



Research Data and Integrity

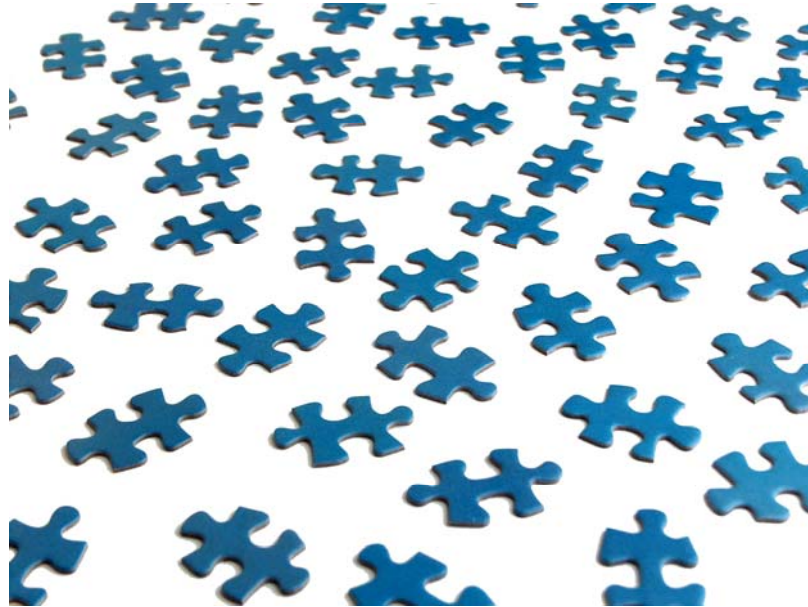
IT' S A MATTER OF PUBLIC TRUST

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June 14, 2018

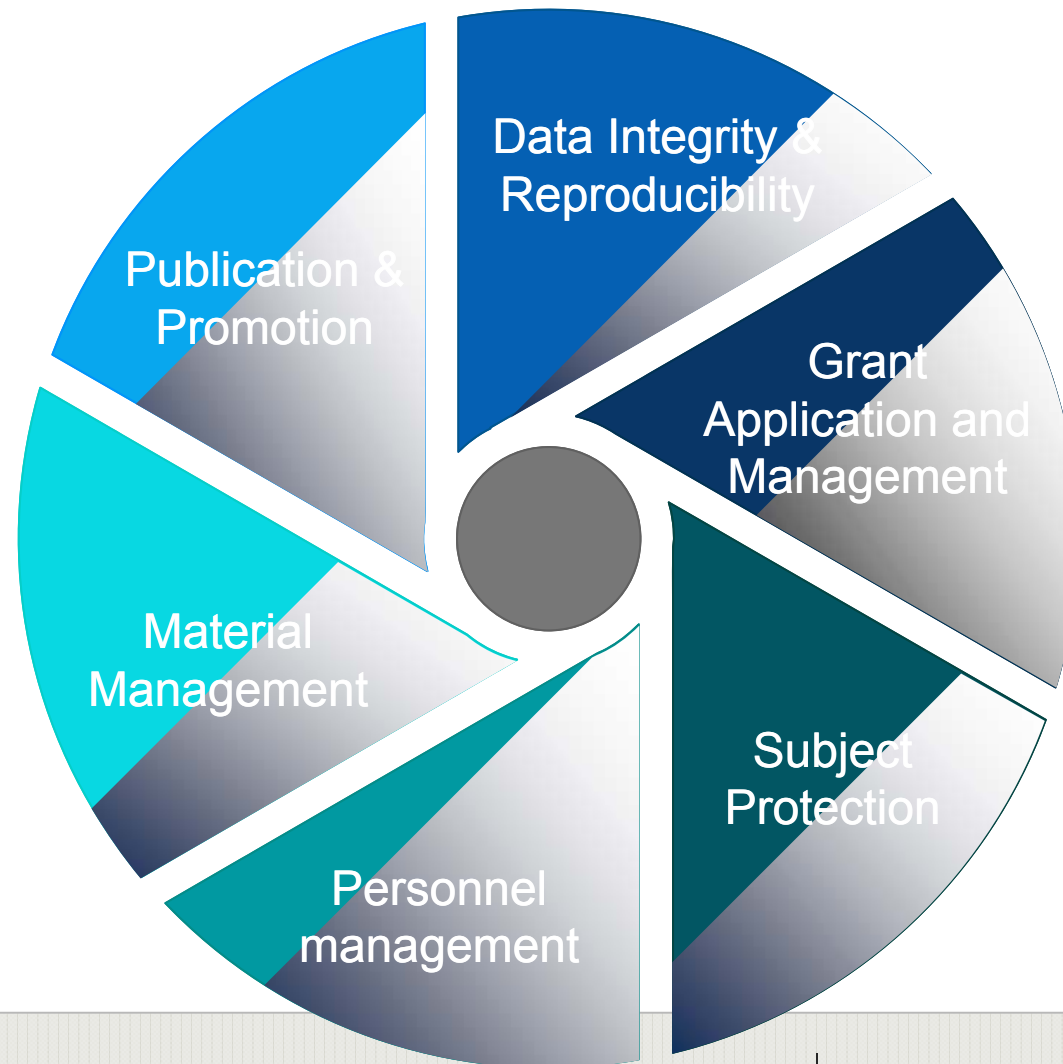
Faculty Disclosure

- Pfizer (through my husband)* helps pay Gretchen's mortgage

- *P.S. Thanks honey!



Academic Scientist Have Many Responsibilities



Agenda

- Research Misconduct
 - History/Trends
 - Risk Factors and What You Can Do

Recent History



Science, “Poehlman Sentenced to 1 Year of Prison,” by Eli Kintisch on 28 June 2006.

- U.S. v. Poehlman
 - Longitudinal Menopause Study
 - 17 grant applications over 8 years
 - Repaid hundreds of thousands of dollars
 - Sentenced to 1 year and 1 day in prison

- Andrew Wakefield

- Published findings in the *The Lancet* in 1998 suggesting a link between MMR vaccine and autism
- General Medicine College revoked his license
- *The British Medical Journal* also found findings to be “fraudulent” (timelines misrepresented to suggest direct impact of the vaccine)



Photo from The Telegraph, , March 27, 2008 (“MMR-autism link doctor Andrew Wakefield defends conduct at GMC hearing”)

What is Research Misconduct?

