoing apoptosis. An average was taken of the apoptotic index from all five fields of all five slices (25 fields total) which is considered one biological replicate. Negative and positive control sections were stained in parallel to the tumor and heart samples and are available at (https://osf.io/gmcyt/). Original counts are available at (https://osf.io/pbg7x/).

Conclusions

REPRODUCIBILITY PROJECT
Cancer Biology

Dose administration

Mice were intravenously injected (IV) by tail vein, based on body weight on injection day. For tumor ar
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TUNEL analysis

TUNEL (EMD Millipore,
Bondarenko and Dr. Andr
A1 microscope and a 40x
40x objective, by Dr. Bond
Bondarenko and Ugolkov
with H or P designation to
was calculated as an apop
apoptosis was expressed a
tissue sample was calculat
cells/microscopic view or
selected microscopic fields
with the following formula
was taken of the apoptotic
is considered one biologic
in parallel to the tumor an
Original counts are availal

Statistical analysis

Statistical analysis was performed with R software (RRID: SCR_001905), version 3.2.3 (R Core Team, 2016). All data csv files and analysis scripts are available at (https://osf.io/xu1g2/). Confirmatory statistical analysis was pre-registered (https://osf.io/9hr2d/) before the experimental work began as outlined in the Registered Report (Kandela et al., 2015). Additional exploratory analysis (area under the curve) was performed using the weights of the mice over the treatment period. Data were checked to ensure assumptions of statistical tests were met. A meta-analysis of a common original and replication effect size was performed using a random effects model and the *metafor* R package (Viechtbauer, 2010). (available at https://osf.io/ymxaz/). The original study data were extracted *a priori* from the published figures by determining the mean and upper/lower error values for each data point. The extracted data were published in the Registered Report (Kandela et al., 2015) and were used in the power calculations to determine the sample sizes for this study. In the meta-analyses where Glass' Δ was used, because of unequal variance between the two conditions being compared, the standard deviation of DOX + PBS was used in the calculations.

Conclusions

REPRODUCIBILITY PROJECT
Cancer Biology

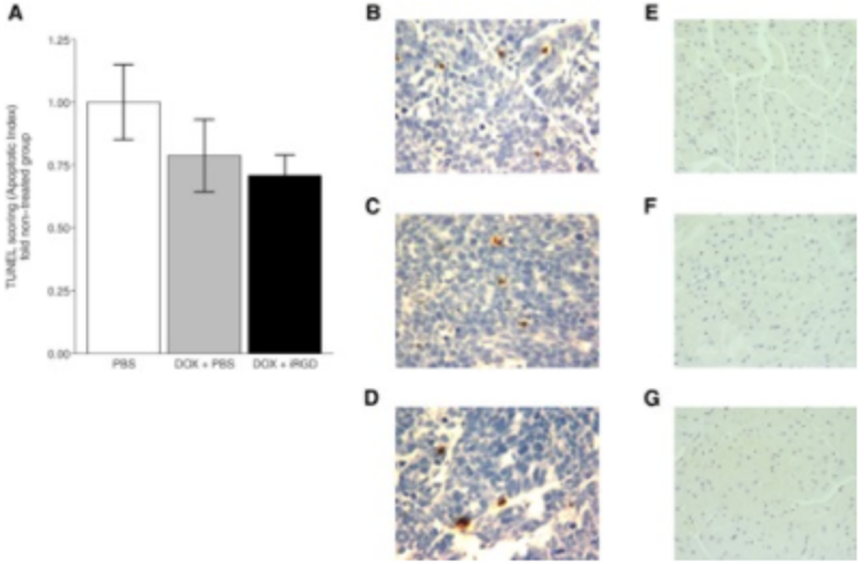


Figure 4. Download figure | Open

TUNEL staining of mouse tissues.

Mice bearing orthotopic 22Rv1 human prostate tumors were intravenously injected wi
alone (PBS), 1 mg/kg DOX and PBS (DOX + PBS), or 1 mg/kg DOX and 4 μmol/kg of
(DOX + iRGD). TUNEL staining was performed on tumor and heart sections of each animal. (**A**) Boxplot of mean apoptotic index calculated from TUNEL stained tumor sections. TUNEL scores were normalized to the average score of tumors from PBS treated mice. Means reported and error bars represent s.e.m. Number of mice per condition (n=6; n=18 mice total). One-way ANOVA on apoptotic index of all groups; $F(2, 15) = 1.378$, $p=0.282$. Planned contrast between DOX + PBS and DOX + iRGD; $t(15) = 0.435$, $p=0.670$ with *a priori* alpha level = 0.05. Representative images of TUNEL staining of tumor sections from PBS (**B**), DOX + PBS (**C**), or DOX + iRGD (**D**) treated mice. Representative images of TUNEL staining of heart sections from PBS (**E**), DOX + PBS (**F**), or DOX + iRGD (**G**) treated mice. Additional details for this experiment can be found at https://osf.io/7eynw/.

All RP:CB papers point to the OSF components which host not only the selected representative images, but all images collected, methods, analyzes, and figure generation.

