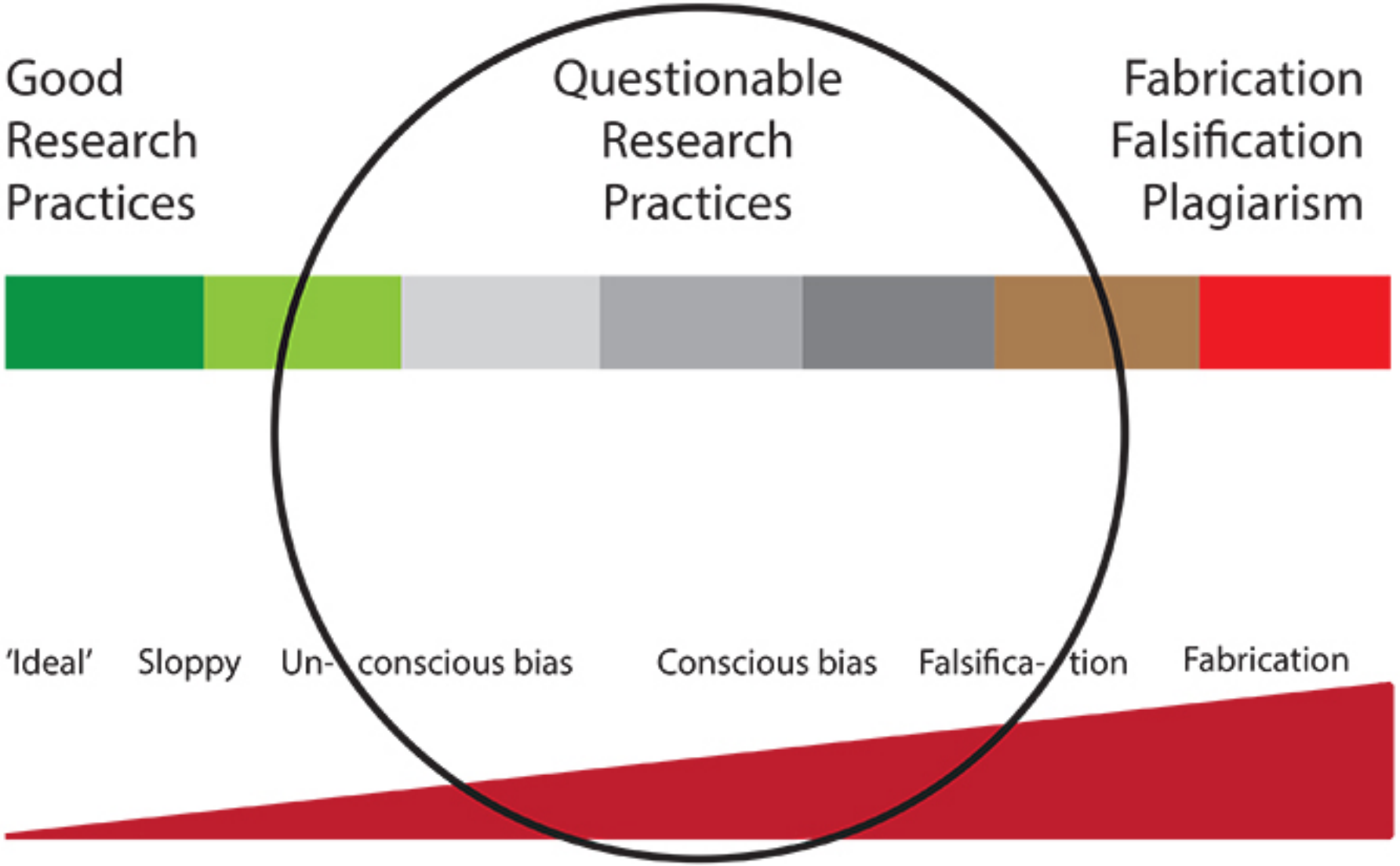
Improving Research Quality in Thailand: The Reproducibility Problems

Prasit Palittapongarnpim, M.D.



http://www.vib.be/en/news/Pages/Research-misconduct---The-grey-area-of-Questionable-Research-Practices.aspx

Improving Quality of Research Needs to be Done in Several Aspects

- Safety
- Ethics (Patient rights, Animal rights, Conflict of Interest),
- Reproducibility
  - Responsible Conduct of Research
    - Mentoring,…
    - Research Integrity (US-NIH definition:)
      - Fabrication
      - Falsification
      - Plagiarism
- Scientific Impact
- Usefulness

Why should we concern about research reproducibility?

11 FEBRUARY 2016 | VOL 530 | NATURE | 141 US NEWS

REPLICATION

Biotech giant posts negative results

Amgen papers seed channel for discussing reproducibility.

BY MONYA BAKER

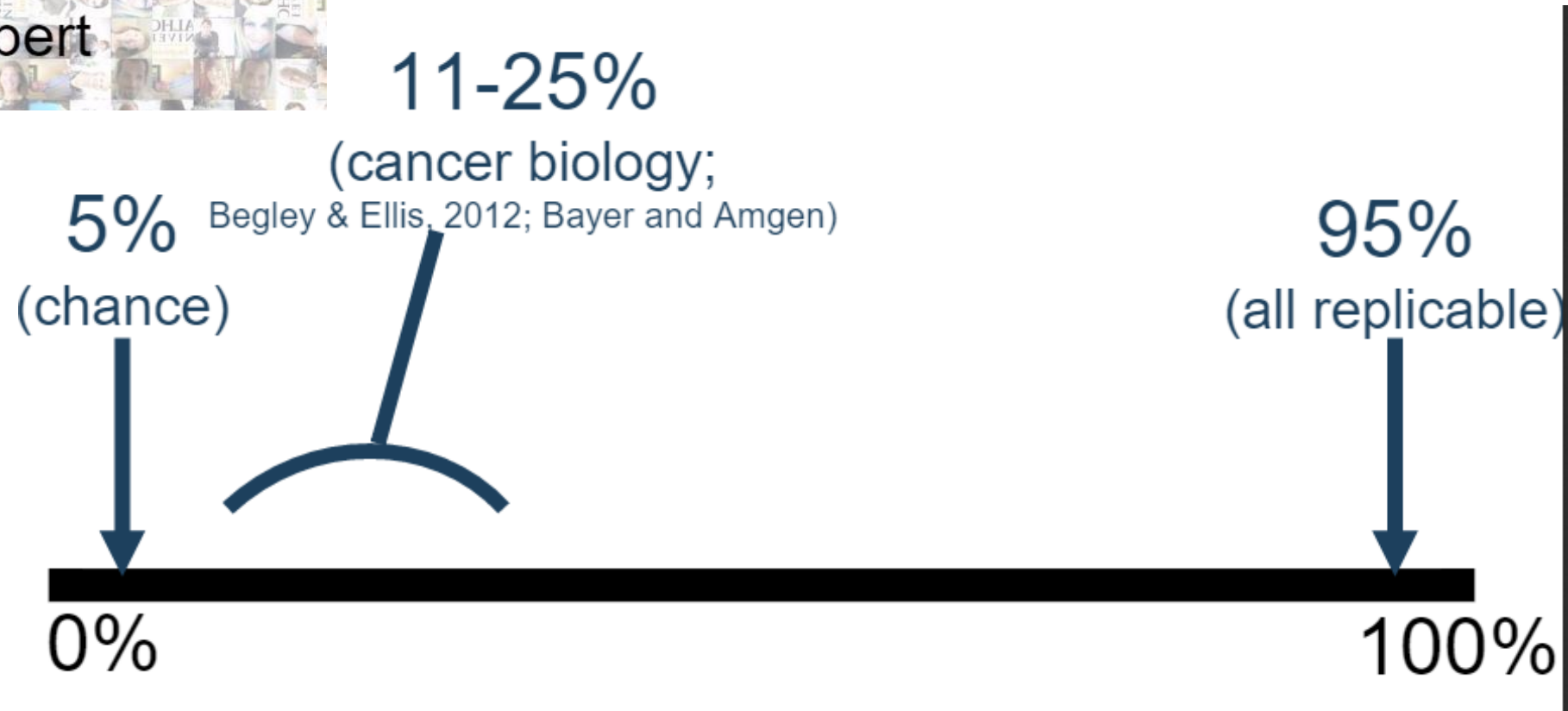
make strong conclusions that someone else's

