Scientific fraud/sloppiness in data handling/data reproducibility

Quality control in science

The university perspective

Measures to ensure good scientific practice

Klaus-Michael Debatin
University Children‘s Hospital Ulm
Member DFG Senate
"By ensuring that efforts are infused with rigour from start to finish, the research community might protect itself from the sophistry of politicians, disentangle the conflicted motivations of capital and science, and secure real value for money for charitable givers and taxpayers through increased value and reduced waste."

Institutions must do their part for reproducibility

Begley, Buchan, Dirnagl Nature 2015

Research Waste/EQUATOR Conference

REWARD

http://researchwaste.net/

Increasing value and reducing waste in biomedical research conference

28th – 30th September 2015, Edinburgh

NIH plans to enhance reproducibility

Collins and Tabak


How to Make More Published Research True

John P. A. Ioannidis1,2,3,4*

PLOS Medicine 2014

High drug attrition rates—where are we going wrong?

Hutchinson, Kirk; Nat Rev Clin Onc 2011
Scientific fraud/sloppiness in data handling/data reproducibility

Quality control in science

The university perspective

Measures to ensure good scientific practice

• Cases
• Problem(s)
• Measures to ensure quality control in science
• Unexpected finding, reproducibility of experiments (never done ?) ?
• Retracted 1991 by all authors except I-K
• Case running 1986 – 1996
• Sloppyness in data handling vs. faking data
Highly exciting data on first steps of mammalian development
Retracted in 1992
Data entirely fabricated
Dr. Staudt took immediate action to directly uncover the fraud
ORI at NIH already in place
Retraction: Stimulus-triggered fate conversion of somatic cells into pluripotency

Haruko Obokata, Teruhiko Wakayama, Yoshiki Sasai, Koji Kojima, Martin P. Vacanti, Hitoshi Niwa, Masayuki Yamato & Charles A. Vacanti

Nature 511, 112 (03 July 2014) | doi:10.1038/nature13598
Published online 02 July 2014 | Corrected online 23 July 2014
Article (January, 2014)
Correction (July, 2014)

Retraction: Bidirectional developmental potential in reprogrammed cells with acquired pluripotency

Haruko Obokata, Yoshiki Sasai, Hitoshi Niwa, Mitsutaka Kadota, Munazah Andrabi, Nozomu Takata, Mikiko Tokoro, Yukari Terashita, Shigenobu Yonemura, Charles A. Vacanti & Teruhiko Wakayama

Nature 511, 112 (03 July 2014) | doi:10.1038/nature13599
Published online 02 July 2014 | Corrected online 23 July 2014

- Highly exciting data in a top fashion field (stem cell reprogramming)
- "Too good to be true": adding acid or stress reprograms differentiated cells
- Data mostly fabricated or experiments shown not done
- Retraction within 6 months
The major German scandal in biomedicine leading to the so far largest investigation of scientific fraud in Germany with subsequent action by the DFG and universities.

Of 347 papers 1985-1996 published by the Hermann group, only 132 were cleared of any suspicion of fraud. 94 papers definitely contained manipulated data. Most of the work was on cytokines, at that time a fashionable field with multiple photo shop data, copy and paste, reuse of data etc. All “in line” with data or concepts already published by others.

A highly dedicated “follower of fashion”. All fakes escaped the reviewers attention. Scientific fraud was uncovered by whistleblowing.


The Editorial Board of The Journal of Experimental Medicine regrets to inform its readership that due to scientific misconduct, the results of the above named paper are not valid. A letter dated April 30, 1997 was received from Guido Adler, M.D., the Dean of the School of Medicine at the University of Ulm. In his letter, Dr. Adler states that “fraud was uncovered in the laboratory of Friedhelm Herrmann and Marion Brach. In a series of papers major results were fabricated [including]: . . .

Kiehntopf M, Herrmann F, Brach M. J. Exp. Med. 181, 793, 1995.”
Common aspects in (some) of these cases?

