BRAZILIAN

REPRODUCIBILITY

INITIATIVE

A multicenter systematic assessment of Brazilian biomedical science

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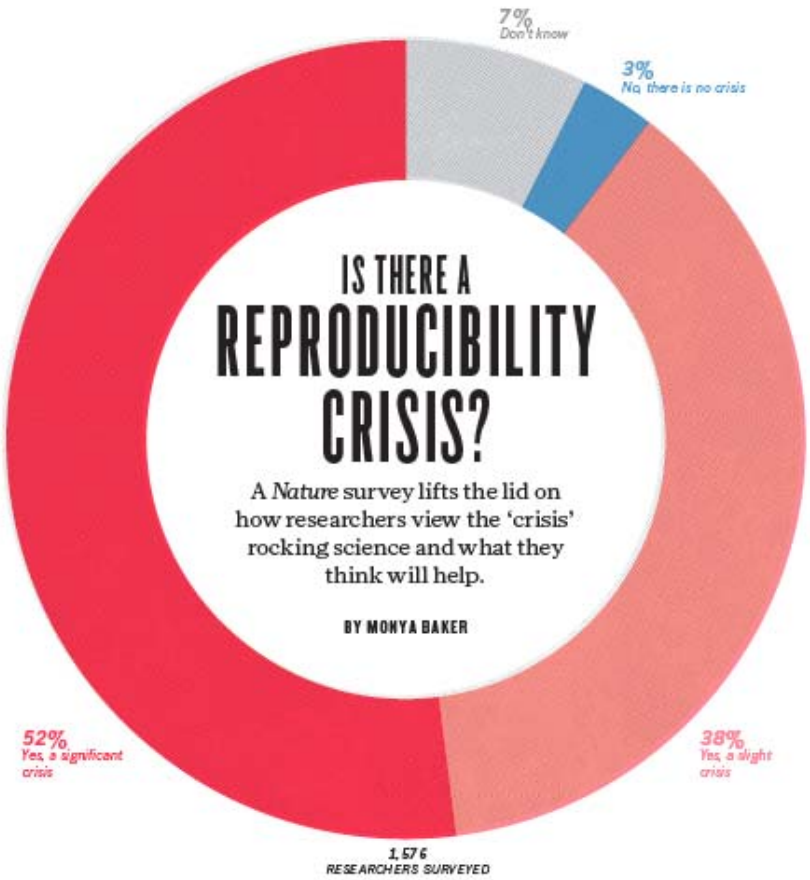
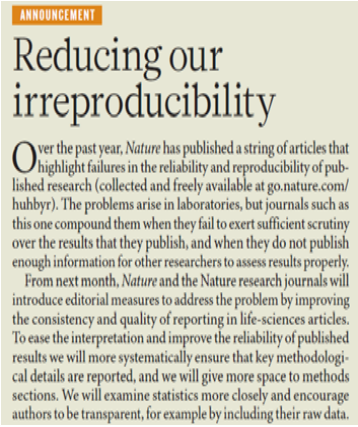
6th WCRI – June 2019

NÚCLEO DE CONFIABILIDADE CIENTÍFICA E NEUROCIÊNCIAS

Cutting straight to the chase…

- I can probably skip over why we think research reproducibility is an important topic…

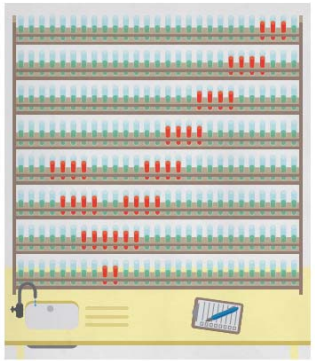



ANNOUNCEMENT

Reducing our irreproducibility

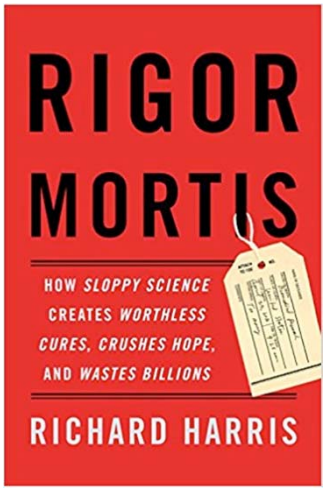
Over the past year, *Nature* has published a string of articles that highlight failures in the reliability and reproducibility of published research (collected and freely available at go.nature.com/huhbyr). The problems arise in laboratories, but journals such as this one compound them when they fail to exert sufficient scrutiny over the results that they publish, and when they do not publish enough information for other researchers to assess results properly.

From next month, *Nature* and the Nature research journals will introduce editorial measures to address the problem by improving the consistency and quality of reporting in life-sciences articles. To ease the interpretation and improve the reliability of published results 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.



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.

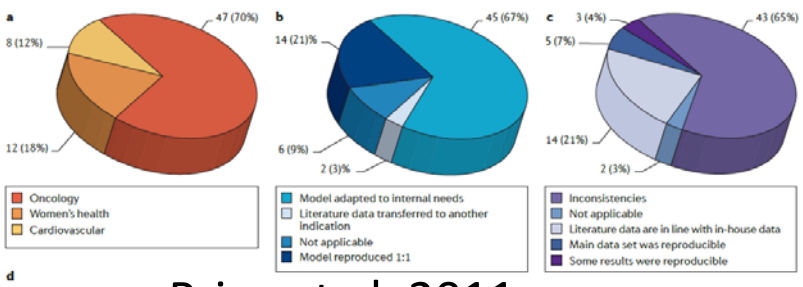


That said…

- We still have very little data on the reproducibility of basic biomedical research.