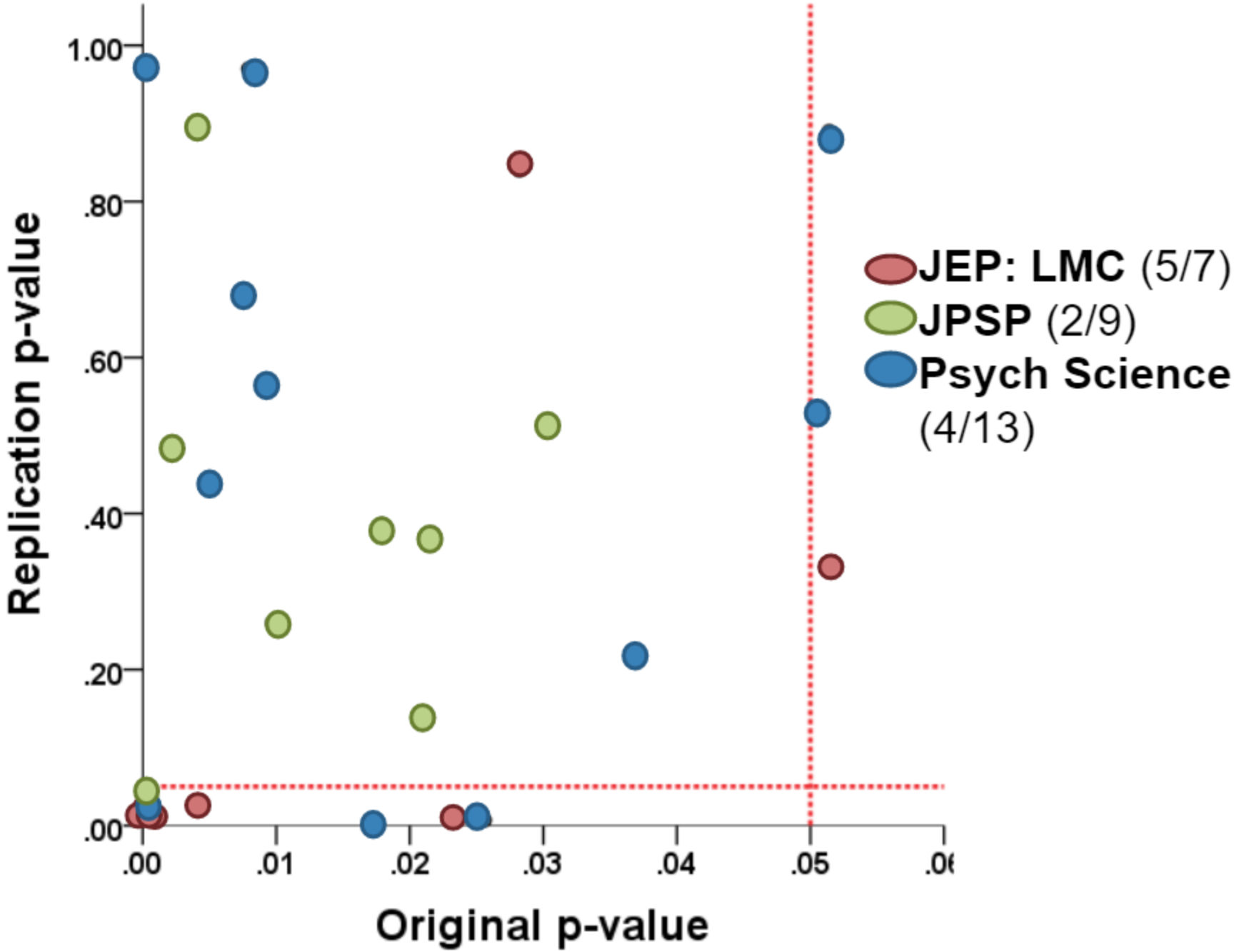
Over the past decade, before pursuing a particular line of research, scientists (including C.G.B.) in the haematology and oncology department at the biotechnology firm Amgen in Thousand Oaks, California, tried to confirm published findings related to that work. Fifty-three papers were deemed 'landmark' studies (see 'Reproducibility of research findings'). It was acknowledged from the outset that some of the data might not hold up, because papers were deliberately selected that described something completely new, such as fresh approaches to targeting cancers or alternative 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.

Reproducibility Project: Psychology

(Preliminary) Results

Elizabeth A. Gilbert
University of Virginia




1.00
.80
.60
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.20
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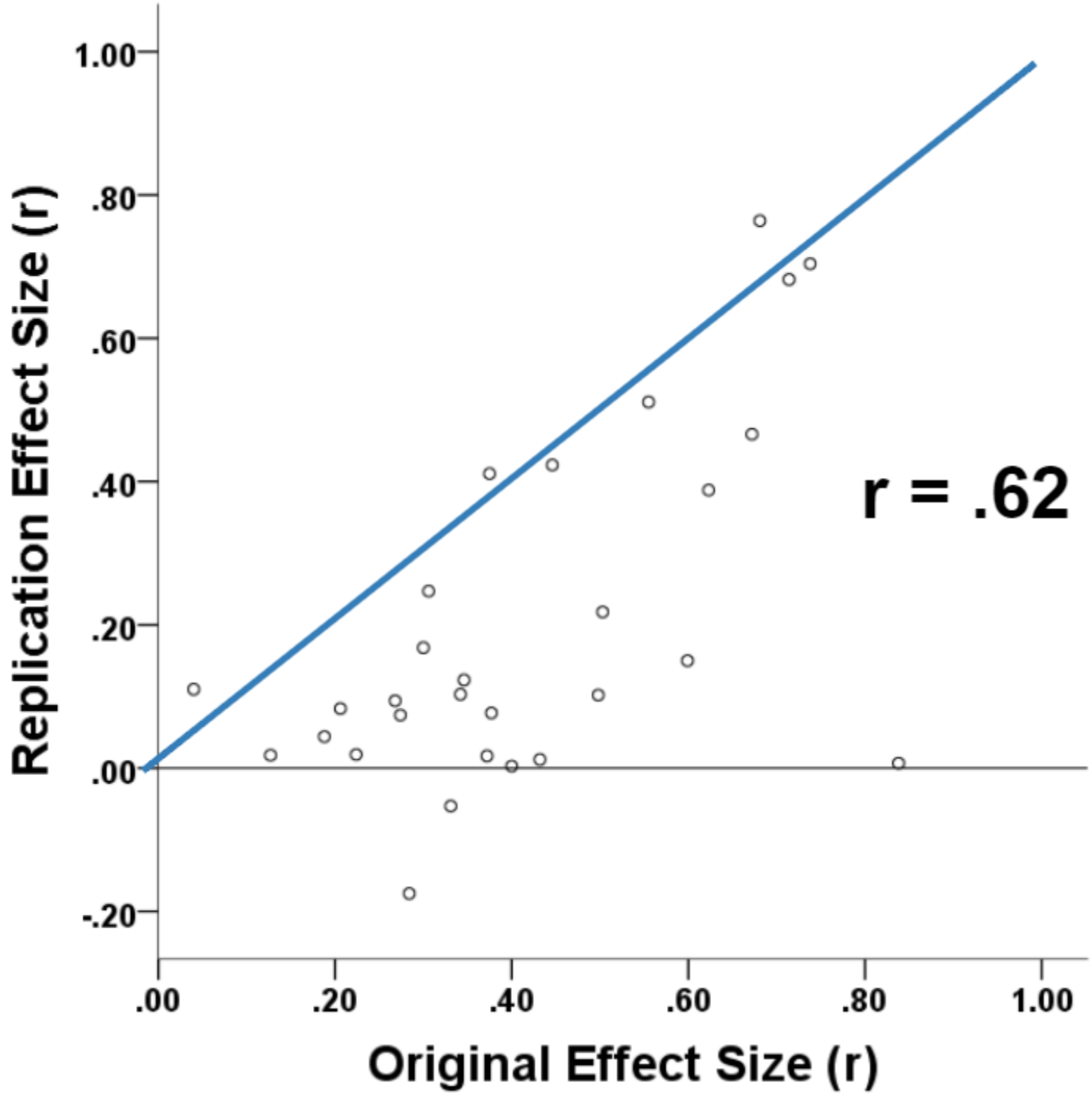
Replication p-value
.00
.01
.02
.03
.04
.05
Original p-value
JEP: LMC (5/7)
JPSP (2/9)
Psych Science (4/13)


