Plagiarism and Scientific Misconduct

- **Problematic/questionable science**
  - Typical cases: intentional fabrication/manipulation of data
    - Wenbing, Han-Yi, Chuanfu
  - Not-so-typical cases:
    - Lindsey, Horace
  - Fake science:
    - Scott
  - Innocent errors:
    - Kate
- **Good science or just copycats?**
  - Perception, language problem, or plain ignorance?
    - Prashant, Ben, Ed
  - The race to be the first – data/material use agreements
    - CJ
- **Why should we care - issues you and I face**
  - The peer review system: Mark
  - Citation problem: Baggi
  - others

Wenbing's pick: Retraction of Deb *et al.*, *Science* 311 (5763) 992-996.

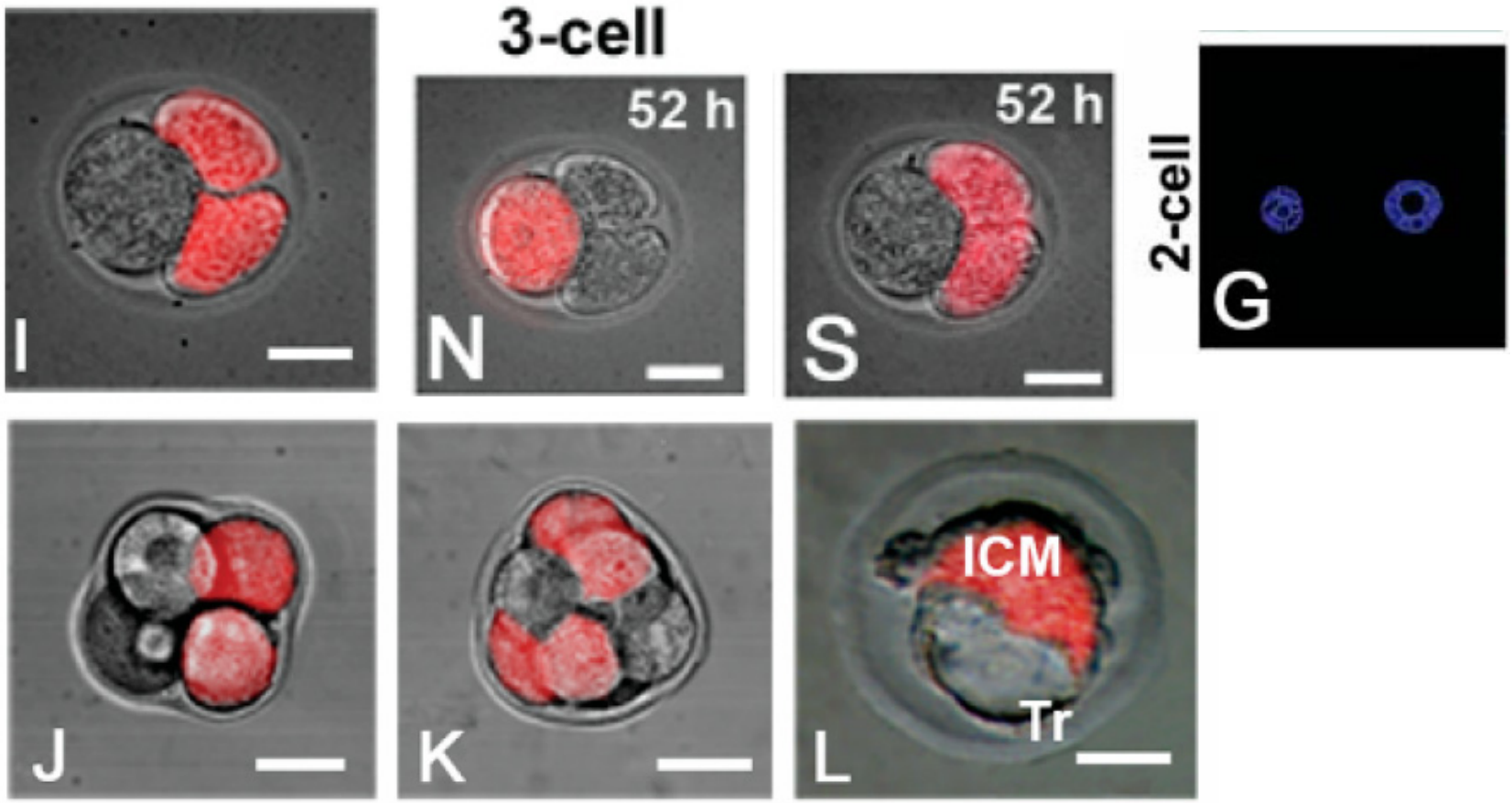
Science 27 July 2007:
Vol. 317. no. 5837, p. 450
DOI: 10.1126/science.317.5837.450b

K. Deb, M. Sivaguru, H. Y. Yong, R. M. Roberts, *Science* **311**, 992 (2006).

Retraction

We wish to retract our Report "*CDX2* gene expression and trophectoderm lineage specification in mouse embryos" (1). Allegations of research misconduct were received by the University of Missouri-Columbia (MU) Provost, and an investigation found that the first author (K.D.) engaged in research misconduct by intentionally falsifying and fabricating digital images in the preparation of Figs. 4I; 4N; 4S; 2G; 3, J to L; S2, V to X; and S6, I to K accompanying the *Science* article. In addition, the original raw image files for the majority of the figures in the paper have not been located (the exceptions being the confocal scanning images in Figs. S1, S3, S4, S5, and S6), raising the possibility that the data they represent may also be suspect. We have decided to withdraw the article in its entirety in view of the fact that the paper was founded at least in part on falsified or fabricated images.

digital images fabricated



Han-Yi's pick

~ from thescientist.com

News:

Renal researchers faked data

Posted by Bob Grant

[Entry posted at 13th July 2009 04:22 PM GMT]

View comments(26) | Comment on this news story

Two researchers conducting animal studies on immunosuppression lied about experimental methodologies and falsified data in 16 papers and several grants produced over the past 8 years, according to the Office of Research Integrity (ORI).