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

Florian Prinz, Thomas Schlange and Khusru Asadullah



Prinz et al. 2011

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.

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 & Ellis, 2012

Errington et al. (ongoing)

Reproducibility vs. incentives

- Much of the debate on irreproducibility hovers around wrong incentives.

Scientific Utopia: II. Restructuring Incentives and Practices to Promote Truth Over Publishability

Brian A. Nosek, Jeffrey R. Spies, and Matt Motyl

The natural selection of bad science

Paul E. Smaldino[1] and Richard McElreath[2]

Volume

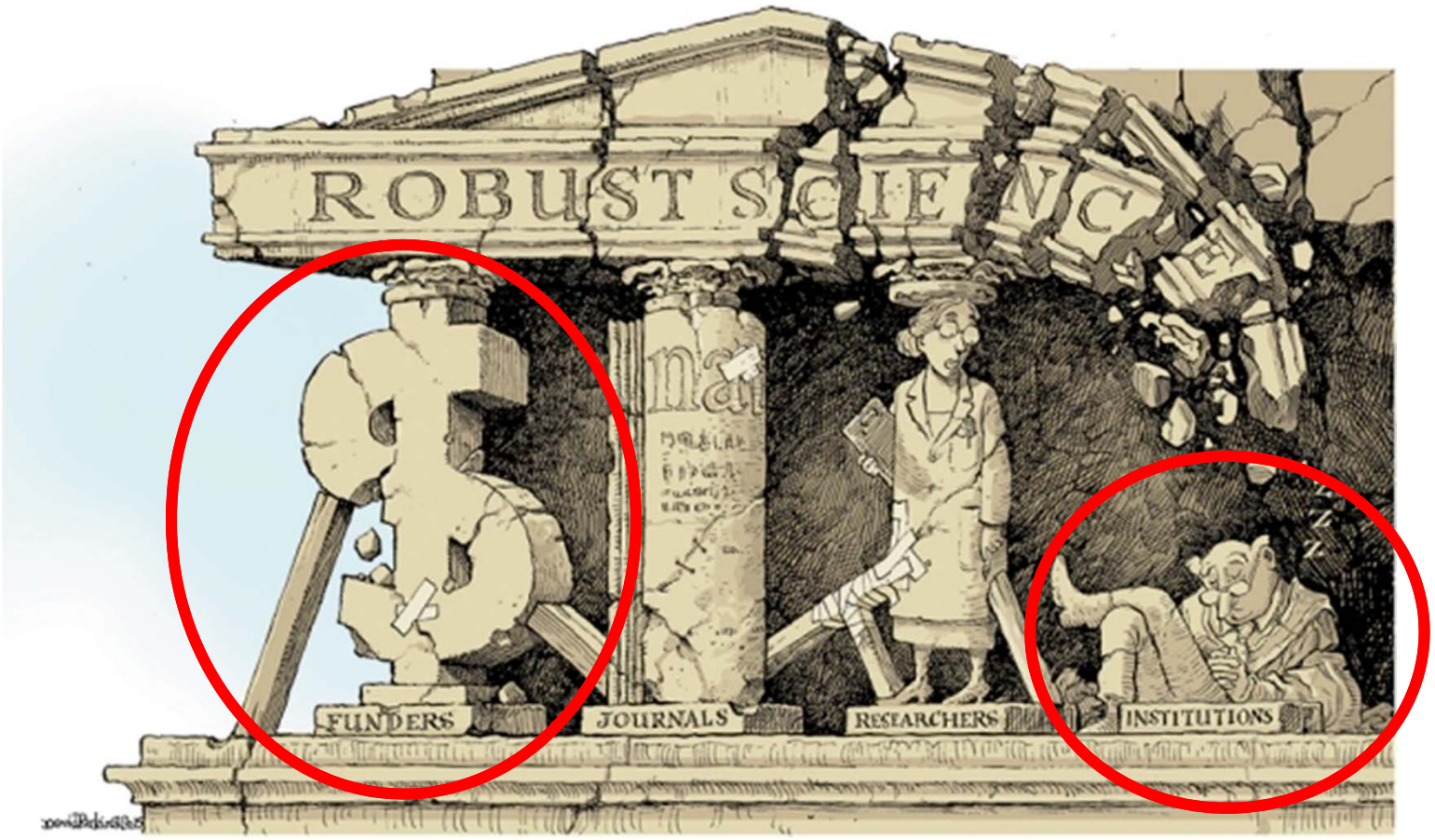
Rigor/Reproducibility?

(...)

Novelty/Impact

A disconnected debate

- Interestingly, existing data on reproducibility are usually not connected to the levels in which incentives occur.