Replication Effect Size (r)
1.00
.80
.60
.40
.20
.00
-.20
.00
.20
.40
.60
.80
1.00
Original Effect Size (r)
r = .62

Department of Justice

GLAXOSMITHKLINE SETTLEMENT

FACT SHEET

- GSK has agreed to plead guilty and pay $3 billion as part of this criminal and civil resolution.

- Largest combined federal and state health resolution in the history of the United Stat

GSK has agreed to pay $1 billion in criminal penalties, which is the second-largest penalty for a drug company in a single criminal plea:

- $159,768,000 criminal fine for the misbranding of Paxil.
- $554,433,600 criminal fine for the misbranding of Wellbutrin.
- $43,185,600 criminal forfeiture related to Paxil and Wellbutrin.
- $242,612,800 criminal fine related to Avandia.

Outcome Switching

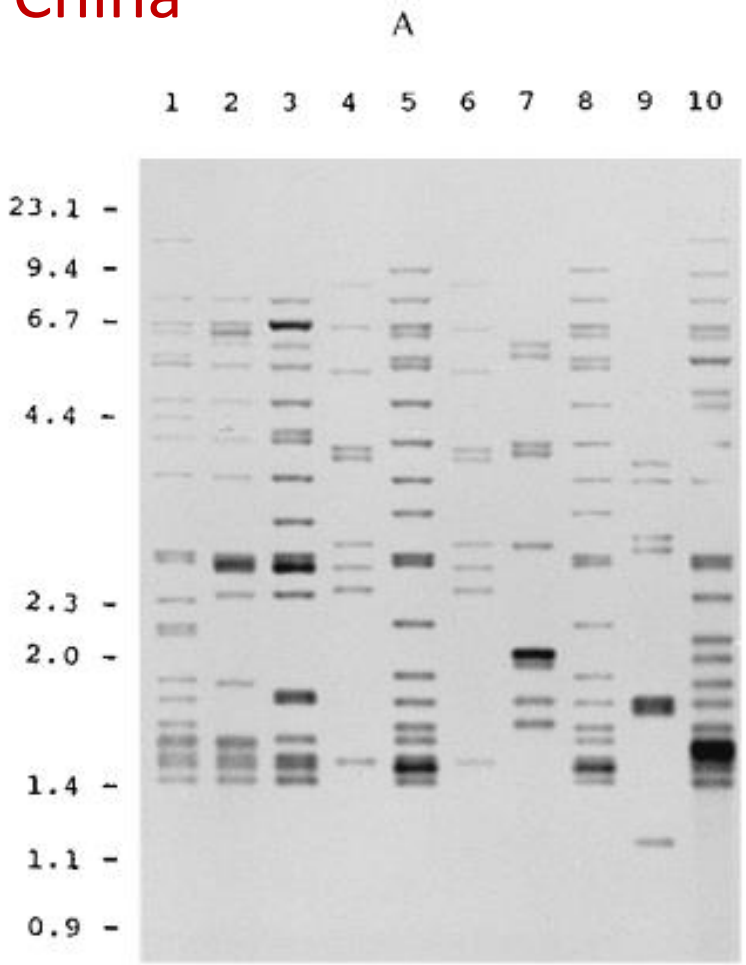
- GSK conducted three placebo-controlled clinical studies to study Paxil's safety and efficacy in treating depression in patients under age 18. In all three studies, GSK failed to demonstrate efficacy on the endpoints identified in the study protocols.

- Nevertheless, GSK hired a contractor to write an article on one of the studies that was published in July 2001 in the Journal of the American Academy of Child and Adolescent Psychiatry (JAACAP). The article stated that Paxil "is generally well tolerated and effective for major depression in adolescents." The article did not explicitly state that the study failed to demonstrate efficacy on either of its two primary endpoints or on any of the secondary endpoints that had been identified in the study protocol.

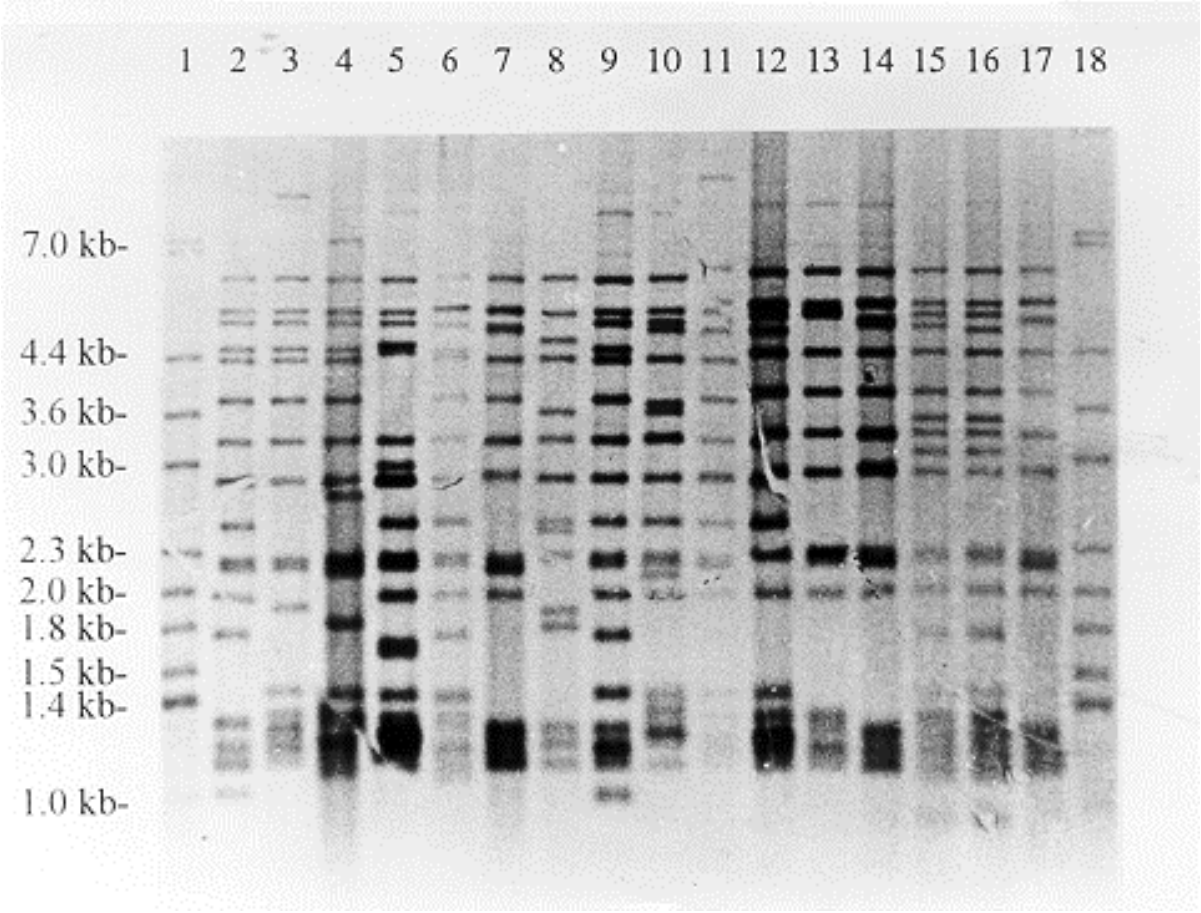
https://prescriptionintelligence.com/the-dark-art-of-outcome-switching/Jan 20, 2016