- Productivity and/or results too good to be true
- Recognition that missing links would represent a breakthrough
- Knowing the answer to their research question
- Knowing that individual experiments may not be exactly reproducible
- Outstanding intellect, well informed in the field
- High pressure on career and/or reputation
- Hubris

- Institution/mentor/supervisor/environment that favors “stars“ (also to increase their own reputation)
- Journals like superpositive “exciting“ data
Scientific fraud and normal science
Ruud Abma
Faculty of Social and Behavioral Sciences / Descartes Centre
Utrecht University

Science in transition - Workshop Quality and Corruption

Until recently, the incidence of scientific fraud was unknown. Hard evidence is still lacking, but we do know more: estimates range from 2% (Fanelli, 2009) to 10% (John, 2011) of people admitting to having falsified data themselves and about 14% having observed in it colleagues.

Fraud is usually not detected by reviewers or referees. Almost always it is co-workers who blow the whistle (Stroebe et al, 2012). Why? Because they are in close contact with the perpetrator and his or her daily routine and also have an overview of the total of his research activities.

Between brackets the number of fraudulent publications:
1. Yoshitaka Fuji, anaesthesiologist, Japan (172)
2. Dipak K. Das, heart surgeon, USA (145)
4. Friedhelm Hermann en Marion Brach, physicians, Duitsland, 1994-1997 (94)
5. Diederik Stapel, social psychologist, Nederland, 1997-2011 (69)
7. Scott Reuben, physician, VS, 1996-2009 (21)
8. Alirio Mendelez, immunologist, Singapore (21)
11. Roger Poisson, physician, Canada, 1977-1990 (14)
12. Luk van Parijs, biologist, België/VS, 2000-2004 (11)
14. Marc D. Hauser, primatologist, VS, 1995-2010 (9)
The other problem: reproducibility

Only 20-25% of published data in line with in-house findings

Scientific findings (oncology) were (entirely) confirmed in only 11% of the cases

Raise standards for preclinical research
C. Glenn Begley & Lee M. Ellis
Nature 483, 531–533 (29 March 2012)

Table 1: Reproducibility of research findings

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

<table>
<thead>
<tr>
<th>Journal impact factor</th>
<th>Number of articles</th>
<th>Mean number of citations of non-reproduced articles</th>
<th>Mean number of citations of reproduced articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20</td>
<td>21</td>
<td>248 (range 3–800)</td>
<td>231 (range 82–519)</td>
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<tr>
<td>5–19</td>
<td>32</td>
<td>169 (range 6–1,909)</td>
<td>13 (range 3–24)</td>
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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.
BLAME IT ON THE ANTIBODIES

Antibodies are the workhorses of biological experiments, but they are littering the field with false findings. A few evangelists are pushing for change.

BY MONYA BAKER

NATURE, 21 May 2015
Reproducibility of research and preclinical validation: problems and solutions

Lajos Pusztai, Christos Hatzis and Fabrice Andre


<table>
<thead>
<tr>
<th>Box 1</th>
<th>Contributing factors to poor reproducibility and counter measures</th>
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<tbody>
<tr>
<td><strong>Contributors to poor reproducibility</strong></td>
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<tr>
<td>- Unrecognized experimental variables</td>
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<td>- Poor documentation of methodology</td>
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<td>- Selective reporting</td>
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<td>- Misinterpretation of noise as an indication of a positive finding</td>
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<td>- Inappropriate statistics or deceptive analysis</td>
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<td>- Data fabrication</td>
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<td>- Academic and financial incentives to publish premature results</td>
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<tr>
<td><strong>Possible counter measures</strong></td>
<td></td>
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<tr>
<td>- Standard operating procedures and relevant control experiments</td>
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<tr>
<td>- Detailed protocols and meticulous laboratory log books, publication of software codes and raw data</td>
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<tr>
<td>- Accounting for all experiments and deposition of all raw data</td>
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<tr>
<td>- Publication of experimental protocol and raw data, appropriate statistics, awareness of biases during data analysis</td>
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<td>- Prospective statistical planning and analysis blinded to outcome (if possible)</td>
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<td>- Laboratory supervision and culture of respect for negative results</td>
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<tr>
<td>- Venues for publication of negative results, more diverse research funding, changes in academic promotion practices</td>
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</table>