Begley et al., 2015

The Brazilian case

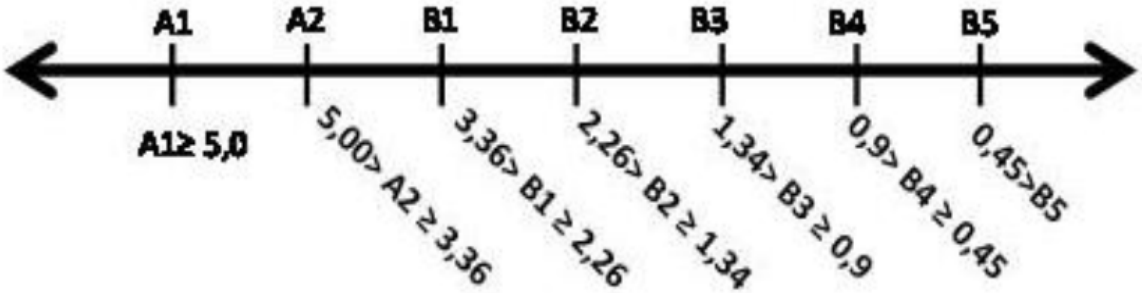
- In Brazil, incentives are mostly provided by large national or state agencies that set criteria for large-scale evaluations.

CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

FAPESP
SÃO PAULO RESEARCH FOUNDATION

FAPERJ
Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro

CAPES

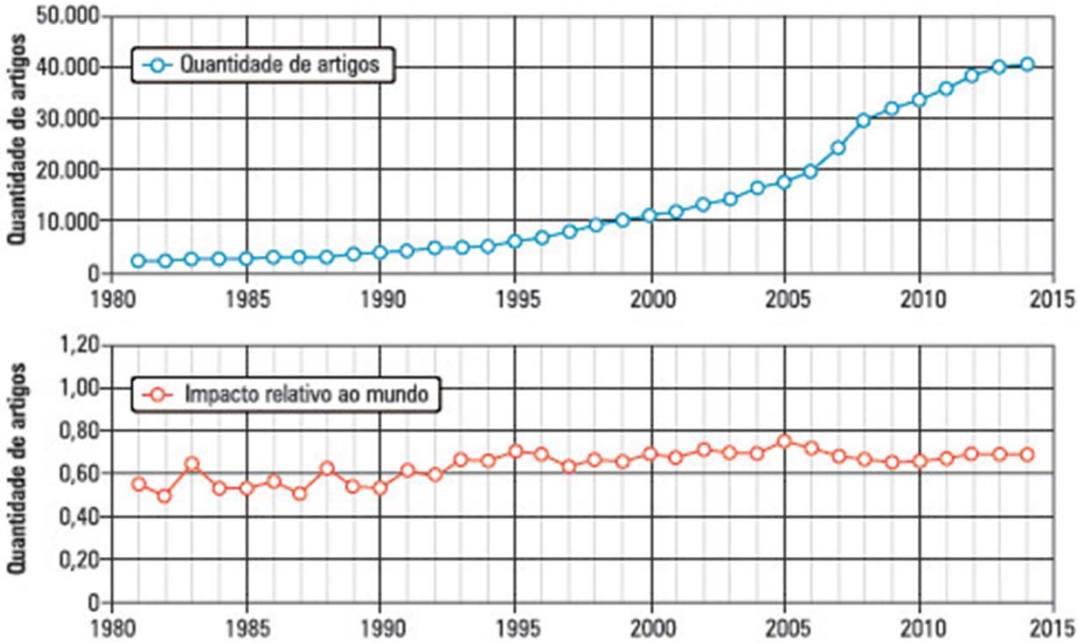


What agencies worry about...

- There is optimism about the growth of Brazilian science, and worries about its lack of impact.

Quantity

Impact

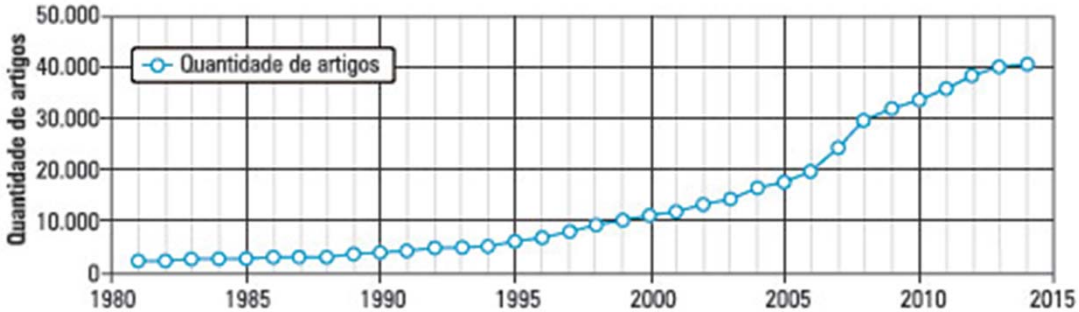


Fonte: Dados da Thomson-Reuters InCites compilados por CH Brito Cruz para a palestra "Desafios para a Pesquisa no Brasil"

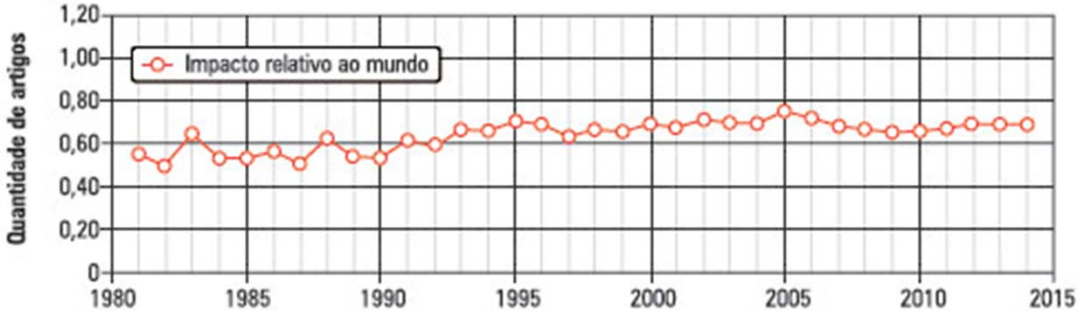
... and what they *should* worry about.