Reproducibility Problems: IS6110 RFLP of *M. tuberculosis*

1995 China



1997 Thailand



JOURNAL OF CLINICAL MICROBIOLOGY, Aug. 1999, p. 2607–2618 Vol. 37, No. 8
0095-1137/99/$04.00+0

Comparison of Methods Based on Different Molecular Epidemiological Markers for Typing of *Mycobacterium tuberculosis* Complex Strains: Interlaboratory Study of Discriminatory Power and Reproducibility

K. KREMER,[1]* D. VAN SOOLINGEN,[1] R. FROTHINGHAM,[2] W. H. HAAS,[3] P. W. M. HERMANS,[4] C. MARTÍN,[5] P. PALITTAPONGARNPIM,[6] B. B. PLIKAYTIS,[7] L. W. RILEY,[8] M. A. YAKRUS,[9] J. M. MUSSER,[10] AND J. D. A. VAN EMBDEN[11]

Diagnostic Laboratory for Infectious Diseases and Perinatal Screening[1] and Research Laboratory for Infectious Diseases,[11] National Institute of Public Health and the Environment, 3720 BA Bilthoven, and Laboratory of Pediatrics, Erasmus University Rotterdam, 3000 DR Rotterdam,[4] The Netherlands; Molecular Mycobacteriology Laboratory, University of Heidelberg, 69120 Heidelberg, Germany[3]; Durham VA Medical Center, Durham, North Carolina 27705[2]; National Center for Infectious Diseases[7] and Diagnostics and Molecular Epidemiology Section,[9] Centers for Disease Control and Prevention, Atlanta, Georgia 30333; School of Public Health, University of California, Berkeley, Berkeley, California 94720[8]; Institute for the Study of Human Bacterial Pathogenesis, Department of Pathology, Baylor College of Medicine, Houston, Texas 77030[10]; Department of Microbiology, University of Zaragoza, 50009 Zaragoza, Spain[5]; and Department of Microbiology, Mahidol University, Bangkok 10400, Thailand[6]

DNA target	Method used	Reproducibility (%)[a]
IS*6110*	RFLP (*Pvu*II)	100
IS*6110*	Mixed-linker PCR	100
IS*6110*	IS*6110* inverse PCR	6
IS*6110*/MPTR	IS*6110* ampliprinting	39
IS*6110*/PGRS	DRE-PCR	58
PGRS	RFLP (*Alu*I)	100
DR locus	Spoligotyping	94
DR locus	RFLP (*Alu*I)	100
ETRs A–E	VNTR typing	97
$(GTG)_5$	RFLP (*Hinf*I)	94
Total genome	APPCR	71
IS*1081*	RFLP (*Pvu*II)	100

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ScienceDirect
journal homepage: www.elsevier.com/locate/IJMYCO

JOURNAL OF CLINICAL MICROBIOLOGY, Jan. 1997, p. 273–277 Vol. 35, No. 1
0095-1137/97/$04.00+0

Use of a PCR Method Based on IS*6110* Polymorphism for Typing *Mycobacterium tuberculosis* Strains from BACTEC Cultures

ISABEL OTAL,* SOFÍA SAMPER, M. PILAR ASENSIO, M. ASUNCIÓN VITORIA, M. CARMEN RUBIO, RAFAEL GÓMEZ-LUS, AND CARLOS MARTÍN

Departamento de Microbiología, Medicina Preventiva, y Salud Pública, Universidad de Zaragoza, 50009 Zaragoza, Spain

Molecular typing and differentiation of *Mycobacterium tuberculosis* clinical isolates using Double Repetitive Element PCR and Duplex PCR

CrossMark

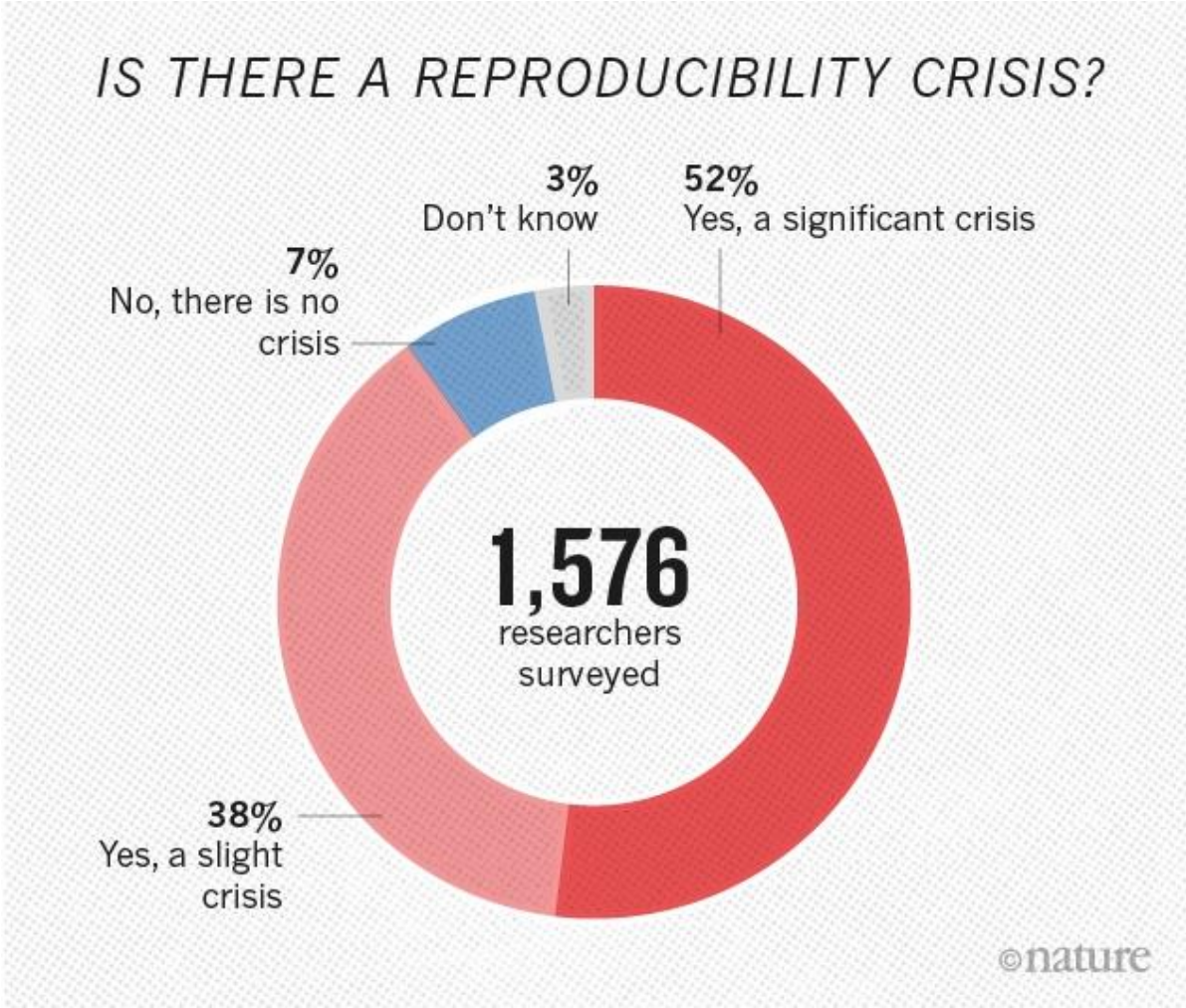
Last citation in 2015

Kathirvel Maruthai [a], *Thirumurugan Ravibalan* [a,b], *Kommoju Vallayyachari* [a], *Surendar Kesavan* [a], *Antony V. Samrot* [b], *Muthuraj Muthaiah* [a,*]