The scientists, Judith Thomas and Juan Contreras, formerly at the University of Alabama at Birmingham (UAB), falsely reported that they performed double kidney removals on several rhesus macaques in experiments designed to test the effectiveness of two immune suppressing drugs -- Immunotoxin FN18-CRM9 and 15-deoxyspergualin (15-DSG) -- in preventing rejection of a single transplanted kidney.

Elevated T Regulatory Cells in Long-Term Stable Transplant Tolerance in Rhesus Macaques Induced by Anti-CD3 Immunotoxin and Deoxyspergualin[1]

Clement K. Asiedu,* Karen J. Goodwin,* Gansuvd Balgansuren,* Stacie M. Jenkins,* Stéphanie Le Bas-Bernardet,* Uuganbayar Jargal,* David M. Neville, Jr.,† and Judith M. Thomas[2]*

RETRACTED August 2008

What happened?

- Judith Thomas & Juan Contreras (UAB) ~ immunosuppression
- Immunotoxin FN18-CRM9 &15-deoxyspergualin (15-DSG)
- $23 million from NIH
- Remove one kidney → transplant

→ ~~remove second kidney after 1 month~~

- inflated the apparent effectiveness of the drugs
- Reported in 2006 by Thomas
- 16 publication retracted

haryana-online.com

May be true, but definitely not right

Retraction for Asiedu et al., *J Immunol* 175 (12) 8060-8068.

The Journal of Immunology, 2006, 177: 2023.

Retraction: Elevated T Regulatory Cells in Long-Term Stable Transplant Tolerance in Rhesus Macaques Induced by Anti-CD3 Immunot oxin and Deoxyspergualin

Clement K. Asiedu, Karen J. Goodwin, Gansuvd Balgansuren, Stacie M. Jenkins, Stéphanie Le Bas-Bernardet, Uuganbayar Jargal, Judith M. Thomas and David M. Neville, Jr.

It has come to our attention that a recently uncovered error compromises some of the data presented in our paper: Asiedu C. K., K. J. Goodwin, G. Balgansuren, S. M. Jenkins, S. Le Bas-Bernardet, U. Jargal, D. M. Neville, Jr., and J. M. Thomas. 2005. Elevated T regulatory cells in long-term stable transplant tolerance in rhesus macaques induced by anti-CD3 immunotoxin and deoxyspergualin. *J. Immunol.* 175: 8060–8068.

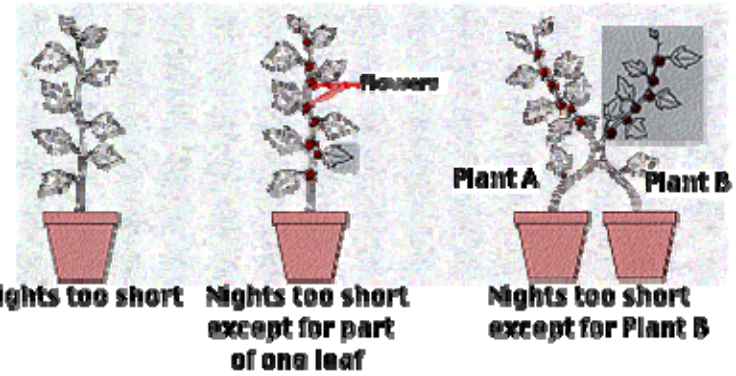
We have learned that assessment of kidney allograft function included several animals that possessed an intrinsic kidney and had not undergone bilateral nephrectomies as reported. Consequently, my coauthors and I think that data and conclusions relating to the duration of operational tolerance were overestimated and invalid.

Although, (1) the in vitro cellular and molecular characterization of rhesus regulatory T cells subsets is entirely valid, and (2) the highest frequency of $CD4^{+}CD25^{+}$ T regulatory cells we reported was in recipient 98R317, who underwent bilateral nephrectomy and is currently functioning 5.4 years on his kidney allograft, the relevance of the findings to stable kidney allograft tolerance remains unproven at this point. Thus, in the interest of scientific accuracy and ethical standards, we retract the article cited above.

We express regret to all in the scientific community whose work on tolerance might have been impacted by this unfortunate error.

Chuanfu's pick: The story of florigen

Julius von Sachs (1832-1897); German botanist

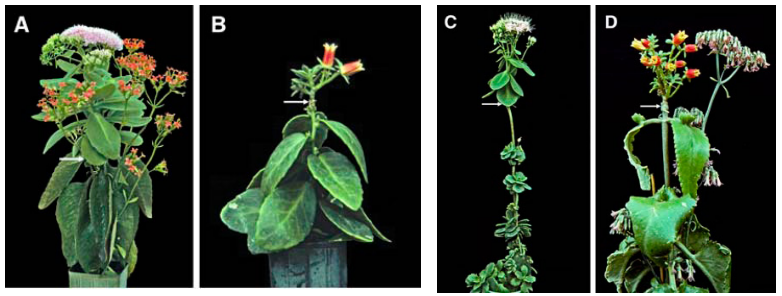


Garner and Allard, 1920 ⇒ **Photoperiodism**: plants response to the relative length of day and night

Knott, 1934 ⇒
- day length is perceived by the leaves, whereas flower formation takes place in the shoot apical meristem
- signal can also be transmitted from a flowering partner (donor) via a graft union to a nonflowering partner (receptor).

