Research Misconduct

It’s a Matter of Public Trust

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Faculty Disclosures

- Pfizer pays GB’s mortgage
- DB – I wish!
Agenda

• Research Misconduct
  • History and Trends
  • What Is It and Process
  • Risk Factors and Recognition
  • What We Can Do
Research Misconduct

- Examples in History:
  - Isaac Newton – calculations fit observations rather than other way around
  - Louis Pasteur – used competitor’s vaccine against anthrax but never acknowledged it in publications – instead said it was his own
  - Source - Michael Kalichman, of the University of California, San Diego
Research misconduct has always taken place

The Piltdown Man

The missing link between apes and humans (human cranium, ape-like jaw)

Found in England in 1912
Hoax finally exposed in 1953
Recent History

- **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)
Recent History

Duke – Anil Potti

- 3 active clinical trials
- Fall Out:
  - ACS – Duke repaid $729,000
  - 11 malpractice settlements to date, at least 2 lawsuits currently pending
  - 2/3 of 40 publications to be retracted, in whole or in part
What is Research Misconduct?

- Principles and Procedures for Dealing with Faculty Misconduct
  - [http://hms.harvard.edu/content/principles-and-procedures-dealing-allegations-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.
Finding of Research Misconduct

• There is a significant departure from accepted practices of the relevant research community; and

• The misconduct is committed intentionally, or knowingly, or recklessly; and

• The allegation is proven by a preponderance of evidence.
Research Misconduct Process

• Allegation - Where It Can Come From
  ◦ In-person Complaint
  ◦ Anonymous Contact from Complainant
  ◦ Office of Research Integrity, or NSF OIG
  ◦ Journals
  ◦ Blogs – Retraction Watch, ScienceFraud.org,
  ◦ Clare Francis

• Preliminary Assessment

• Sequestration of data & Notification of Accused
  ◦ ALL potentially relevant data

• Inquiry
• Investigation
• Reporting
Research Misconduct Process, cont.

- Report to our Standing Committee on Faculty Conduct
- Recommendations to Dean Flier and (if applicable) President of Affiliated Institution
- Decision by Deciding Officials
- Reporting as may be suggested or required:
  - Current employer
  - Letters of Reference
  - Board of Registration in Medicine
  - NIH/NSF/DoD/FDA/other federal authorities
  - Journals
Incidence of Misconduct: A Look at Retractions

Fang et al., PNAS, 2012
You receive a call from *Nature*

- You are the corresponding author of a paper
- The Editor of *Nature* contacts you to tell you that they have received concerns that Figure 3A has been falsified.
- What do you do?
How Easy it Can Be

What's in a picture?
The temptation of image manipulation

Rossner and Yamada 166 (1): 11
Published July 6, 2004 // JCB vol. 166 no. 1 11-15

• http://jcb.rupress.org/content/166/1/11.full
Manipulation of Blots

Rossner M, Yamada KM J Cell Biol 2004;166:11-15
Cleaning up gels - what is acceptable and what is not?
though PKCδ levels were unchanged by pIRES-DNPKCδ (Fig. 3, B and C), there was a significant decrease in the activating (Tyr311) phosphorylation of PKCδ (Fig. 3, B and C), confirming the dominant negative effect.

### Prolonged effect of PKCδ inhibition on eNOS expression

PFAECs were exposed to rottlerin (10 μM) for 24 h and then analyzed for eNOS protein expression by Western blot analysis. eNOS protein expression was also compared in cells overexpressing a dominant negative PKCδ mutant, pIRES-DNPKCδ. Our data indicated that PKCδ inhibition significantly reduced eNOS protein levels (Fig. 4, P < 0.05 vs. control). To determine if this effect was at the level of transcription, we transfected PFAECs with a 1.6 kb eNOS promoter construct linked to a luciferase reporter gene (51) in the presence or absence of the dominant negative PKCδ mutant and then incubated with or without rottlerin. We then analyzed eNOS promoter activity after a further 24 h. Our data indicate that PKCδ inhibition with either rottlerin or dominant negative PKCδ mutant overexpression significantly reduces eNOS promoter activity (Fig. 5, P < 0.05 vs. control).