[a] *Department of Microbiology, Intermediate Reference Laboratory, Government Hospital for Chest Diseases, Gorimedu, Puducherry 605006, India*

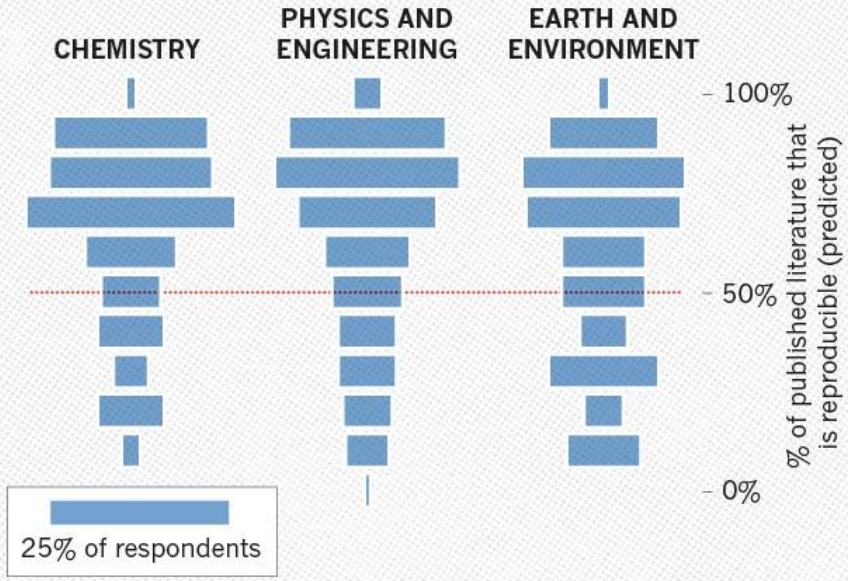
[b] *Department of Biotechnology, Sathyabama University, Chennai 600119, Tamilnadu, India*

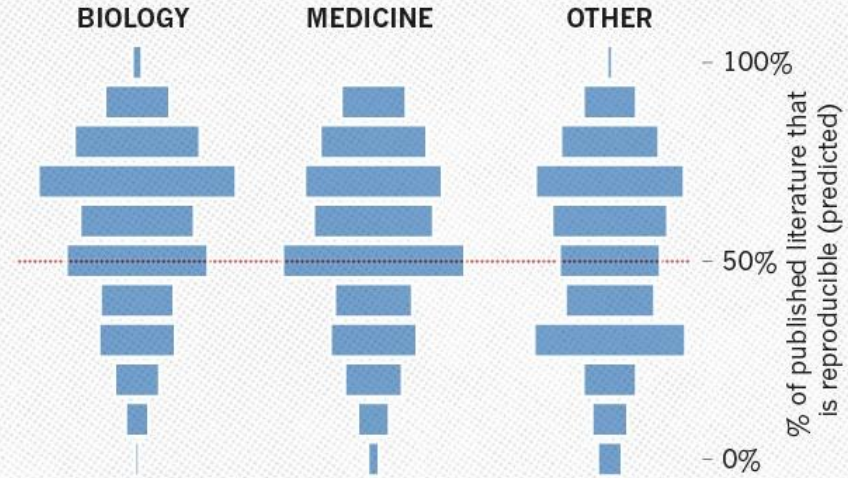
M. Baker, Nature 2016; 533:454-6. 26 May 2016



HOW MUCH PUBLISHED WORK IN YOUR FIELD IS REPRODUCIBLE?

Physicists and chemists were most confident in the literature.

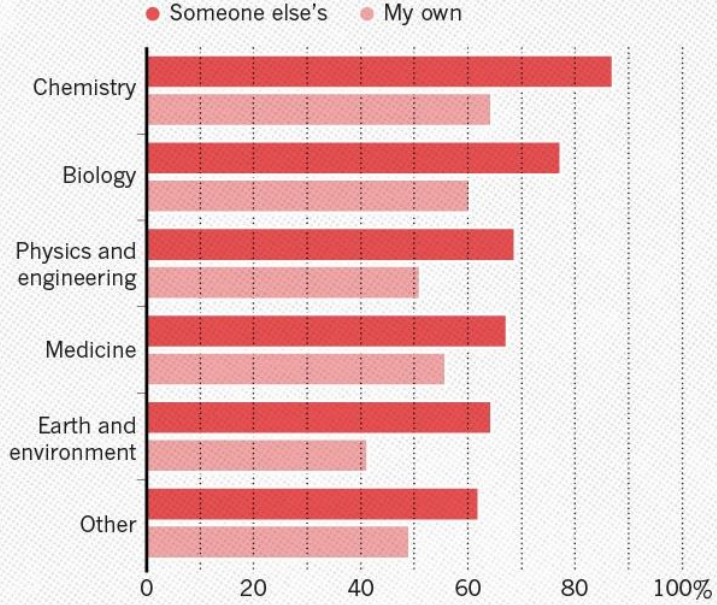




Number of respondents from each discipline:
Biology **703**, Chemistry **106**, Earth and environmental **95**, Medicine **203**, Physics and engineering **236**, Other **233**

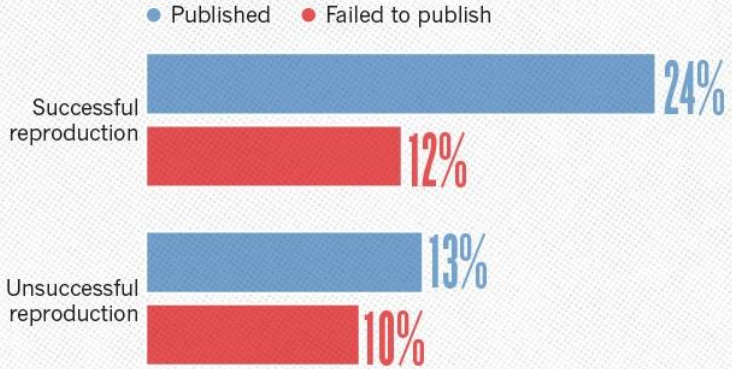
HAVE YOU FAILED TO REPRODUCE AN EXPERIMENT?

Most scientists have experienced failure to reproduce results.



HAVE YOU EVER TRIED TO PUBLISH A REPRODUCTION ATTEMPT?

Although only a small proportion of respondents tried to publish replication attempts, many had their papers accepted.



Number of respondents from each discipline:
Biology **703**, Chemistry **106**, Earth and environmental **95**, Medicine **203**, Physics and engineering **236**, Other **233**

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REPRODUCIBILITY OF RESEARCH FINDINGS