Chailakhyan, 1936 ⇒ introduced the term "florigen": specific substances with a regulatory function

Zeevaart, 1958, 1982 ⇒



SDP-LDP LDP-SLDP LSDP-LDP LSDP-SLDP

universal in plants

Chemical extractions

a specific ratio of known hormones and metabolites

Science
AAAS

The mRNA of the Arabidopsis Gene FT Moves from Leaf to Shoot Apex and Induces Flowering

Tao Huang, *et al.*
Science **309**, 1694 (2005);
DOI: 10.1126/science.1117768

**Tao Huang,[1] Henrik Böhlenius,[1] Sven Eriksson,[1]
François Parcy,[2] Ove Nilsson[1]***

Day length controls flowering time in many plants. The day-length signal is perceived in the leaf, but how this signal is transduced to the shoot apex, where floral initiation occurs, is not known. In *Arabidopsis*, the day-length response depends on the induction of the *FLOWERING LOCUS T* (*FT*) gene. We show here that local induction of *FT* in a single *Arabidopsis* leaf is sufficient to trigger flowering. The *FT* messenger RNA is transported to the shoot apex, where downstream genes are activated. These data suggest that the *FT* mRNA is an important component of the elusive "florigen" signal that moves from leaf to shoot apex.

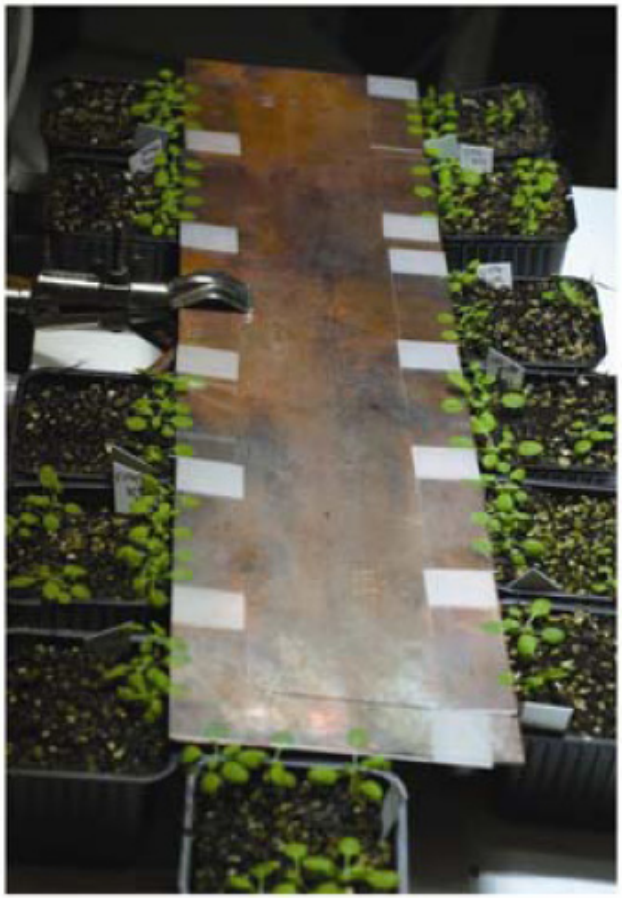
Tao Huang

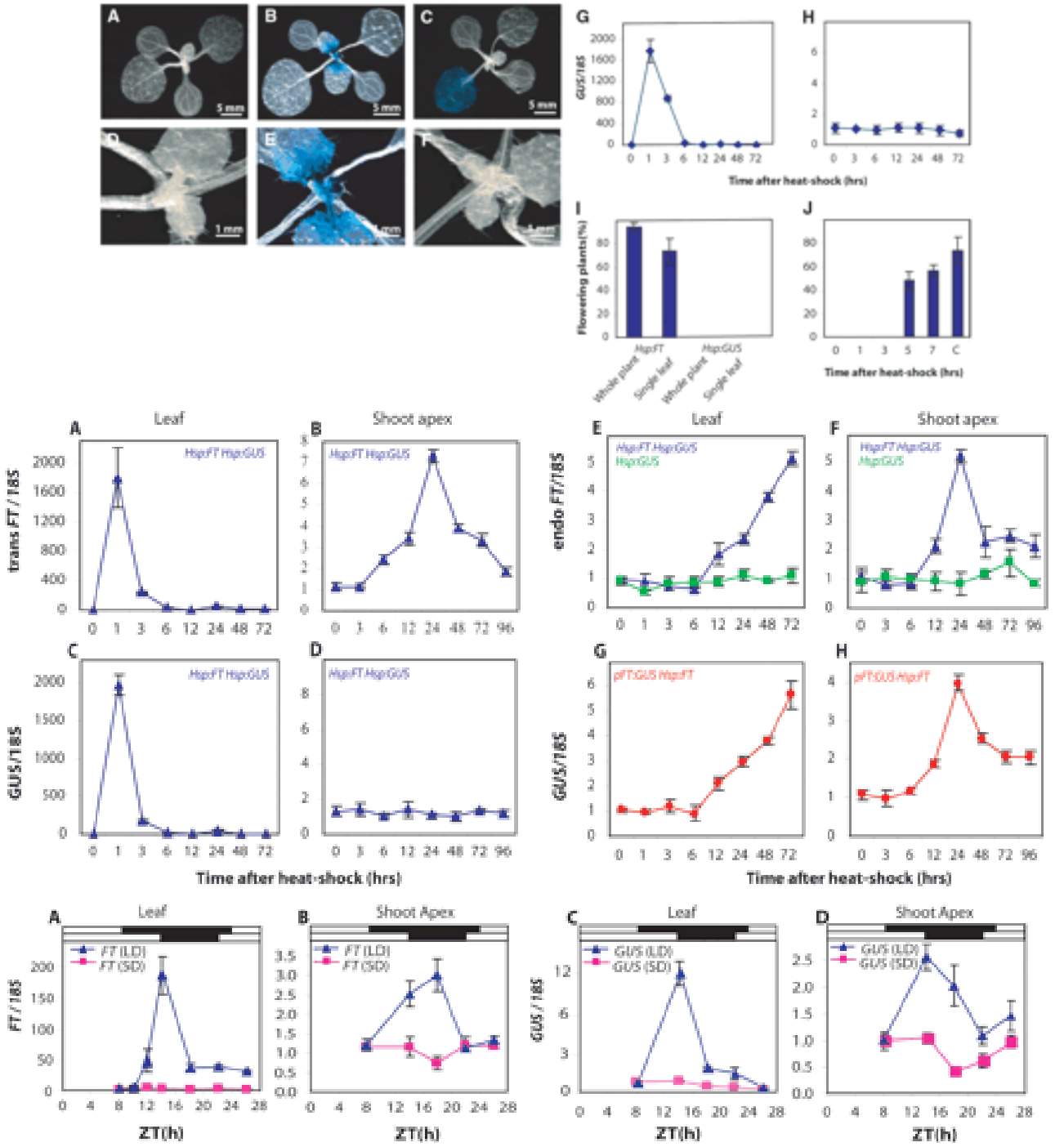
Ove Nilsson

Hsp
heat shock-inducible promoter

FT
FLOWERING LOCUS T

GUS




A
B
C
D
E
F
5 mm
1 mm
G
H
GUS/18S
Time after heat-shock (hrs)
I
J
Flowering plants(%)
HspFT
HspGUS
Whole plant
Single leaf
Time after heat-shock (hrs)
Leaf
Shoot apex
trans FT / 18S
HspFT HspGUS
endo FT/18S
HspGUS
GUS/18S
pFT:GUS HspFT
Time after heat-shock (hrs)
FT / 18S
FT (LD)
FT (SD)
ZT(h)
Shoot Apex
GUS / 18S
GUS (LD)
GUS (SD)

Science 23 December 2005:
Vol. 310. no. 5756, pp. 1880 - 1885
DOI: 10.1126/science.310.5756.1880a

BREAKTHROUGH OF THE YEAR:

3 Blooming Marvelous

T. Huang *et al.*, "The mRNA of the *Arabidopsis* Gene *FT* Moves from Leaf to Shoot Apex and Induces Flowering," *Science* **309**, 1694 (2005)
M. Abe *et al.*, "FD, a bZIP Protein Mediating Signals from the Floral Pathway Integrator FT at the Shoot Apex," *Science* **309**, 1052 (2005)
P.A. Wigge *et al.*, "Integration of Spatial and Temporal Information During Floral Induction in *Arabidopsis*," *Science* **309**, 1056 (2005)