- Principles and Procedures for Dealing with Faculty Misconduct
 - <http://hms.harvard.edu/content/principles-and-procedures-dealing-allegations-faculty-misconduct>
 - "Research Misconduct" means fabrication, falsification, or plagiarism in
 - **proposing**,
 - **performing**, or
 - **reviewing** research, or
 - in **reporting** research results.
 - 42 CFR 93

Research Misconduct Definition

- **Fabrication** is making up data or results and recording or reporting them
- **Falsification** is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record
- **Plagiarism** is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit
- Research misconduct does **not** include **honest error** or **differences of opinion** 42 CFR 92

Research Misconduct, Definition cont.

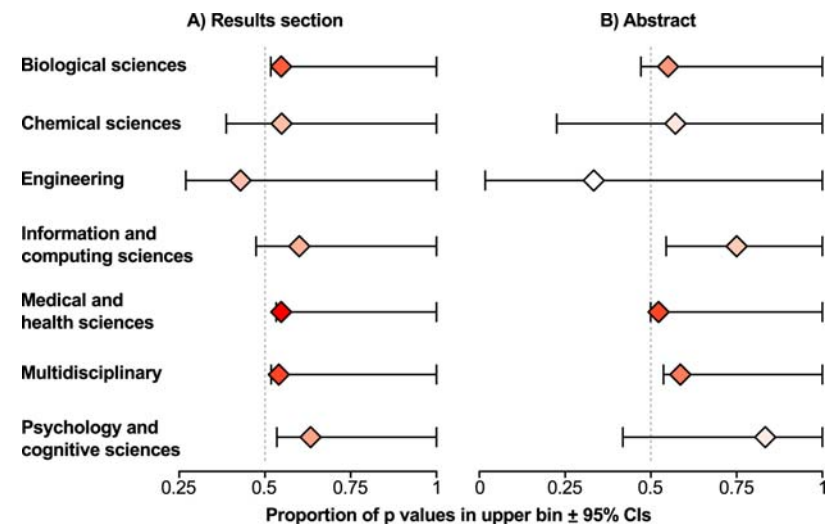
- Following the investigation, a finding of research misconduct requires: (42 CFR Sec. 93.104):
 - (a) There be a significant departure from accepted practices of the relevant research community; and
 - (b) The misconduct be committed **intentionally, knowingly, or recklessly**; and
 - (c) The allegation be proven by a **preponderance** of the evidence.