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

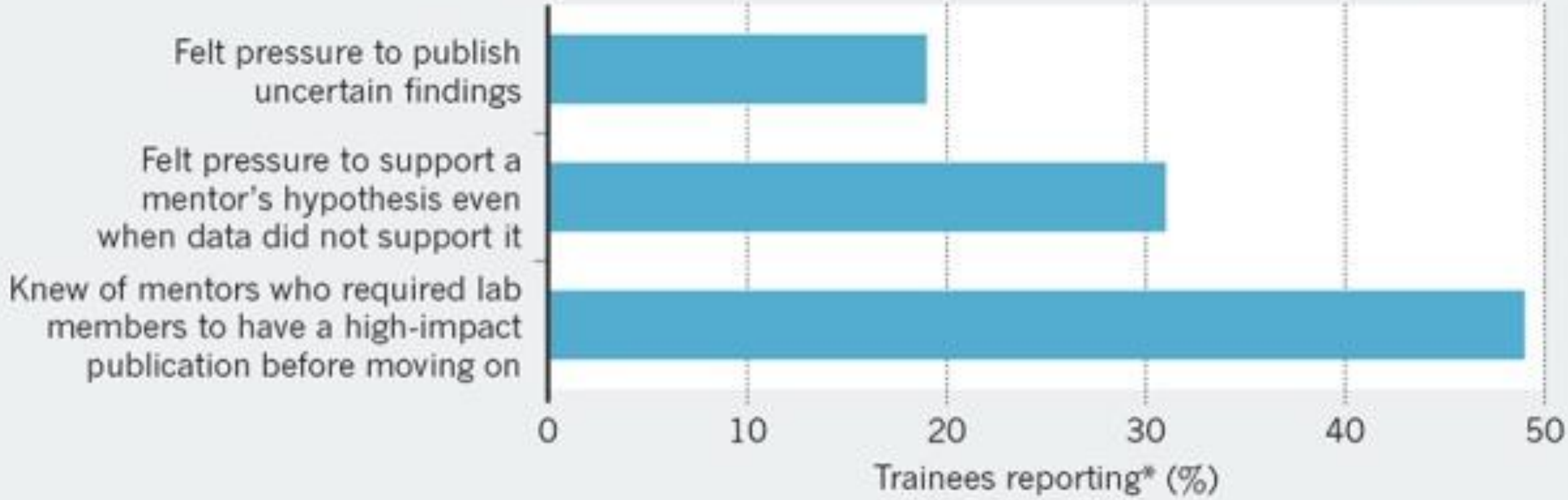
Journal impact factor	Number of articles	Mean number of citations of non-reproduced articles*	Mean number of citations of reproduced articles
>20	21	248 (range 3–800)	231 (range 82–519)
5–19	32	169 (range 6–1,909)	13 (range 3–24)

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.

many variables that are hard to control. Non-replication does not necessarily mean 'not true'," Sheng adds. ■

PRESSURED FINDINGS

A survey of US biomedical trainees suggests that the push to publish spurs unreliable results.



*Online survey of ~140 trainees at the MD Anderson Cancer Center in Houston, Texas.

What are the cause of the problems? Who are responsible?

- Wrong materials: wrong cell lines, etc.
- Poor maintenance of instruments
- Poor data recording
- Wrong statistical analysis
- Selective reporting, omitting some results not fitting theory.
- Research Misconduct
- Pressure to publish
- Inadequate mentoring
- Conflict of interest

What are the cause of the problems? Who are responsible?

Commonly Cited

- Selective Reporting. Omitting some results not fitting theory
- Pressure to publish
- Inadequate replication in the lab
- Wrong statistical analysis
- Inadequate mentoring/poor oversight

Other possible causes

- Wrong materials: wrong cell lines, etc.
- Poor maintenance of instruments
- Poor study designs
- Poor data recording and maintenance.
- Selective reporting
- Conflict of interest
- Research Misconduct

Classification of misconduct (1)

Misconduct that distorts scientific knowledge

- Fabrication – reporting of non-existent data
- Falsification – selective reporting of data

Misconduct that misleads the scientific community

- Authorship: Plagiarism, 'Guest' authors, 'Ghost' authors
- Duplicate publication
- Abuse of the peer-review process

"FFP" = Fabrication, Falsification, Plagiarism

Teaching Research Ethics to Bioscience Students, May 2011

"You don't want to do it like that": some (in)famous examples of research misconduct

http://tinyurl.com/ydwtdilt2011

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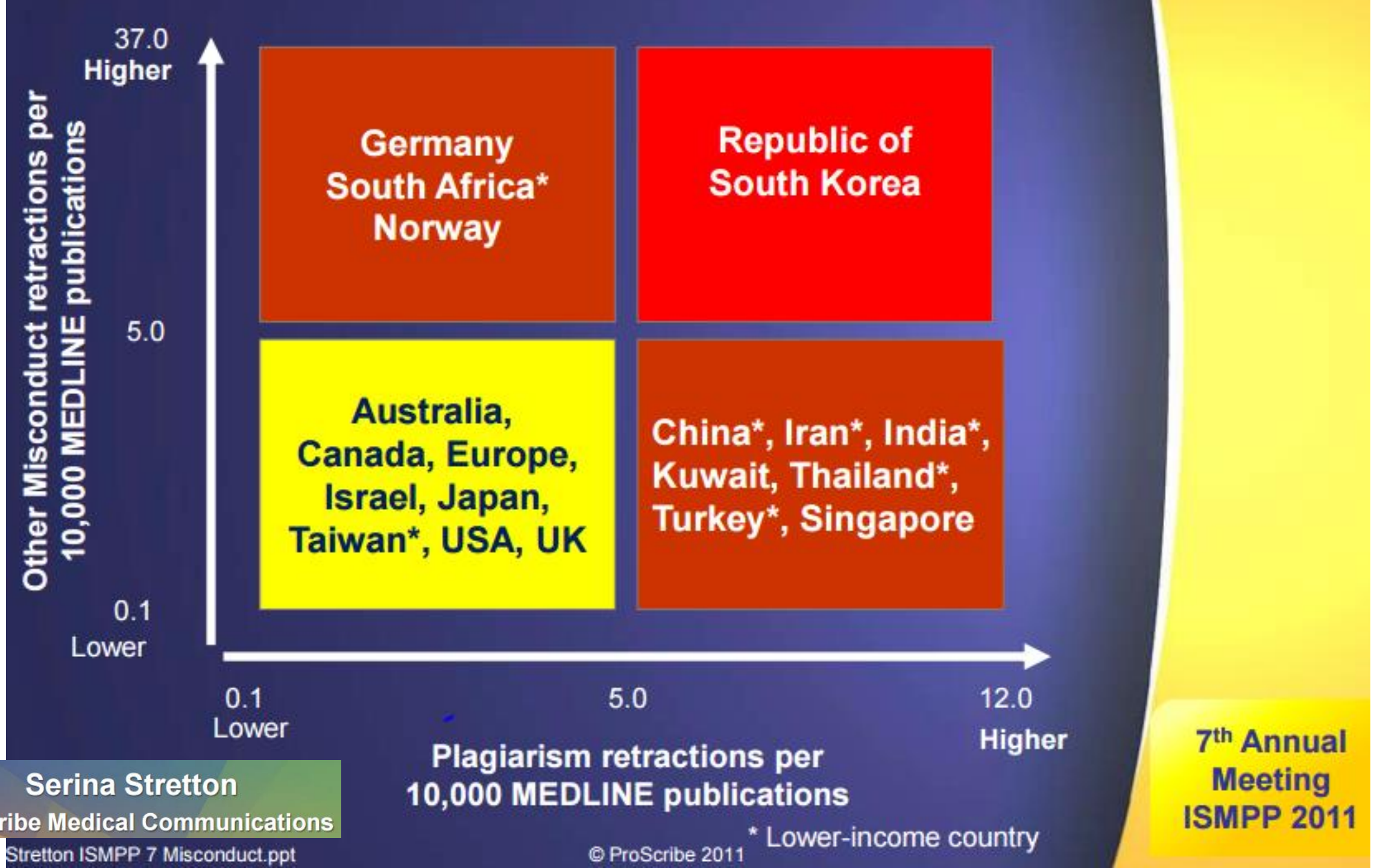
University of Leicester

Plagiarism (my personal view)