A. Maizel *et al.*, "The Floral Regulator LEAFY Evolves by Substitutions in the DNA Binding Domain," *Science* **308**, 260 (2005)
M. Ashikari *et al.*, "Cytokinin Oxidase Regulates Rice Grain Production," *Science* **309**, 741 (2005)
M. Ueguchi-Tanaka *et al.*, "*GIBBERELLIN INSENSITIVE DWARF1* Encodes a Soluble Receptor for Gibberellin," *Nature* **437**, 693 (2005)
N. Dharmasiri *et al.*, "The F-Box Protein TIR1 is an Auxin Receptor," *Nature* **435**, 441 (2005)
S. Kepinski and O. Leyser, "The *Arabidopsis* F-Box Protein TIR1 is an Auxin Receptor," *Nature* **435**, 446 (2005)
S.J. Lolle *et al.*, "Genome-Wide Non-Mendelian Inheritance of Extra-Genomic Information in *Arabidopsis*," *Nature* **434**, 505 (2005)

Retraction

WE WISH TO RETRACT OUR RESEARCH ARTICLE "THE MRNA OF THE *ARABIDOPSIS* GENE *FT* MOVES from leaf to shoot apex and induces flowering" (*1*). After the first author (T.H.) left the Umeå Plant Science Centre for another position, analysis of his original data revealed several anomalies. It is apparent from these files that data from the real-time RT-PCR were analyzed incorrectly. Certain data points were removed, while other data points were given increased weight in the statistical analysis. When all the primary real-time RT-PCR data are subjected to correct statistical analysis, most of the reported significant differences between time points disappear. Because of this, we are retracting the paper in its entirety.

In new experiments, we have reproduced the floral induction caused by a heat-shock induction of *FT* in a single leaf, but we have failed to detect movement of the transgenic *FT* mRNA from leaf to shoot apex. We therefore retract the conclusion that *FT* mRNA is part of the floral inductive signal moving from leaf to shoot apex.

We deeply regret any scientific misconceptions that have resulted from the publication of these data.

The first author of the paper (T.H.) strongly objects to the retraction of the paper and has therefore declined to be an author of the retraction.

Our related *Science* Report on the *CO*/*FT* regulatory module in trees (*2*) is not affected by this Retraction. In this paper, T.H. was involved in the construction and analysis of the *PtCENL1* experiments reported in the Supporting Online Material. These data have been reevaluated and found to be correctly reported.