**Effect of Akt inhibition on eNOS expression and activity.** To further elucidate the potential role of the PKC/PI3K/Akt axis in regulating eNOS expression, we utilized an adenoviral construct to overexpress a dominant negative mutant of Akt in PFAECs. Initial Western blot analyses confirmed the overexpression of the dominant negative Akt mutant. We found that Akt expression was approximately twofold higher in dominant negative Akt mutant-transduced cells compared with GFP-transduced cells (Fig. 6, A and B, P < 0.05 vs. GFP control). We next determined if the dominant negative Akt mutant had effects on eNOS phosphorylation at Ser1177 or total eNOS expression. Our data indicate that the overexpression of the dominant negative Akt mutant significantly decreased both total eNOS protein levels (Fig. 6, C and D, P < 0.05 vs. control), and eNOS phosphorylation at Ser1177 (Fig. 6, B and D, P < 0.05 vs. control). These changes were associated with decreased NO generation (Fig. 6, E, P < 0.05 vs. control). Furthermore, we found that overexpression of the dominant negative Akt mutant significantly decreased eNOS promoter activity (Fig. 7, P < 0.05 vs. control).

**Effect of endogenous NO on eNOS expression.** Our data indicate that the inhibition of PKC/PI3K/Akt signaling leads to decreased NO generation and a subsequent decrease in NOS expression. Thus, we next determined whether the decrease in NOS expression was causally related to the reduced NO generation. Initially, we confirmed that the eNOS inhibition using ETU decreased NO generation. We found that NOx levels were significantly decreased after 24 h of ETU (100 μM) treatment (Fig. 8A, P < 0.05 vs. control). Furthermore, the reduction of NO generation caused significant decreases in both eNOS protein activity (Fig. 8B, P < 0.05 vs. control) and eNOS protein levels (Fig. 8C, D, P < 0.05 vs. control). To verify that NO signaling is involved in regulating eNOS promoter activity, cells were treated with both ETU and the NO donor, sodium nitroprusside (SNP). Our data indicate that the addition of SNP prevents the ETU-mediated reduction in eNOS promoter activity (Fig. 9A) and eNOS protein levels (Fig. 9B, B and C).

**DISCUSSION**

In the fetus, pulmonary vascular resistance is high and pulmonary blood flow is low. With the initiation of ventilation and oxygenation at birth, pulmonary vascular resistance decreases, and pulmonary blood flow increases. Increasing evidence suggests that changes in pulmonary vascular tone are mediated by NO, possibly in response to increased shear stress on the pulmonary arterial endothelium (20, 28, 30). eNOS plays an important role in providing the NO necessary to allow these birth-related changes. In a number of clinical conditions, the pulmonary circulation fails to undergo the normal transition to postnatal life, resulting in persistent pulmonary hypertension of the newborn (PHN) (27). Thus, a better understanding of
Intermediate - making “mosaic” images - combining images
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You cannot mix and match bands from various gels that were run at different times or exposed for different amounts of time...

If you are going to splice lanes together (from the same gel) that are noncontiguous, you MUST insert a thin black or white line between the lanes and explicitly mention this in the figure legend...
Cutting and pasting gels - what is acceptable?

Our original figure - different gels clearly separated
Cut, pasted and “enhanced” - TOTALLY UNACCEPTABLE
Acceptable enhancement

Adobe Photoshop “levels” command was applied to entire image - no data are created or removed.
Unacceptable enhancement

Adobe Photoshop “levels” command was applied to green channel only, and only one portion of the image.
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.

• What about self-plagiarism?

• HMS White Paper on Plagiarism and Research Misconduct:
  
  * [http://hms.harvard.edu/sites/default/files/assets/About_Us/COI/files/plagiarism_statement_121510.pdf](http://hms.harvard.edu/sites/default/files/assets/About_Us/COI/files/plagiarism_statement_121510.pdf)
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?
lipoic acid injection reduces sensitivity to noxious thermal and mechanical stimuli in 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 (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 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 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 DRG cells are involved in mediating colonic pain transmission (136, 137). In this context, it is notable that
Mode: Similarity Report

sources:

1. 1,020 words / 4% - CrossCheck
   Shin, H.S., "T-type Ca\(^{2+}\) channels as therapeutic targets in the nervous system". Current Opinion in Pharmacology, 2008;02

2. 467 words / 2% - CrossCheck

3. 381 words / 2% - CrossCheck
   Shin, H.S., "T-type Ca\(^{2+}\) channels and absence epilepsy". Cell Calcium, 2006;08.

4. 380 words / 2% - Internet from Mar 11, 2010
   www.inneurosci.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 Ca\(^{2+}\) 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
sleep, pain, and even fear disorders. In addition, we expect that the study of T-type channels in the neurobiology of cognition will continue to evolve. Figure Legends Figure 1.