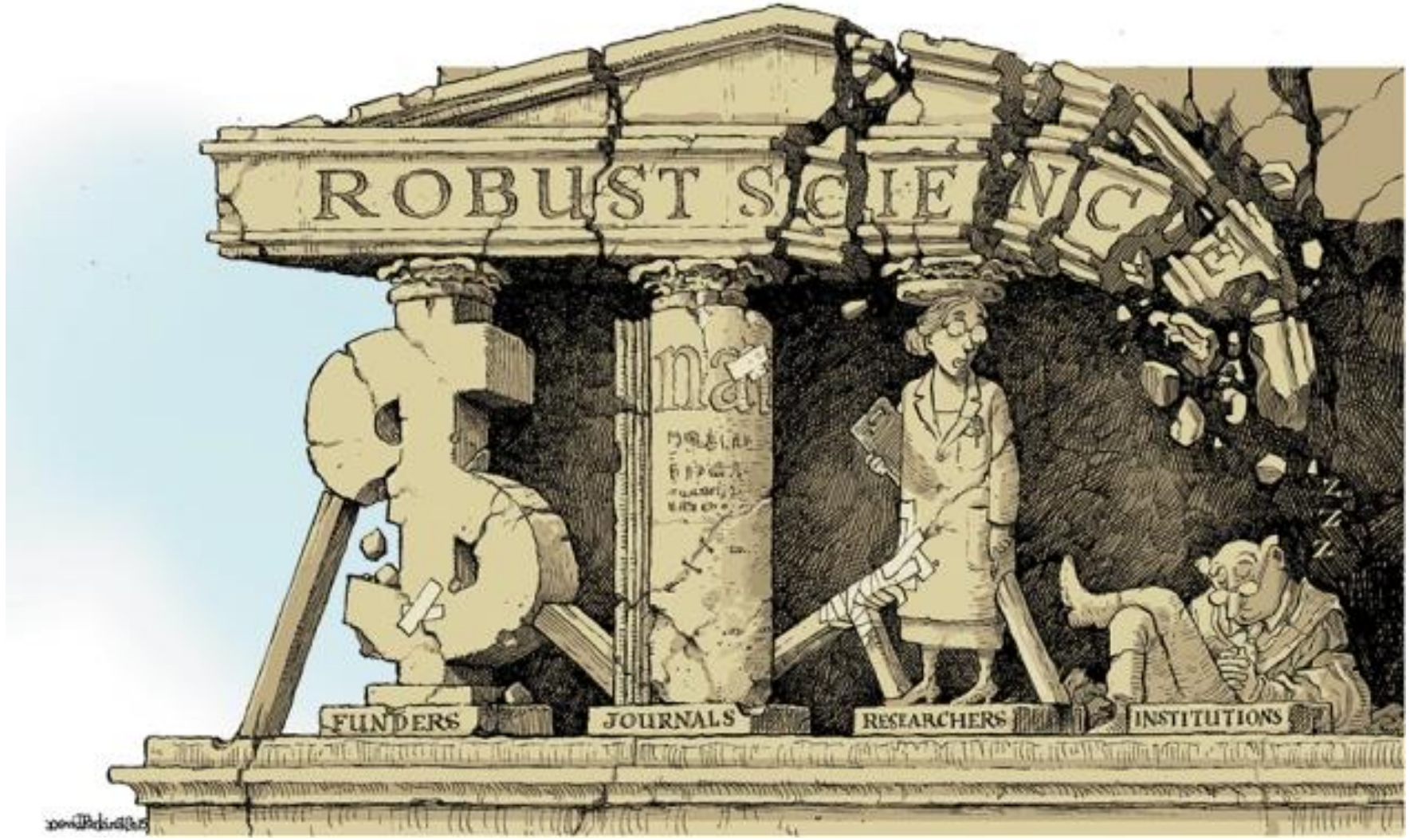
JohnW · 10 months ago

I once had a Thai Ma student who chose to give a seminar presentation on plagiarism (the choice of topic was almost completely free - just something connected to education). He presented a set of powerpoint slides taken from the internet. Nothing added, nothing removed. It was beyond irony...

- The current concepts of intellectual property rights were mostly absent in traditional Thai culture.
- The only sure way to protect one's own idea was to keep it secretive.
- In traditional Buddhism teaching, copying the original wording is actually encouraged.
- Several practices in Thai scientific community still reflect the ignorance of plagiarism issues, e.g.
  - In scientific presentation, the authors of the original works are rarely mentioned.
  - People do not bother to claim ownership of a new idea eventhough it happens to be expressed by a colleague, even in scientific meeting.



Serina Stretton
ProScribe Medical Communications


ROBUST SCIENCE
FUNDERS
JOURNALS
RESEARCHERS
INSTITUTIONS

The Corrective Measures

- More robust experimental designs.
- Better statistical analysis
- Better mentoring
- Redoing the work/asking someone else to repeat the works.
- Better documentation
- Standardization of experimental methods. Lab protocols can gradually diverge.
- Pre-registration- rarely practiced.
- System to handle research misconduct (Allegation, Assessment, Inquiry and Investigation), including the protection of whistle-blower.

Many landmark findings in preclinical oncology research are not reproducible, in part because of inadequate cell lines and animal models.

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.

Efforts over the past decade to characterize the genetic alterations in human cancers have led to a better understanding of molecular drivers of this complex set of diseases. Although we in the cancer field hoped that this would lead to more effective drugs, historically, our ability to translate cancer research to clinical success has been remarkably low[1]. Sadly, clinical trials in oncology have the highest failure rate compared with other therapeutic areas. Given the high unmet need in oncology, it is understandable that barriers to clinical development may be lower than for other disease areas, and a larger number of drugs with suboptimal preclinical validation will enter oncology trials. However, this low success rate is not sustainable or acceptable, and investigators must reassess their approach to translating discovery research into greater clinical success and impact.

Many factors are responsible for the high failure rate, notwithstanding the inherently difficult nature of this disease. Certainly, the limitations of preclinical tools such as inadequate cancer-cell-line and mouse models[2] make it difficult for even ▶

We recommend the following steps to change the culture of oncology research and improve the relevance of translational studies:

- More opportunities to present negative data. Preclinical investigators should be required to report all findings, regardless of the outcome. To facilitate this, funding agencies, reviewers and journal editors must agree that negative data can be just as informative as positive data.
- Journal editors must play an active part in initiating a cultural change. There must be mechanisms to report negative data that are accessible through PubMed or other search engines. There should be links to journal articles in which investigators have reported alternative findings to those in an initial (sometimes considered landmark) publication. One suggestion is to include 'tags' that report whether the key findings of a seminal paper were confirmed.
- There should be transparent opportunities for trainees, technicians and colleagues to discuss and report troubling or unethical behaviours without fearing adverse consequences.
- Greater dialogue should be encouraged between physicians, scientists, patient advocates and patients. Scientists benefit from learning about clinical reality. Physicians need better knowledge of the challenges and limitations of preclinical studies. Both groups benefit from improved understanding of patients' concerns.
- Institutions and committees should give more credit for teaching and mentoring: relying solely on publications in top-tier journals as the benchmark for promotion or grant funding can be misleading, and does not recognize the valuable contributions of great mentors, educators and administrators.
- Funding organizations must recognize and embrace the need for new cancer-research tools and assist in their development, and in providing greater community access to those tools. Examples include support for establishing large cancer cell-line collections with easy investigator access (a simple, universal material-transfer agreement); capabilities for genetic characterization of newly derived tumour cell lines and xenografts; identification of patient selection biomarkers; and generation of more robust, predictive tumour models.

CHALLENGES IN IRREPRODUCIBLE RESEARCH

Science moves forward by corroboration – when researchers verify others' results. Sc
advances faster when people waste less time pursuing false leads. No research pape
considered to be the final word, but there are too many that do not stand up to further

There is growing alarm about results that cannot be reproduced. Explanations include
levels of scrutiny, complexity of experiments and statistics, and pressures on researc
Journals, scientists, institutions and funders all have a part in tackling reproducibility.
taken substantive steps to improve the transparency and robustness in what we publi
promote awareness within the scientific community. We hope that the articles contain
collection will help.