HENRIK BÖHLENIUS,[1] SVEN ERIKSSON,[1] FRANÇOIS PARCY,[2] OVE NILSSON[1]

[1]Umeå Plant Science Centre, Department of Forest Genetics and Plant Physiology, Swedish University of Agricultural Sciences, SE-90183 Umeå, Sweden. [2]Laboratoire de Physiologie Cellulaire Végétale, Département Réponse et Dynamique Cellulaires (DRDC/PCV), Unité Mixte de Recherche 5168 [(UMR) Joint Research Unit], Centre National de la Recherche Scientifique (CNRS), Commissariat à l'Energie Atomique (CEA), Institut National de la Recherche Agronomique (INRA), Université Joseph Fourier, 17 rue des Martyrs, batiment C2-38054, Grenoble Cedex 9, France.

References

1. T. Huang, H. Böhlenius, S.Eriksson, F. Parcy, O. Nilsson, *Science* **309**, 1694 (2005).
2. H. Böhlenius *et al.*, *Science* **312**, 1040 (2006).

Science
AAAS

CO/FT Regulatory Module Controls Timing of Flowering and Seasonal Growth Cessation in Trees
Henrik Böhlenius, *et al.*
Science **312**, 1040 (2006);
DOI: 10.1126/science.1126038

FT Protein Movement Contributes to Long-Distance Signaling in Floral Induction of Arabidopsis
Laurent Corbesier, *et al.*
Science **316**, 1030 (2007);
DOI: 10.1126/science.1141752

Hd3a Protein Is a Mobile Flowering Signal in Rice
Shojiro Tamaki, *et al.*
Science **316**, 1033 (2007);
DOI: 10.1126/science.1141753

Florigen has a long history of disappointing people. We're getting there, but the race is intense, and we need to keep cool heads.

-Willliam Lucas, UC Davis plant biology professor

Then, how do we deal with data point (outlier) removal?

1. Something wrong with an equipment. All data generated from that equipment should be discarded, not some of them.

2. Not uniform condition: close to light, fan, door, cooler etc.; watering, soil, insect, pathogen infection.

3. Plants develop differently, even sowed the seeds or transferred cuttings to soil at the same time.

4. Before attempting to remove any abnormal data points for unclear reason, repeat the experiment will help make the decision.

Lindsey's pick

Charlatanry in forensic speech science: A problem to be taken seriously

A. Eriksson and F. Lacerda

International Journal of Speech, Language and the Law (2007)

Giving Your Competitors a Bad Name

- Review article by two experts studying the sounds of speech was peer-reviewed and published
- Argued a lack of scientific basis for determining emotional stress by analyzing the sound of one's voice, which was basis for a product developed by Nemesysco Ltd.
- Targeted Mr. Liberman personally
- Nemesysco Ltd. Threatened to sue for defamation if article wasn't retracted

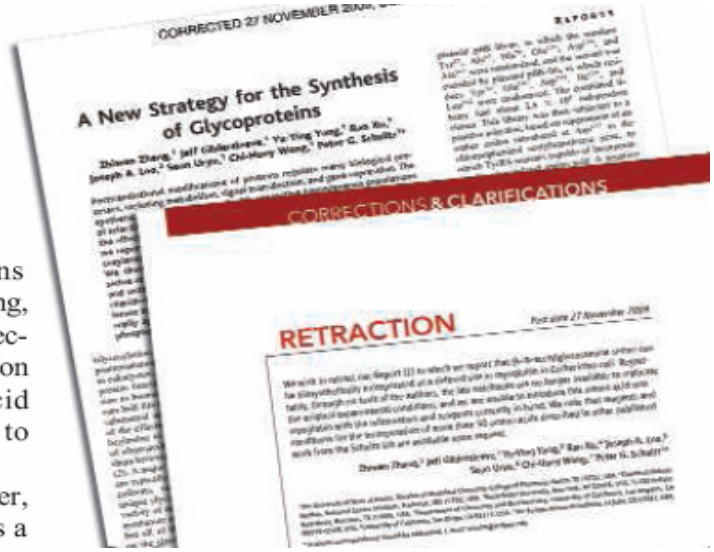
Happy Ending?

- Paper is still in print
- Journal has agreed to print a rebuttal letter
- The technology is still being used – by the UK government

Horace's pick

SCIENTIFIC INTEGRITY

A Dark Tale Behind Two Retractions



The notices published in *Science* last month and online in the *Journal of the American Chemical Society* (*JACS*) in September were brief: Two papers from a prominent chemistry lab were being retracted because the results couldn't be replicated. Part of the story behind the retractions is anything but straightforward, however. It involves an extortion attempt and a threat of suicide.

studying the effect of different ways proteins are modified. On 11 November 2004, Zhang, Schultz, and their colleagues published a second paper in *JACS* reporting the incorporation into a protein of a sugar-loaded amino acid that's a core unit in glycoproteins central to inflammation and cellular recognition.

At about the time of the *Science* paper, Eric Tippmann joined the Schultz lab as a

replicating it. Tippmann says he reviewed Zhang's work closely in the fall of 2006. In September 2006, Tippmann spoke at a Schultz group meeting outlining reasons why he thought Zhang's work was likely incorrect.

Schultz says the concerns raised were serious enough that he asked a group of lab members to try to replicate the work in Zhang's *Science* paper in addition to several other important discoveries Zhang had made. That task, however, was complicated by the fact that Zhang's lab notebooks, describing his experiments in detail, were missing. Schultz says that in the early fall of 2006, the notebooks were in Schultz's office. But at some point after that they were taken without his knowledge and have never resurfaced.