The Rest of the Iceberg

The File Drawer problem

Researcher degrees of freedom

- p-hacking
- HARKing
- Arbitrary stopping
- Acting on confirmation bias
- Selective reporting of subsets



Megan Head, Luke Holman, Rob Lanfear, Andrew Kahn, and Michael Jennions, "The Extent and Consequences of P-Hacking in Science" (2015) *PLoS Biology*

Some examples

- A collaborator tries to undercut your position as first author on a manuscript.
- You discover that a colleague in the lab has been eliminating data points from a database without statistical analysis.
- You can regularly hear the PI in the next lab screaming at the members of that lab and understand from them that he is pushing for results to support a publication, and the competing renewal of his program project grant.



Common hurdles and pitfalls



- Overwhelmed, uninterested, and even poorly intended mentors
- Uncertainty of grant funding
- Competition
- Increased regulatory requirements
- Complexity of collaborations/multidisciplinary and global research
- Data reproducibility
- Authorship disputes
- Public trust vs. skepticism

You receive an email from *Science*

- As part of its review process, *Science* used iThenticate to assess whether any part of your submission had been previously published. They've identified some issues.
- How do you respond? Consider the following factors:
 - 1 sentence or many?
 - Which section?
 - Introduction, methods, results?
 - Anything other than text copied?

sources:

- 1 1,020 words / 4% - CrossCheck
[Shin, H.S.. "T-type Ca²⁺ channels as therapeutic targets in the nervous system". *Current Opinion in Pharmacology*, 200802.](#)
- 2 467 words / 2% - CrossCheck
[E. Cheong. "Deletion of phospholipase C 4 in thalamocortical relay nucleus leads to absence seizures". *Proceedings of the National Academy of Sciences*, 12/22/2009.](#)
- 3 381 words / 2% - CrossCheck
[Shin, H.S.. "T-type Ca²⁺ channels and absence epilepsy". *Cell Calcium*, 200608.](#)
- 4 380 words / 2% - Internet from Mar 11, 2010
www.jneurosci.org
- 5 348 words / 1% - CrossCheck
[Jungryun Lee. "T-Type Calcium Channels and Thalamocortical Rhythms in Sleep: A Perspective from Studies of T-Type Calcium Channel Knockout Mice". *CNS & Neurological Disorders - Drug Targets \(Formerly Current Drug Targets - CNS & Neurological Disorders\)*, 02/01/2007.](#)
- 6 293 words / 1% - Publications
Khosravani, Houman Zamponi, Gerald W.. "Voltage-gated calcium channels and idiopathic generalized epilepsies.", *Physiological Reviews*, July 2006 Issue
- 7 268 words / 1% - Internet from Jul 2, 2010
in.physiology.org
- 8 221 words / 1% - CrossCheck
[Hee-Sup Shin. "Genetic Studies on the Role of T-Type Ca²⁺ Channels in Sleep and Absence Epilepsy". *CNS & Neurological Disorders - Drug Targets \(Formerly Current Drug Targets - CNS & Neurological Disorders\)*, 12/01/2006.](#)

193 words / 1% - CrossCheck

lipoic acid injection reduces

sensitivity to noxious thermal and mechanical stimuli in 296

mice (120). Collectively, these observations agree

with the results that no low-threshold Ca2+ current remains in small DRG neurons of CaV3.2/ mice (31)—cells known to be peripheral nociceptors 1

(218). Thus, these results provide explicit evidence for the role of

CaV3.2 T-type channels in pain perception and propose that CaV3.2 may be a good candidate to target for treatment of pain at the 39

peripheral level. Inflammatory and visceral pain CaV3.2/ mice also show a decreased pain response to visceral pain, an observation that agrees with a previous report that no low-threshold

Ca2+ currents remained in small dorsal root ganglion (DRG) neurons in these 242

mice (31). This result proposes that small DRG neurons conduct substantial role in carrying visceral pain signals. Recently, it was reported that

T-type Ca2+ channels in primary sensory neurons in colonic and 73

DRG cells are involved in mediating colonic pain transmission (136, 137). In this context, it is notable that CaV3.2

174

TC neurons were often shifted from tonic to low-threshold burst firing (J), whereas wild-type TC neurons never showed such a transition in firing mode (I). The bottom panel displays the applied current steps. Injection of prepulses, which slightly hyperpolarized the membrane potentials, elicited low-threshold burst firing in PLC4/ TC neurons (L), but not in wild-type TC neurons (K). (M) Spike numbers in a burst induced by various prepulses that hyperpolarized the membrane potentials to between -73 and -63 mV in wild-type (closed circle) and PLC4/ (open circle) TC neurons.