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<tr>
<th>Box 2</th>
<th>Three-pronged funding schema</th>
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<tbody>
<tr>
<td><strong>Innovative Research Grant (12–36 months)</strong></td>
<td>Discovery oriented, research question driven, high risk for failure</td>
</tr>
<tr>
<td><strong>Replication Grant (12–24 months)</strong></td>
<td>Reproduce important published results with minor or no changes in experimental design</td>
</tr>
<tr>
<td><strong>Product Development Grant (12–36 months)</strong></td>
<td>Turn reproducible results into practically useful product</td>
</tr>
</tbody>
</table>
Randy Schekman, Nobel Prize 2013:
„...These luxury journals are supposed to be the epitome of quality...
While they publish many outstanding papers, they do not publish only outstanding papers. Neither are they the only publishers of outstanding papers“...

Peter Higgs, Nobel Prize 2013:
„...... Today, I wouldn’t get an academic job: It’s as simple as that. I don’t think I would be regarded as productive enough“....

The vicious cycle of biomedical research

| Scientists need to publish new, positive and spectacular results for professional advancement |
| Publish or perish ! |
| Non-reproducible research findings |
| Failure to translate bench findings into effective therapies |
| Institutions and funders support researchers who publish new, positive and spectacular results in high IF journals |
| Journals need to publish new, positive and spectacular results to promote their IF |
| Positive findings are a career must ! |

Money (and reputation) for individual scientists and institutions goes with performance. Performance is measured by total amount of grant money acquired by scientist/institution and total IF
The issues

• Low rate of reproducible preclinical data e.g. on drug targets (20 – 40%) and gene expression profiles (10-40%)

• 60-80% failure rate in phase II – III clinical trials.
Costs for taking a drug to the clinic = over 800 Mio USD due to a 3-4 in 5 failure rate (costs for one agent around 160 Mio USD)

• 2% of scientists admitted to have fabricated, falsified or modified data at least once
33% admitted questionable research practices. Rates observed in colleagues are 14% and 72% respectively (Fanelli, PLOS one 2009)

• “Benevolent mistakes“ vs outright fraud:
  poor experimental design  fabrication
  sloppy data management  falsification
  bias in interpretation of data  plagiarism

• According to Medline 0.03% of 17.8 Mio published papers 1980-2014 were retracted (Gunn, Nature 2014)

The culture

• Progress in science means continual production of positive results, only novelty counts for journals and scientists prefer new truth and discovery

• Lack of incentives to report negative results (journals are not interested)

• Lack of incentives to replicate experiments or recognize inconsistencies (journals and grant agencies are not interested)

• Impact factor = Impact ?
Are cumulative IF + acquired grant money the right figures to judge/measure performance ?
Six Questions

• Were experiments performed blinded?
• Were basic experiments repeated?
• Were all the results presented?
• Were there positive and negative controls?
• Were reagents validated?
• Were statistical tests appropriate?
**A Checklist for Journals**

1. Rigorous statistical analysis
2. Transparency in reporting
   - Standards
   - Replicates
   - Statistics
   - Randomization
   - Blinding
   - Sample-size estimation
   - Inclusion and exclusion criteria
3. Data and material sharing
4. Consideration of refutation
5. Establishing best practice guidelines for
   - Image based data
   - Antibodies
   - Cell lines
   - Animals

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**Principles and Guidelines for Reporting Preclinical Research**

The signatories represent journals that publish preclinical biological research — an area of research that encompasses both exploratory studies and hypothesis-testing studies, with many different designs. The reproducibility of these studies is expected to vary. The journals agree to adhere to the following principles with the aim of facilitating the interpretation and repetition of experiments as they have been conducted in the published study. These measures and principles do not obviate the need for replication and reproduction in subsequent investigations to establish the robustness of published results across multiple biological systems.