After considerable effort, Schultz says his students were able to replicate most of the work. The biggest exception was the work that served as the basis for the 2004 *Science* and *JACS* papers. "It was clear the glycosylated amino acid work could not be reproduced as reported. So we tried to figure out what was going on," Schultz says.

In the midst of this process, events took an ominous turn. On 1 March 2007, Zhang received an e-mail that listed the author as "michael pemulis," who claimed to have discovered "fraud" in multiple papers. If Zhang did not send $4000 via overnight mail to a post office box in San Diego, the e-mail sender said he or she would reveal this "fraud" to faculty at Scripps and UT Austin. "They will investigate you. … pete will retract all your post-doctoral work. you lose job. … Texas will fire you before you tenure," the e-mail states.

Scripps. At Lerner's urging, Schultz and Zhang then contacted the San Diego Police Department, which forwarded their case to its electronic crimes unit. About a month later, in April 2007, Zhang says the officer in charge of the case told him that they had a suspect and asked whether he wanted to press charges. Zhang says he decided not to do so in hopes the situation would blow over.

It didn't blow over. In November 2007, an anonymous letter was sent to officials at several institutions, including Scripps; UT Austin; the University of California, Berkeley; and *Science*'s editorial department. The letter stated that it was from "a member of PGS [Peter G. Schultz] lab" and called the 2004 *Science* paper a "fake." "I feel like leaving science or committing suicide," the letter stated. Zhang says that when he saw the letter, "my jaw dropped again."

The disturbing events haven't stopped. Zhang says over the past 2 years, he has received several anonymous phone calls at his UT Austin office phone number in which the caller hasn't said anything and then hangs up. Zhang says he's tried calling the number that pops up on his caller ID, but a recording on the other end says it is a long distance calling card center in Mississippi. Zhang says he and his family have become unnerved: "We don't feel safe anymore." The stress has gotten so high, that his wife and children moved away from Texas some time ago and have since been in virtual hiding. "It's horrible," Zhang says. "I'm just trying to be a good scientist. This is not science."

The events, Schultz says, affected him deeply as well. "It put me in a situation where I felt there was an extra burden on me to find out what was going on, given the threats," he says. Today, after years of effort, Schultz says he feels he and his students are starting to understand what may have gone wrong with the original experiments. Although still preliminary, it appears that the problem might be with the enzyme that they thought was binding to the unnatural amino acid and incorporating it in the protein. A test with a different glycosylated amino acid shows that it actually binds the unnatural amino acid not in the normal "active site" but at another site. Here it then prompts a conventional natural amino acid to be incorporated in the active site, giving a false positive reading. In the end, Schultz says, Tippmann was right to have doubts. "There was something wrong with the work."

That meant the *Science* and *JACS* papers needed to be retracted. Zhang says Schultz contacted him in July and suggested that the papers be pulled. Zhang was preparing for his tenure review at UT Austin and says he was concerned that retracting the papers would prove damaging to his chances of receiving tenure. Nevertheless, after Schultz and Zhang talked it over, they agreed to retract both papers. After receiving signed agreement from each of the authors, a process that took several weeks, Schultz sent the retractions to *Science* and *JACS* on 11 August.

JACS quickly accepted the retraction. But editors at *Science* informed Schultz that the journal's editorial practice requires that they get signatures directly from all authors wishing to retract a paper. During that process, Zhang informed *Science*'s executive editor, Monica Bradford, of the extortion e-mail and the missing lab notebooks. In response, *Science*'s editor-in-chief, Bruce Alberts, called Schultz to suggest that the retraction letter in *Science* should state that the lab notebooks were missing through no fault of the authors; that wording helped explain why they had trouble replicating the experiments. In the end, the retraction was published on 27 November.

> *"There was somebody who did this, really turned lives upside down, and made doing science a lot harder than it had to be."*
>
> —RICHARD LERNER, SCRIPPS RESEARCH INSTITUTE

The summer brought other developments. On 7 August, Tippmann, now a lecturer at the University of Cardiff in the U.K., co-authored a paper that laid out several reasons why Zhang's original glycosylated amino acid experiments could not have worked. And in October, Zhang was told he would be denied tenure by UT Austin. For his part, Tippmann says he's sorry that Zhang has had to undergo this ordeal, but that his involvement has been entirely limited to the science, and he had nothing to do with the missing notebooks, the March 2007 e-mail sent to Zhang, or the November 2007 letter. Schultz says he and his Scripps colleagues will continue to search for answers. Lerner concludes: "There was somebody who did this, really turned lives upside down, and made doing science a lot harder than it had to be."

—ROBERT F. SERVICE

With reporting by Michael Torrice.

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This article has been retracted

Science 16 January 2004:
Vol. 303. no. 5656, pp. 371 - 373
DOI: 10.1126/science.1089509

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REPORTS

A New Strategy for the Synthesis of Glycoproteins

Zhiwen Zhang,[1] Jeff Gildersleeve,[1] Yu-Ying Yang,[1] Ran Xu,[1] Joseph A. Loo,[2] Sean Uryu,[1] Chi-Huey Wong,[1] Peter G. Schultz[1]*

Posttranslational modifications of proteins regulate many biological processes, including metabolism, signal transduction, and gene expression. The synthetic challenges associated with generating homogeneous populations of selectively modified proteins, however, have hindered detailed studies of the effects of these modifications on protein structure and function. Here, we report an approach to the cotranslational synthesis of selectively glycosylated proteins in which the modified amino acid is genetically encoded. We show that myoglobin containing ß–*N*-acetylglucosamine (GlcNAc)–serine at a defined position can be expressed in *Escherichia coli* in good yield and with high fidelity. The ß-GlcNAc moiety can be recognized by a saccharide-binding protein, or subsequently modified with a galactosyltransferase to build more complex carbohydrates. This approach should be generally applicable to other posttranslational modifications such as protein phosphorylation, acetylation, and methylation.