Intrinsic firing properties of TC neurons located at the ventrobasal complex. (A) Burst firing patterns elicited by 100-ms pulses of negative step-current inputs at 70 mV. Holding membrane potentials were maintained by DC current input. The amount of current injected is indicated below each trace; pA, picoampere. Scale bars: 100 ms (horizontal) and 50 mV (vertical). (B) Burst firing patterns elicited by positive step-current inputs at -80 mV. Note the increasing firing frequency of lower-frequency spikes in wild-type TC neurons with positive input currents greater than 700 pA. Only high-frequency spikes are missing in CaV3.1/TC neurons. (C) Tonic firing patterns elicited by positive step-current inputs at -60 mV. Low-frequency spikes are elicited equally in wild-type and CaV3.1/TC neurons. (D) The relationship between the number of spikes and the amount of current injected. The number of spikes during 100-ms positive step-current inputs when membrane potentials are held at -60 mV (left) or -80 mV (right).

Modified from Reference (106). Figure 2. Baclofen-induced SWDs in wild-type and CaV3.1/mice. Top: Representative EEG traces show that injection of baclofen induces abundant SWD.
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 PLCβ4 leads to the genesis of absence seizures. (A) Lentiviral vectors containing control shRNA or an shPLCβ4 construct were injected bilaterally into wild-type mice and EEGs were recorded from frontal and parietal lobes. Lower panel: mice injected with LV-shPLCβ4 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-shPLCβ4 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-shPLCβ4 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).

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activity in wild-type mice and negligible SWD activity in CaV3.1/
mice. Bottom: The frequency of SWD events is plotted against time for CaV3.1/ and wild-type mice. Modified from Reference

(A) Representative traces of total Ca2+ currents of the four genotypes,

CaV2.1+/+; CaV3.1+/+ (wild-type), CaV2.1; CaV3.1+/+, CaV2.1; CaV3.1/+ and CaV2.1; CaV3.1/,

are shown. The bar graph shows a quantitative comparison of the currents among the four genotypes. (B) Top EEG traces of the relevant genotypes. Bottom: Power spectrum analysis of the EEG patterns of the two genotypes,

CaV2.1; CaV3.1/+ and CaV2.1; CaV3.1/.

(C) Comparison of the frequency of SWD events among mice with different genetic compositions. The effects of the CaV3.1 gene dose on the expression of SWDs in different absence model mice are compared. Modified from Reference
in the synaptic plasticity of spinal lamina I projection neurons that mediate hyperalgesia (92). Thus,

**CaV3.1**

may play a role in the

central sensitization in the spinal dorsal horn to develop neuropathic pain.

A study exhibited that intrathecal administration of CaV3.3 antisense oligonucleotides significantly relieve thermal hyperalgesia and tactile allodynia caused by chronic compression of the DRG of rats (227), raising the possibility that the CaV3.3 subtype in the spinal cord may also be involved in the pathogenesis of neuropathic pain.

Subtype-specific and region-specific roles of T-type channels

T-type channels show subtype-specific and region-specific roles in pain pathways. At the spinal level, the
Risk Factors

- Poor Record Keeping
  - Reliance solely on electronic files without established standards and systems for organizing such files
- Insufficient Guidance/Training/Mentorship Regarding Acceptable Standards
- Foreign Educated Trainees Unfamiliar with Acceptable Standards
- Faculty & Trainee stress levels
- No Third Party Review of Original Primary Data
  - Establish redundancies where appropriate & challenge data
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
• Maintain a complete set of verifiable data
  - Be careful about shared files
  - Ensure versioning/audit trail of primary data
  - Consider saving files in original file format as derived from machine/instrument
What can we do?

• 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

• Beware of honorary authorship (eg Gerald Schatten in the Hwang fraud case)

• Raise awareness

• Pay attention to trainee stress levels

• What else?
Other Oddities

- **Who's Afraid of Peer Review? John Bohannon**
  - "A spoof paper concocted by Science reveals little or no scrutiny at many open-access journals."
  - Science 4 October 2013: Vol. 342 no. 6154 pp. 60-65 DOI: 10.1126/science.342.6154.60

- **Mystery over obesity ‘fraud’ – Nature News**
  - "Researcher baffled after his results appear in bogus paper."
    - WITHDRAWN: Identification of meteorin and metrnl as two novel pro-differentiative adipokines: Possible roles in controlling adipogenesis and insulin sensitivity, Alkistis Vezyraki, Stilianos Kapelouzouc, Nikolaos Fotiadisb, Moses S. Theofilogiannakosa, Evridiki Gerou School of Health Sciences, University of Thessaly, Karies, Trikala, Greece
Questions?

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