Conclusions

> “An article about computational science in a scientific publication is not the scholarship itself, it is merely advertising of the scholarship. The actual scholarship is the complete software development environment, and the complete set of instructions which generated the figures.”

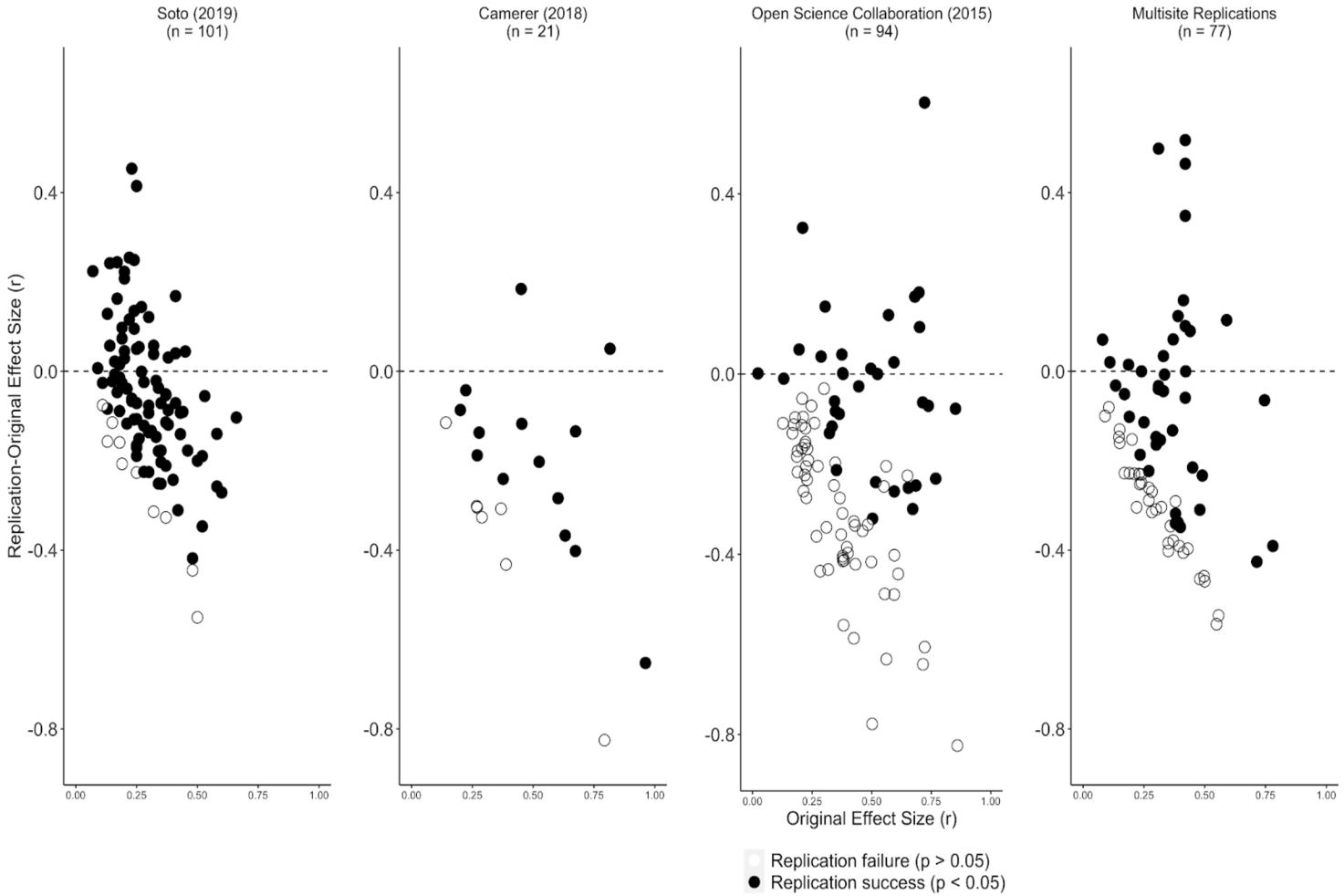
Buckheit & Donoho, 1995

Wavelab and Reproducible Research

Conclusions

REPRODUCIBILITY PROJECT Cancer Biology

Do adopting open science practices increase replicability?



Weaker evidence than original study

Nosek et al., 2022

More information

{Take a picture}

- These slides: https://osf.io/yf259

- Center for Open Science: https://cos.io/
- Reproducibility Project: Cancer Biology: https://cos.io/rpcb
- NASEM Roundtable: https://www.nationalacademies.org/our-work/roundtable-on-aligning-incentives-for-open-science
- TOP Guidelines: https://www.cos.io/top/
- DORA: https://sfdora.org/
- NIH GREI: https://datascience.nih.gov/news/nih-office-of-data-science-strategy-announces-new-initiative-to-improve-data-access
- OSF: https://osf.io/
- Preregistration: https://cos.io/prereg/
- Registered Reports: https://cos.io/rr/
- Addgene: https://www.addgene.org/
- Resources on ELNs: https://datamanagement.hms.harvard.edu/analyze/electronic-lab-notebooks

Tim Errington, tim@cos.io

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