[1] Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.
[2] Department of Biochemistry and Biological Chemistry, University of California at Los Angeles, 405 Hilgard Avenue, 402 Paul D. Boyer Hall, Los Angeles, CA 90095, USA.

* To whom correspondence should be addressed. E-mail: schultz@scripps.edu

Glycosylation is one of the most common posttranslational modifications of proteins in eukaryotes, and it affects a

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Retraction of Zhang *et al.*, *Science* 303 (5656) 371-373.

Science 27 November 2009:
Vol. 326. no. 5957, p. 1187
DOI: 10.1126/science.326.5957.1187-a

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LETTERS

Retraction

We wish to retract our Report (*1*) in which we report that β–N-acetylglucosamine-serine can be biosynthetically incorporated at a defined site in myoglobin in *Escherichia coli*. Regrettably, through no fault of the authors, the lab notebooks are no longer available to replicate the original experimental conditions, and we are unable to introduce this amino acid into myoglobin with the information and reagents currently in hand. We note that reagents and conditions for the incorporation of more than 50 amino acids described in other published work from the Schultz lab are available upon request.

Zhiwen Zhang,[1] Jeff Gildersleeve,[2] Yu-Ying Yang,[3] Ran Xu,[4] Joseph A. Loo,[5] Sean Uryu,[6] Chi-Huey Wong,[7] Peter G. Schultz[7]*

* To whom correspondence should be addressed. E-mail: schultz@scripps.edu

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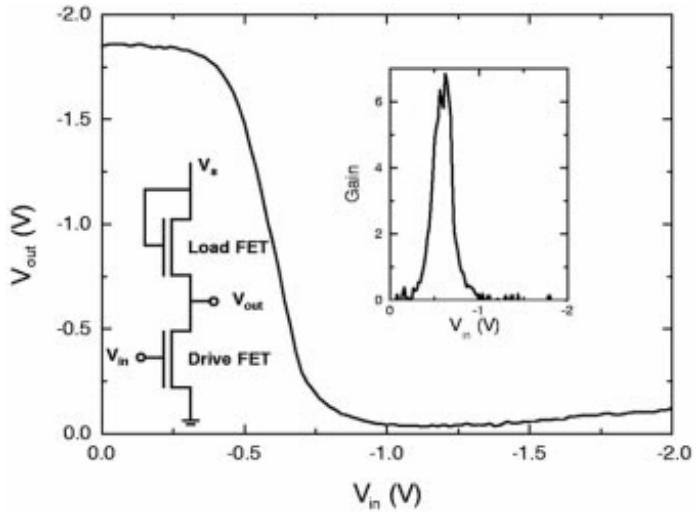
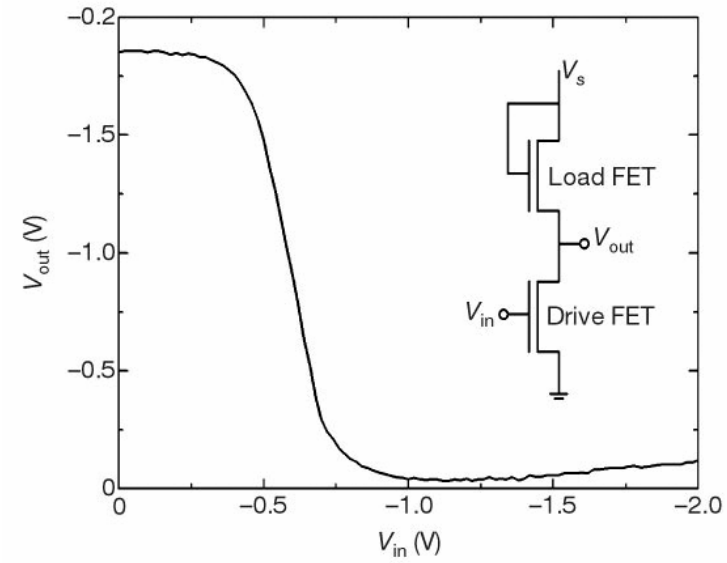
[4] 6330 Buffalo Speedway, Houston, TX 77005, USA.
[5] Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095–1569, USA.
[6] University of California, San Diego, CA 92121, USA.
[7] The Scripps Research Institute, La Jolla, CA 92037, USA.

Reference

1. Z. Zhang *et al.*, *Science* **303**, 371 (2004).[Abstract/Free Full Text]

Scott's pick: **Fabricating Science**





Jan Hendrik Schön

The short, prolific career of an ambitious young physicist.

Kate's pick

MsbA
EmrE

A dolphin's demise 1860

Indians wary of nuclear pact 1863

SCIENTIFIC PUBLISHING

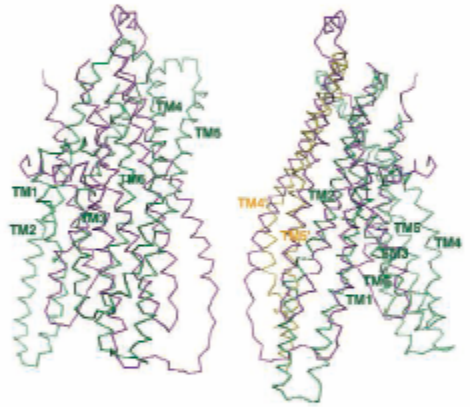
A Scientist's Nightmare: Software Problem Leads to Five Retractions

Until recently, Geoffrey Chang's career was on a trajectory most young scientists only dream about. In 1999, at the age of 28, the protein crystallographer landed a faculty position at the prestigious Scripps Research Institute in San Diego, California. The next year, in a ceremony at the White House, Chang received a Presidential Early Career Award for Scientists and Engineers, the country's highest honor for young researchers. His lab generated a stream of high-profile papers detailing the molecular structures of important proteins embedded in cell membranes.