Modified from References (36, 37). Figure

5. Deletion of thalamic PLC β 4 leads to the genesis of absence seizures. (A) Lentiviral vectors containing control shRNA or an shPLC β 4 construct were injected bilaterally into wild-type mice and EEGs were recorded from frontal and parietal lobes. Lower panel: mice injected with LV- shPLC β 4 showed sporadic SWDs; upper panel: mice injected with pLKO-control never showed such a high-amplitude paroxysmal EEG pattern. (B) Seven of 12 mice injected with LV- shPLC β 4 showed spontaneous SWDs. The number of SWDs varied from 3 to 17 per hour. (C) The total duration of SWDs per minute induced by 20 mg/kg RS(+/-)-baclofen was greater in mice injected with LV- shPLC β 4 than in mice injected with pLKO-control.

Modified from Reference (37). Figure 6.

EEG power density at delta waves was decreased in CaV3.1-/- mice compared with wild-type mice during NREM sleep. Sample traces show EEG and EMG signals recorded from REM (A) and NREM (B) sleep states in

wild-type (CaV3.1+/+) mice (upper) and CaV3.1/ mice (lower).

Is this Plagiarism?

- An investigator copies a paragraph from another researcher's published manuscript, cites the article in the bibliography, but does not indicate that the material is a direct quotation.
- An investigator publishes a book that includes articles written by others. Although she credits the authors with a general acknowledgement, she does not indicate who wrote which article.
- At a national meeting, an investigator projects a slide that includes material from a published paper, but does not attribute the slide to the author.
- An investigator reuses the text she included in both the methods and analysis sections of an article she previously published in her new manuscript.

Is this Plagiarism?

- After a collaboration, Dr. A publishes work based on ideas developed jointly with Dr. B without giving credit to Dr. B.
- HMS White Paper on Plagiarism and Research Misconduct:
 - http://hms.harvard.edu/sites/default/files/assets/About_Us/COI/files/plagiarism_statement_121510.pdf

Questions of Research Integrity

- Data falsification and fabrication
 - **Julie** is a well-liked, trusted and senior postdoctoral fellow in **John's** lab
 - She is actively interviewing for faculty appointments, with a couple options to consider.
 - **Mary** is a new postdoctoral fellow in John's lab, and is working to become expert in the technique Julie mastered so that her work can be continued after she leaves.
 - Mary is having trouble repeating the experiments. They require stimulating the cells, leaving them for 24 hours, then staining the cells, and capturing the image of the experiments using a fluorescent microscope.