- This overlooks the much more pressing question of how much of what we publish is actually solid.

Quantity



Impact



Fonte: Dados da Thomson-Reuters InCites compilados por CH Brito Cruz para a palestra "Desafios para a Pesquisa no Brasil"

Reproducibility?

Taking the problem in our own hands

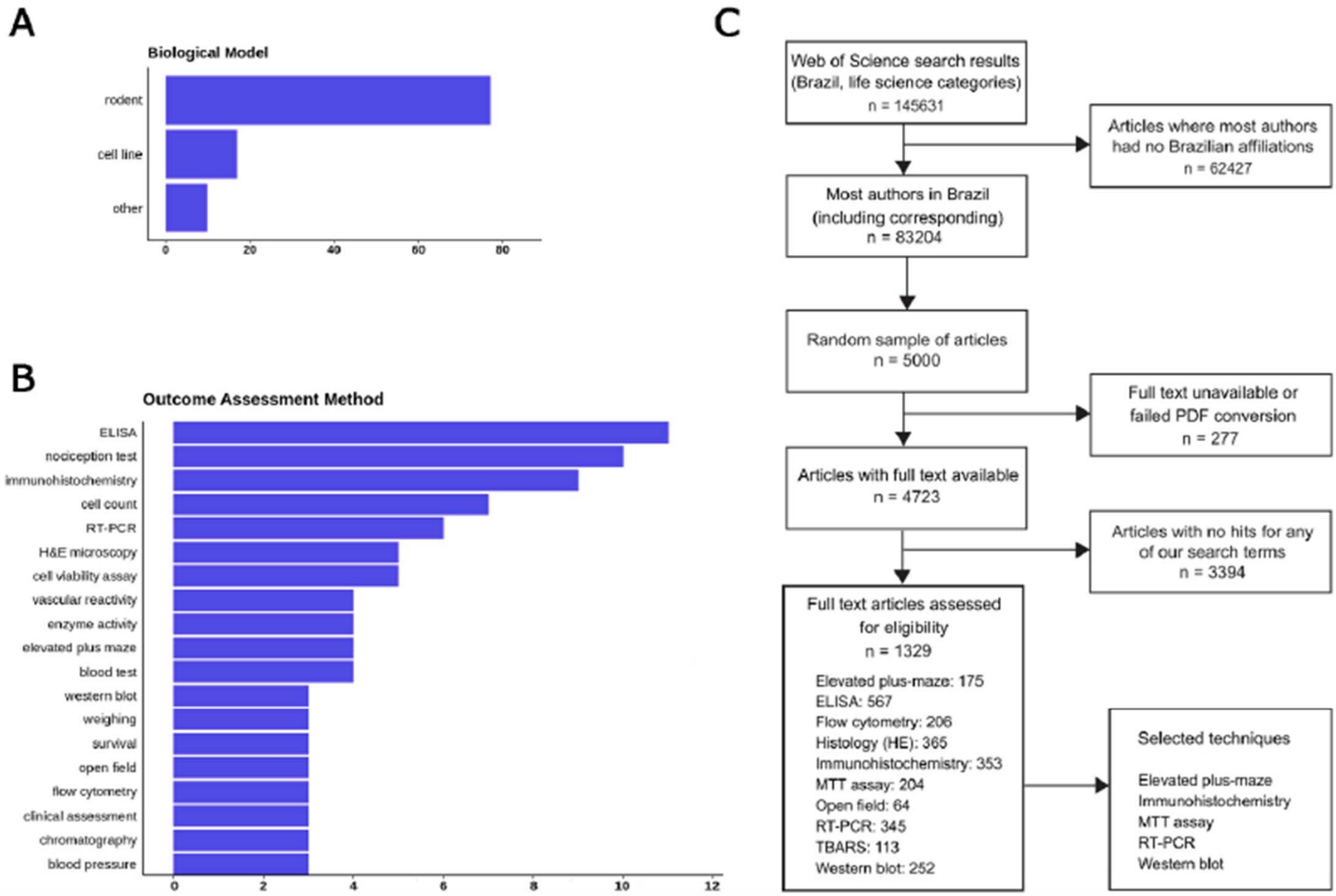
- As answering this question with data seems alien to funding agencies, it becomes a moral obligation of the scientific community.

What is it?

- The Brazilian Reproducibility Initiative is a multicenter effort to estimate the reproducibility of Brazilian biomedical science.

- Our aim is to reproduce between 60 and 100 experiments from Brazilian articles using 3 to 5 common laboratory methods in multiple laboratories.