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*Nov 2014; update Feb 2015*
Measures by the university in general


- **Ombudspersons of the university**
  First port of call for members and staff members of the university wishing to clarify issues concerning good scientific practice or in the event of a suspected case of scientific misconduct.

- **Committee on Responsibility in the Conduct of Science**
  Monitors the guidelines and investigates allegations of scientific misconduct when requested by the ombudspersons

- **Additional consequences**
  The presidency and the faculties can – after proven scientific misconduct – decide about additional measures, e.g. deprivation of degrees, dismissal of staff, informing injured parties including journals and funding agencies (e.g. DFG) that decide about additional consequence
During PhD Program (International Graduate School in Molecular Medicine)

- Good scientific practice, scientific misconduct and fraud are a special focus during contract signing (an *individual conversation* between the managing director and every student).
- Good Scientific Practice is a *compulsory seminar* at the Graduate School since 2008 to be taken at the beginning of the practical work; topics covered are:
  - Process of Developing Scientific Knowledge from developing the scientific question to publication of results
  - Data Management
  - Ownership of data and material
  - Authorship
  - Conflict of Interest
  - Tutorship for young scientists
  - Different scientific cultures
  - Conflicts in cooperation
  - Scientific fraud
  - Basis of Bioethics
- *Seminars “Intellectual Property Rights” and “How to cite correctly”*
- *Random checks* of PhD theses for plagiarism
- *Thesis advisory* by senior scientists compulsorily including an external scientist
- When submitting the thesis, students need to sign a *declaration in lieu of oath confirming Good Scientific Practice*, especially no plagiarism
Quality Control (Graduate School)

Graduate School, PhD Program and PIs

- Accreditation and renewal of accreditation of PIs
- Student representatives in PhD committee
- Evaluation measures
  - Yearly plenary meetings between students and board of directors in order to identify weak points of the programs and new training modules
  - Two meetings per semester with the student representatives in order to discuss current issues
  - Online evaluation program together with the quality assurance board of the Medical Faculty; systematic evaluation of individual activities
  - Evaluation of the program from the supervisors’ viewpoint planned
  - Plenary meetings of the PIs in order to identify requirements from their views and scientific orientation
  - Statistical Monitoring of students (e.g. drop out rate, median time to completion, history of former graduates) and PIs (e.g. publications and grant acquisition)
  - Discussion of evaluation results in the board
- International and interdisciplinary Advisory board (including industry and alumni) meets annually and evaluates activities
- Statement of accounts (financial evaluation)
- Ombudspersons within the graduate school (different from ombudspersons for scientific misconduct)
- Brochure “Good Supervision Practice” for PIs
- Supervision Agreement to be concluded at the beginning
Good scientific practice: Culture and Rules

Labs
- Internal lab control: regular lab seminar and journal club with critical discussion

Universities
- Rules for handling and storage of original data
- Signed responsibility for authorship
- Ombudsman
- Constitutional rules for Good Scientific Practice and handling suspicion/claim for scientific misconduct
- New measures of performance in career development?

Institutions
- Reduce “excitement level”
- Transparency in data provided, reagents and procedures
- Check for overinterpretation of data
- Allow publication of negative results,
- Allow confirmatory studies (“the data are not entirely new”)

Journals/Reviewers:
- Reconsideration of rating of grant applications:
  - originality, novelty, excellence, cumulative IF etc.
- Confirmatory studies are necessary
- Negative data are data!

Grant agencies:
- Open discussion on quality of science
- Impact is not Impact Factor
- WE ARE THE REVIEWERS IN ALL ABOVE!