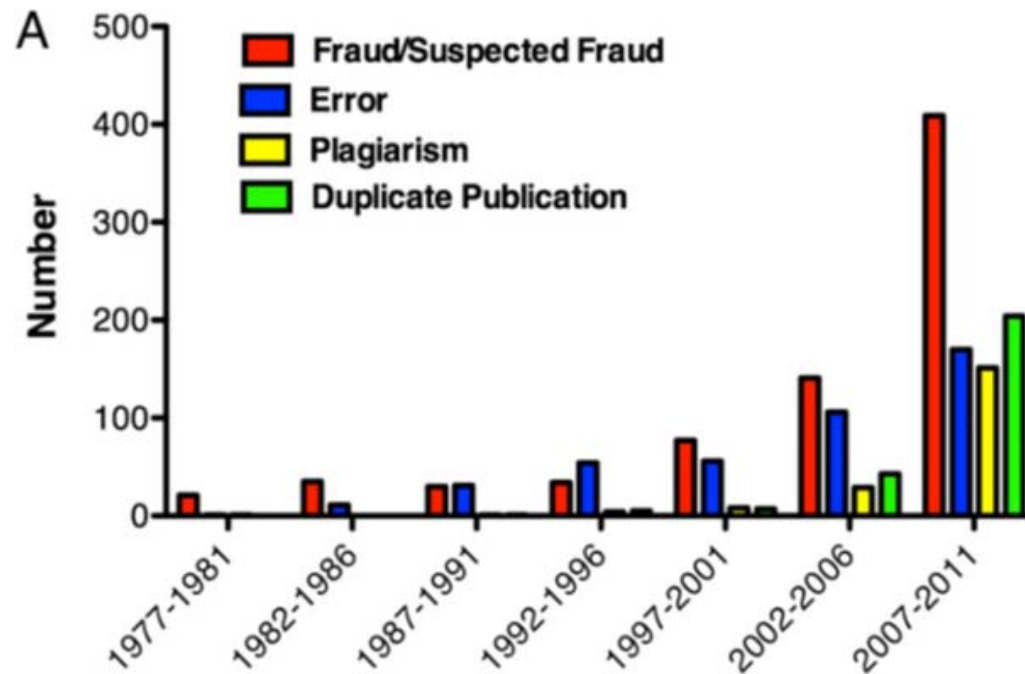
Questions of Research Integrity

- No. 2 – Data falsification and fabrication
 - She asks Julie to assist her, and they run experiments side-by-side so that Mary can follow Julie's technique.
 - After 24 hours, as expected Julie culture showed cell surface expression to Receptor X, but Mary's culture showed the opposite.
 - Mary asked Julie to review Julie's notebooks, sure that she was missing a step. Julie promised to pull her data together when she returned from her latest job talk. In Julie absence, Mary asked John for access to the lab data, but Julie's notes were not stored on the lab server, and so John did not have the materials to share. John expressed concern about Mary's ineptitude in repeating Julie's work.

Questions of Research Integrity

- No. 2 – Data falsification and fabrication, cont.
 - At a loss, Mary turned to the primary paper that Julie had published in Science on this topic, and Mary noted that the image depicted appears to have unusual artifacts. Mary downloaded the image from the journal’s website, and, using ImageJ, was able to determine that Julie had substantially altered the image submitted for publication, potentially to misrepresent the results of the research.
 - What should Mary do?
 - If she tells John, what should John do?
 - What if Mary learns that John is aware Julie falsified data and promoted her work for publication, and included it in grant applications nonetheless?

Incidence of Misconduct: A Look at Retractions



Fang et al., PNAS, 2012

What can we do?

- Develop recordkeeping and review system for your group
- Develop defined onboarding process/orientation for new members of the group/lab focused on data integrity, standards for publishing, expectations
- Periodically review lab notebooks/CRFs
- Review raw data for figures in a journal article and grant
- Welcome comments/criticisms/ideas and challenges to data at group and lab meetings

What can we do?

- Don't always allow presentation in PowerPoint
 - Use Tools – eTBlast, Google to periodically scan for copied text
- Submit images in .tiff/.jpeg. Don't flatten images.
- Nature's Image Integrity Policy:
http://www.nature.com/authors/editorial_policies/image.html
 - “All digitized images submitted with the final revision of the manuscript must be of high quality and have resolutions of at least 300 d.p.i. for colour, 600 d.p.i. for greyscale and 1,200 d.p.i. for line art.”

What can we do?

- Maintain a complete set of verifiable data and never destroy any primary data
 - Be careful about shared files
 - Ensure versioning/audit trail of primary data
- Drafting hint: Don't keep your own previous work open when writing a new manuscript/grant
- Don't rely solely on the peer review process to catch errors and identify issues
- Raise awareness
- What else?

Faculty Policies on Integrity in Science

- Guidelines for Investigators in Scientific Research
- Guidelines for Editors and Authors of Medical Textbooks
- Guidelines for Investigators in Clinical Research
- Principles and Procedures for Dealing with Allegations of Faculty Misconduct
- Faculty of Medicine Statement on Research Sponsored by Industry

Faculty Policies on Integrity in Science, cont.

- Policy on Conflicts of Interest and Commitment
- Authorship Guidelines
- Letters of Reference
- Guidelines for Attribution of Credit and Disposition of Research Products

<http://hms.harvard.edu/content/faculty-policies-integrity-science>

Questions/Concerns/Reports

- Gretchen Brodnicki, J.D., Dean for Faculty and Research Integrity

Gretchen_Brodnicki@hms.harvard.edu

617-432-2496

- Office for Academic & Research Integrity – Anonymous Reporting

https://hms.az1.qualtrics.com/jfe/form/SV_9o5D05etE0EJh2d

617 432 5555