Systematic review of common methods
Selection of target methods
Systematic review of each method
Selection of experiments to replicate
Recruting collaborators
Network of collaborators
Defining protocols
Data analysis
Performing replications
Publication of results and data



Amaral et al., 2019

Methods selection

- 10 candidate methods for further evaluation:

- ELISA
- Western blot
- RT-PCR
- Imunohistochemistry
- H&E microscopy
- Cell viability (MTT)
- Flow cytometry
- Elevated plus maze
- Open field exploration
- Lipid peroxidation (TBARS)

Building our network

- Intensive outreach for laboratories interested in participating (April - November 2018).

Iniciativa Brasileira de Reprodutibilidade
Publicado por Olavo Amaral [?] · 19 h ·

Temos enorme prazer em anunciar que nosso cadastro para laboratórios colaboradores está aberto! Se você trabalha no Brasil, tem experiência em uma de nossas 10 técnicas candidatas e interesse em realizar experimentos de replicação conosco, recebendo financiamento para isso, queremos saber mais sobre você! Preencha a ficha de cadastro de laboratórios disponível em http://reprodutibilidade.bio.br/cadastro e participe como autor deste esforço multicêntrico para avaliar a reprodutibilidade da ciência brasileira!

Cadastro de laboratórios colaboradores - Iniciativa Brasileira de Reprodutibilidade

Quais das seguintes técnicas seu laboratório está apto a executar? *

Marque todas as opções aplicáveis. Estas técnicas foram pré-selecionadas a partir das nossas etapas iniciais de revisão sistemática. Lembre-se que os custos relativos aos experimentos de replicação serão cobertos pela Iniciativa Brasileira de Reprodutibilidade, mas que os laboratórios colaboradores devem ter a infraestrutura necessária para realizá-los.

- [ ] Ensaio de viabilidade celular por MTT
- [ ] ELISA
- [ ] Western Blot
- [ ] PCR
- [ ] Imunohistoquímica ou imunocitoquímica (microscopia confocal)
- [ ] Histologia por Hematoxilina e eosina (microscopia ótica)
- [ ] Labirinto elevado em cruz
- [ ] Exploração em campo aberto
- [ ] Citometria de fluxo
- [ ] Ensaio de TBARS (substâncias reativas ao ácido tiobarbitúrico)