UniSA Framework for the Responsible Conduct of Research

Section 1 General principles of responsible research	Section 2 Management of research data and primary materials	Section 3 Supervision of research trainees	Section 4 Publication and dissemination of findings	Section 5 Authorship	Section 6 Peer review	Section 7 Conflicts of interest	Section 8 Collaborative research across institutions
Policies							
RES-1.1 Responsible practice in research	**RES-17** Ownership and retention of data	**Res-10** Higher degrees by research	**C-5.0** (revisions in progress) Public statements by members of university staff	**RES-12.1** Authorship	**RES-12.1** Authorship		**C-20.2** University activities policy
Associated Codes/Regulations/Guidelines							
		Academic regulations for higher degrees by research Code of good practice: research degrees management and supervision				Code of Ethical Conduct Conflicts of Interest in Research	University activities - research and consultancy guidelines

ORI

Introduction to the Responsible Conduct of Research

Nicholas H. Steneck
illustrations by David Zinn

Revised Edition
August 2007

nature
cell biology

Corresponding Author:

Manuscript Number:

Manuscript Type:

Main Figures:

Main Tables:

Supplementary Figures:

Supplementary Tables:

Supplementary Videos:

Reporting Checklist for Nature Cell Biology

This checklist is used to ensure good reporting standards and to improve the reproducibility of published results. For more information, please read Reporting Life Sciences Research.

Please note that in the event of publication, it is mandatory that authors include all relevant methodological and statistical information in the manuscript.

☐ Check here to confirm that the following information is available in all relevant figure legends (or Methods section if too long):

o are tests one-sided or two-sided?
o are there adjustments for multiple comparisons?
o statistical test results, e.g., P values;
o definition of `center values' as median or mean;
o definition of error bars as s.d. or s.e.m. or c.i.

Note: When technical replicates are reported, error and significance measures reflect the experimental variability and not the variability of the biological process, and it is misleading not to state this clearly. We discourage statistics derived from technical replicates.

For experiments reported in the text but not in the figures, please specify the page number instead of the figure number in the table below.

	Figure Panel or page	**Test**	**S.D. or S.E.M.**	**n value** (This number represents the sample size used to derive statistics. Please explain how samples were defined - cells, dishes, extracts)	**# of times experiment was replicated in laboratory**	***P* value**	**Optional: if n < 5, values provided?** Please provide in a separate spreadsheet titled "Statistics source data"
EXAMPLE	*3c*	*One-way ANOVA*	*s.d.*	*n = 200 cells assessed from 3 fields*	*3 independent experiments*	*yes*	*N/A*

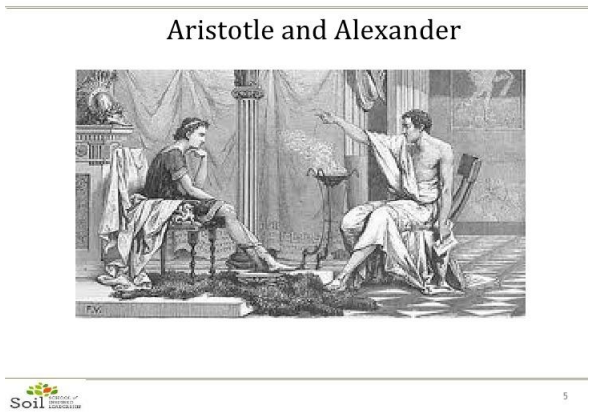
Points to be Discussed: How to prevent the possible crisis?

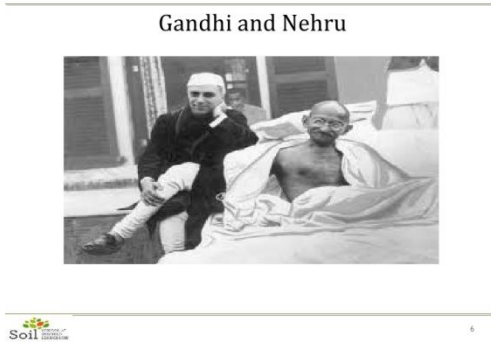
- Is reproducibility a serious problem among Thai researchers?
- Is research misconduct (FFP) a problem?
- What should be a measure?
  - Advocacy
  - Education/Mentoring
  - Thai Journal
  - Financial
  - Regulation/legal
  - Etc.
- Others

Mentoring

- Transfer of experience, viewpoints and expertise from one person to another
- Generally touches personal and professional life
- Helps the persons to solve their problems or attain their goals
- Can be one-time contact, or LT relationship, formal or informal

Gail P. Taylor
MBRS-RISE Program





This person likely was a mentor to you!

- Who helped you to have an Aha! Experience that give insight into yourself or a circumstance…?
- Who said something or gave you a quote that continues to influence your thinking or behavior?
- Who helped you to uncover a part of yourself that had lain dormant and unrecognized?

Mentoring

A fundamental difference between a mentor and an adviser is that mentoring is more than advising; mentoring is a personal as well as a professional relationship. An adviser might or might not be a mentor, depending on the quality of the relationship. . . Everyone benefits from having multiple mentors of diverse talents, ages, and personalities."

- **National Academy of Sciences:** ***Adviser, Teacher, Role Model, Friend: On Being a Mentor to Students in Science and Engineering*** **p. 15**
  http://www.nap.edu/readingroom/books/mentor

“Mentoring” in Academic Education

- Advisers vs Mentors
- An Adviser:
  - Helps the student to acquire and develop the skills needed by independent researchers in their scientific field.
  - Guides the student's research project by:
    - Communicating effectively with the student
    - Reviewing and providing regular feedback on the student's progress
- Mentor is often interchanged with Adviser
  - An Adviser is not always a mentor
  - May not be personally involved.
  - A “mentor” adviser is not necessarily the main mentor…

Mentors Assist by (both professionally and personally)

- Listening- Sounding board for problems
- Informing-
  - Providing wise counsel
  - Suggest possible solutions or information sources.
  - Show how organization works
  - Explain paths to success
- Encouraging- Help them to develop self-confidence and winning behavior
- Inspiring-
  - Direct them towards excellence.
  - Teach by example.
- Exploring- what additional options, interpretations or solutions are available?

- “Psychoanalyzing” –
  - Identify strengths.
  - Identify problem mindsets/behavior that impede success.
- Confronting- non-judgmentally discuss negative attitudes or behaviors
- Refocusing- help mentee to see different future or outcome
- Delegating- Provide mentee with increasing authority and permission to empower self-confidence
- Supporting- Stand by mentee in critical situations

Types of

Mentoring Relationships

- **Structured/Short term**
  - New employees, new grad students
- **Structured/Long term**
  - Groomed to take over position
- **Informal/Short term**
  - Brief contact, strong intervention
- **Informal/Long term**
  - "friendship" mentoring, available to listen and advise

Mentors

- **'The Guide'** Hands on guidance, explaining how and why; creating opportunities to learn
- **'The Challenger'** 'Making Waves'; challenging, stimulating, questioning, probing
- **'The Role Model'** Unseen, largely unfelt. The Mentee unconsciously adopts aspects of the mentor's thinking behaviours and/or style

Mentoring Principles

- **The Mentee drives the Mentoring agenda**
- **Engagement is on a voluntary basis for both the Mentor and the Mentee**
- **The Mentoring relationship is confidential**
- **Mentoring is non-directive in its approach**
- **It is a relationship built upon trust and mutual respect**
- **The Mentor empowers the Mentee to take responsibility for their own learning and career development**
- **The relationship places no obligation on either party beyond its developmental intent**
- **It is distinct and separate from the Performance Management Development System (PMDS) in UCD**

Special Relationships

- **Cross-gender**
  - **Can be of great benefit**
  - **Very common in science**
  - **Problems include:**
    - **Gossip, envy, suspicion, speculation, sexual stereotypes, charges of sexual harassment**
- **Cross-Cultural**
  - **Can arise from:**
    - **Economic class, race, religious background, regional allegiance, family tradition.**
- **Mentoring by supervisor or manager**
  - **Can be very effective**
    - **Can see properly modeled behavior, including authority**
  - **Possible problems associated with authority/power imbalance**
  - **Must be done “carefully, artfully, fairly**