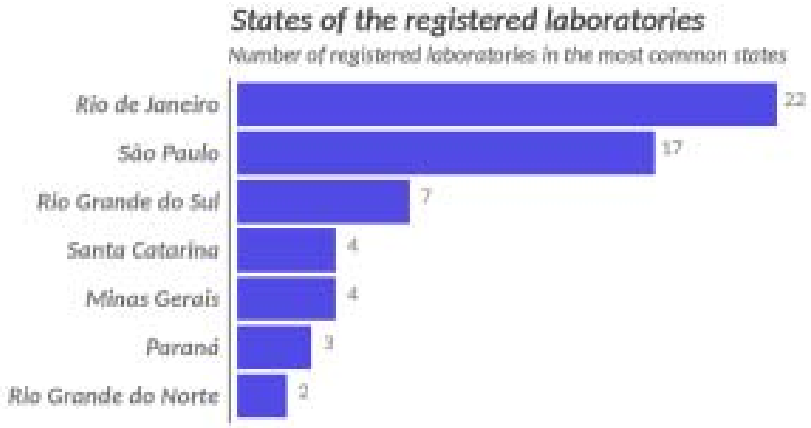
Building our network

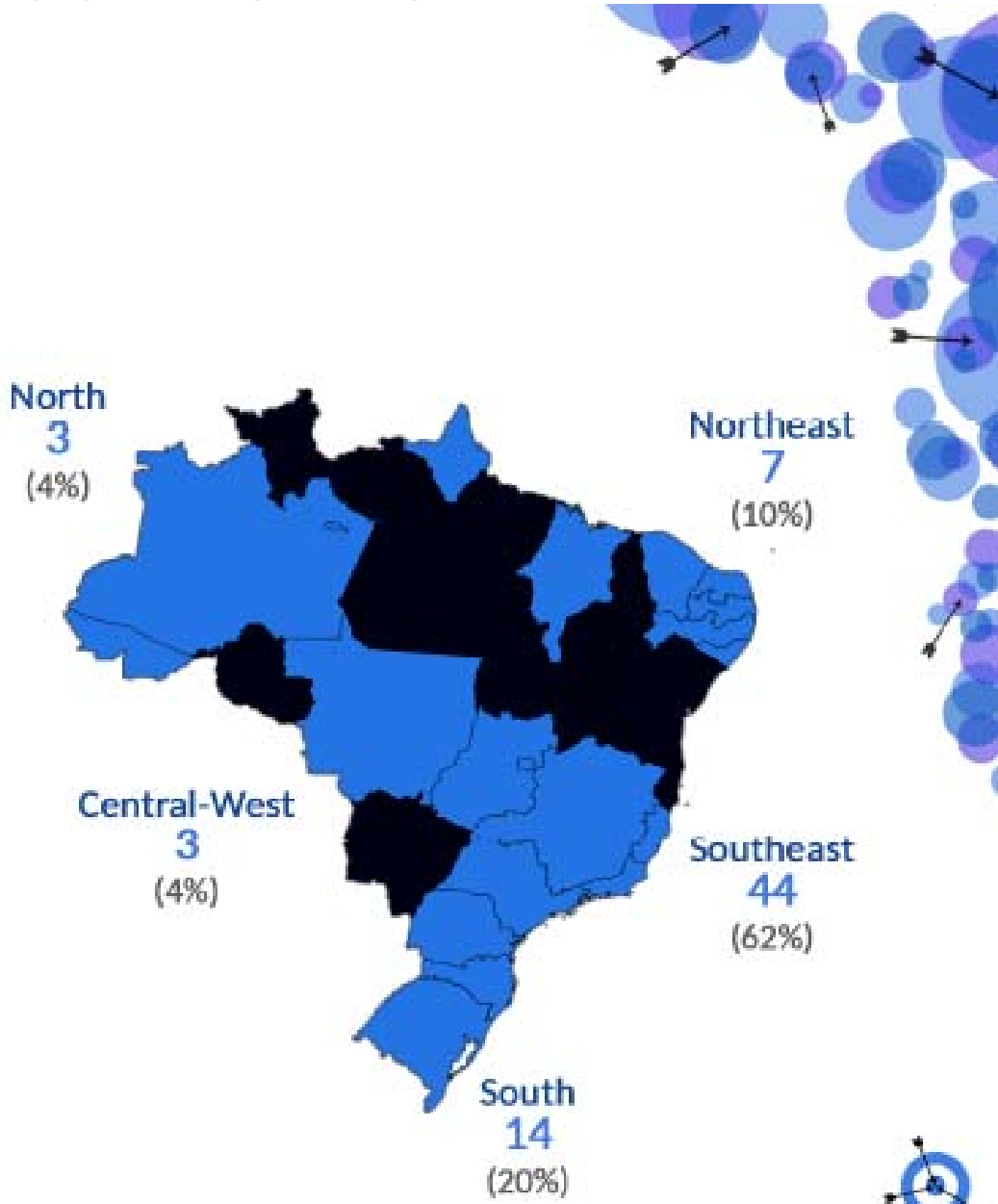
Registered laboratories

71
laboratories

43
institutions

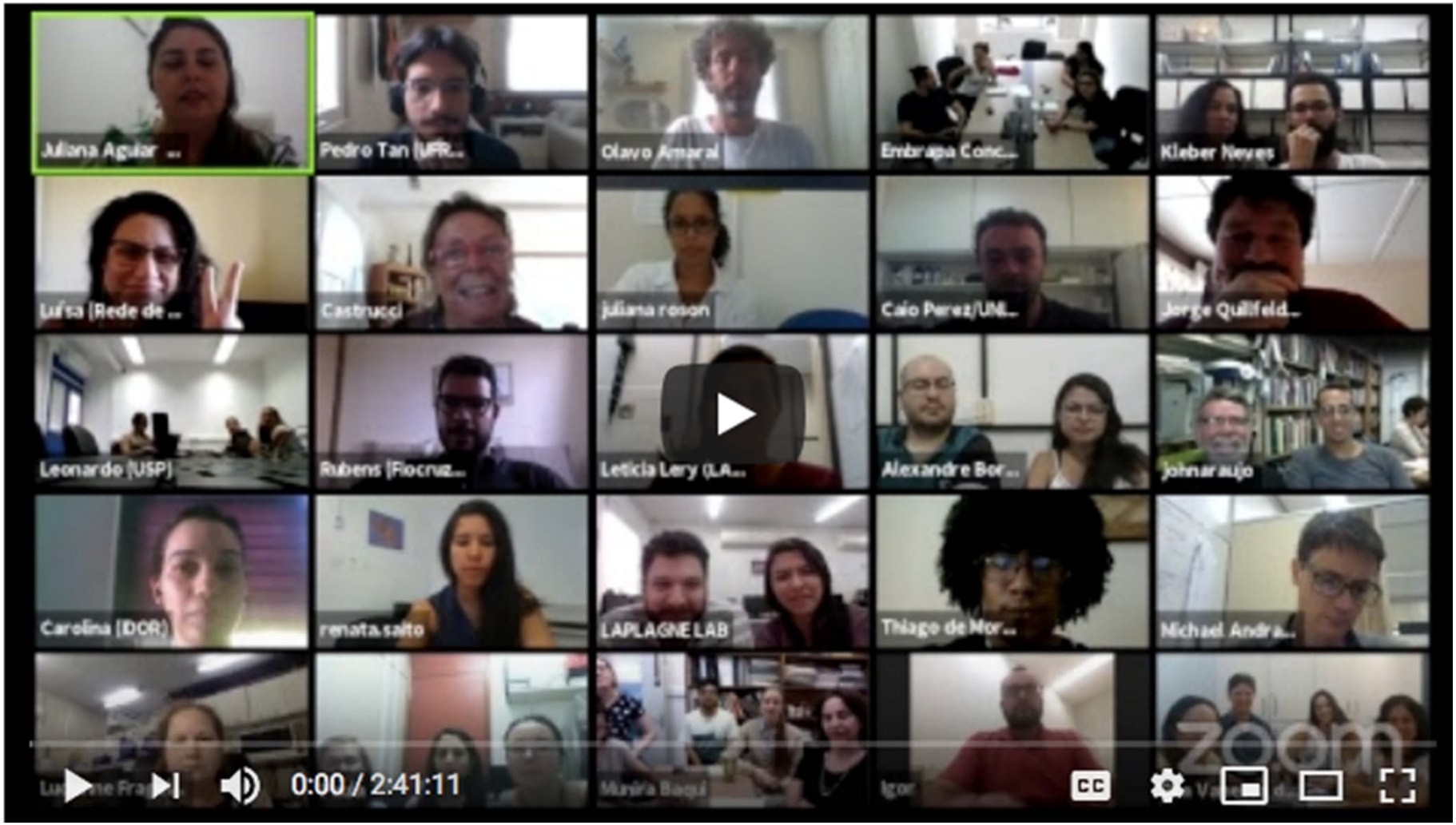
18
states





What we currently look like…

- And that’s less than half of us!



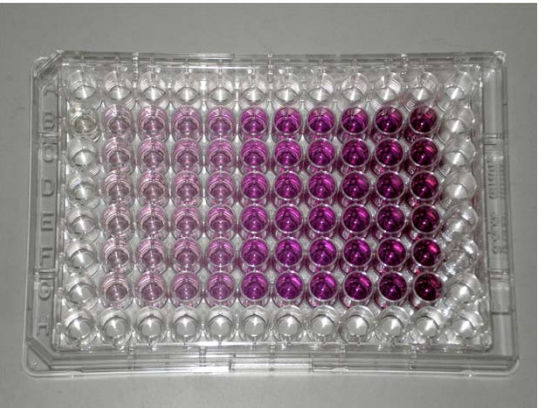
1st wave of experiments

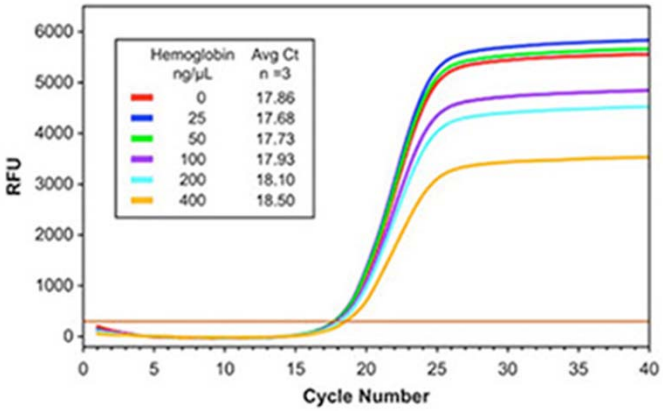
- 67 participating labs.
- 3 methods:

  - MTT assay (cell viability in culture).

  - RT-PCR (mRNA expression in tissue/culture).

  - Elevated plus maze (anxiety task in rodents).
- Cell lines, rats or mice as biological models.

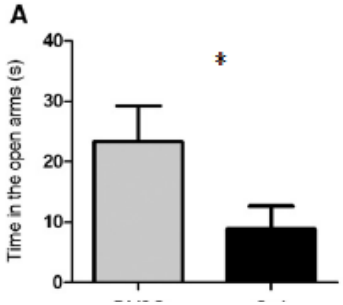




Experiment selection

- 20-year random sample of 30,000 articles in life sciences journals with at least half of authors based in Brazil.
- 20 individual experiments using each method selected by full-text mining + manual screening.
- Each experiment will be replicated in 3 different labs in a blinded fashion with bias control measures.
- Sample size calculated to provide 95% power for each individual replication to detect the original difference.

WEB OF SCIENCE™



‘Naturalistic’ reproducibility

- The published protocol is followed, but gaps are filled (and registered) independently by the 3 replicating labs.
- This should allow us to evaluate the impact of different methodological variables on the variability in results.

Animals and Housing

Balb/c mice were housed in pathogen-free conditions and fed a diet of autoclaved food and water.

****** To complete the information missing above, answer the following questions: ******

What will be the age (in days) of the animals at the beginning of the experiments?

What will be the sex of the animals?

What will be the weight range (g) of the animals at the beginning of the experiments?

What will the temperature in the animal facility be (in °C)?

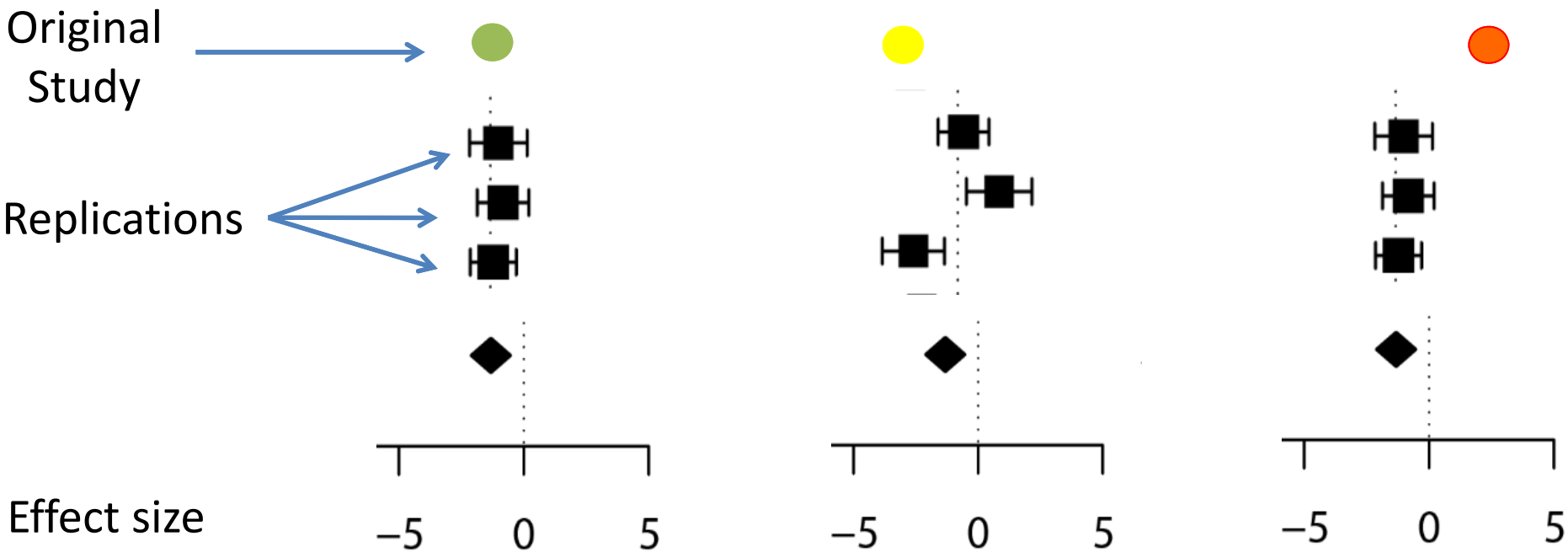
(A)?

(B)?

(C)?

Data Analysis

- Replication success will be defined by the original study's effect size being within the 95% prediction interval defined by a meta-analysis of the replications.
- Using multiple labs will allow us to separate variability due to methodological issues to bias in the literature.



Evaluating predictors

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- Results will allow us to analyze predictors of replication:

- Experimental model/method
- Effect size and statistical significance
- Number of citations and impact factor
- Publication year
- Experience of the principal investigator
- Region and institution of origin
- **Predictions by other researchers**

(Preregistration open at http://reprodutibilidade.bio.br/home!)

Schedule

1st wave of experiments:

- Currently: Development and internal peer review of protocols for each replication experiment.
- August 2019 – December 2020: Experimental replications.

2nd wave (Western blot? Immunohistochemistry?):

- December 2019 – April 2021

Publication of Results

- Expected at **mid-2021**

What we stand to gain

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- We will be the first country to have a systematic estimate of research reproducibility at a national level.
- Dissemination of the debate on research reproducibility across the country (and beyond).
- Development of a culture in which the reproducibility of published findings can and should be evaluated.
- Experience in a collective endeavour to answer a large general-interest question

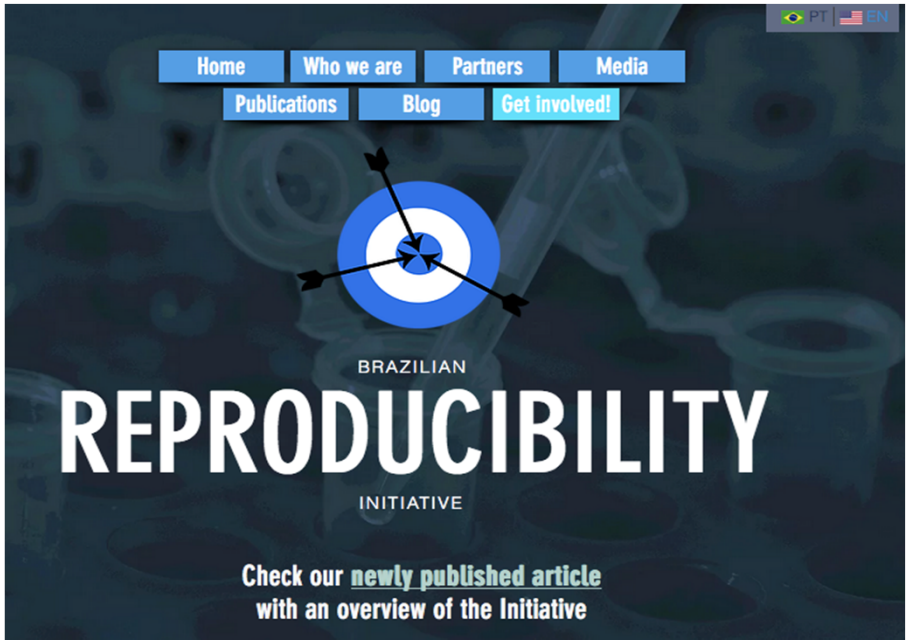
If you want to know more...

Science Forum: The Brazilian Reproducibility Initiative

eLIFE

Olavo B Amaral, Kleber Neves, Ana P Wasilewska-Sampaio, Clarissa FD Carneiro
Federal University of Rio de Janeiro, Brazil

Amaral *et al.* eLife 2019;8:e41602. DOI: https://doi.org/10.7554/eLife.41602



http://reprodutibilidade.bio.br/home

BIOMEDICAL RESEARCH

Brazil's science faces reproducibility test

More than 60 labs will assess the replicability of work by the country's researchers

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http://osf.io/6av7k/

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