Then the dream turned into a nightmare. In September, Swiss researchers published a paper in *Nature* that cast serious doubt on a protein structure Chang's group had described in a 2001 *Science* paper. When he investigated, Chang was horrified to discover that a homemade data-analysis program had flipped two columns of data, inverting the electron-density map from which his team had derived the final protein structure. Unfortunately, his group had used the program to analyze data for other proteins. As a result, on page 1875, Chang and his colleagues retract three *Science* papers and report that two papers in other journals also contain erroneous structures.

"I've been devastated," Chang says. "I hope people will understand that it was a mistake, and I'm very sorry for it." Other researchers don't doubt that the error was unintentional, and although some say it has cost them time and effort, many praise Chang for setting the record straight promptly and forthrightly. "I'm very pleased he's done this because there has been some confusion" about the original structures, says Christopher Higgins, a biochemist at Imperial College London. "Now the field can really move forward."

The most influential of Chang's retracted publications, other researchers say, was the 2001 *Science* paper, which described the structure of a protein called MsbA, isolated from the bacterium *Escherichia coli*. MsbA belongs to a huge and ancient family of molecules that use energy from adenosine triphosphate to transport molecules across cell membranes. These so-called ABC transporters perform many essential biological duties and are of great clinical interest because of their roles in drug resistance. Some pump antibiotics out of bacterial cells, for example; others clear chemotherapy drugs from cancer cells. Chang's MsbA structure was the first molecular portrait of an entire ABC transporter, and many researchers saw it as a major contribution toward figuring out how these crucial proteins do their jobs. That paper alone has been cited by 364 publications, according to Google Scholar.



Flipping fiasco. The structures of MsbA (purple) and Sav1866 (green) overlap little (*left*) until MsbA is inverted (*right*).

Two subsequent papers, both now being retracted, describe the structure of MsbA from other bacteria, *Vibrio cholera* (published in *Molecular Biology* in 2003) and *Salmonella typhimurium* (published in *Science* in 2005). The other retractions, a 2004 paper in the *Proceedings of the National Academy of Sciences* and a 2005 *Science* paper, described EmrE, a different type of transporter protein.

Crystallizing and obtaining structures of five membrane proteins in just over 5 years was an incredible feat, says Chang's former postdoc adviser Douglas Rees of the California Institute of Technology in Pasadena. Such proteins are a challenge for crystallographers because they are large, unwieldy, and notoriously difficult to coax into the crystals needed for x-ray crystallography. Rees says determination was at the root of Chang's success: "He has an incredible drive and work ethic. He really pushed the field in the sense of getting things to crystallize that no one else had been able to do." Chang's data are good, Rees says, but the faulty software threw everything off.

Ironically, another former postdoc in Rees's lab, Kaspar Locher, exposed the mistake. In the 14 September issue of *Nature*, Locher, now at the Swiss Federal Institute of Technology in Zurich, described the structure of an ABC transporter called Sav1866 from *Staphylococcus aureus*. The structure was dramatically—and unexpectedly—different from that of MsbA. After pulling up Sav1866 and Chang's MsbA from *S. typhimurium* on a computer screen, Locher says he realized in minutes that the MsbA structure was inverted. Interpreting the "hand" of a molecule is always a challenge for crystallographers, Locher notes, and many mistakes can lead to an incorrect mirror-image structure. Getting the wrong hand is "in the category of monumental blunders," Locher says.

On reading the *Nature* paper, Chang quickly traced the mix-up back to the analysis program, which he says he inherited from another lab. Locher suspects that Chang would have caught the mistake if he'd taken more time to obtain a higher resolution structure. "I think he was under immense pressure to get the first structure, and that's what made him push the limits of his data," he says. Others suggest that Chang might have caught the problem if he'd paid closer attention to biochemical findings that didn't jibe well with the MsbA structure. "When the first structure came out, we and others said, 'We really ▶

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RETRACTED 22 DECEMBER 2006; SEE LAST PAGE

RESEARCH ARTICLE

RETRACTED 22 DECEMBER 2006; SEE LAST

REPORTS

RETRACTED 22 DECEMBER 2006; SEE LAST

Science 2006 Dec

LETTERS

edited by Etta Kavanagh

Retraction

WE WISH TO RETRACT OUR RESEARCH ARTICLE "STRUCTURE OF MsbA from *E. coli*: A homolog of the multidrug resistance ATP binding cassette (ABC) transporters" and both of our Reports "Structure of the ABC transporter MsbA in complex with ADP•vanadate and lipopolysaccharide" and "X-ray structure of the EmrE multidrug transporter in complex with a substrate" (*1*–*3*).

The recently reported structure of Sav1866 (*4*) indicated that our MsbA structures (*1*, *2*, *5*) were incorrect in both the hand of the structure and the topology. Thus, our biological interpretations based on these inverted models for MsbA are invalid.

An in-house data reduction program introduced a change in sign for anomalous differences. This program, which was not part of a conventional data processing package, converted the anomalous pairs (I+ and I–) to (F– and F+), thereby introducing a sign change. As the diffraction data collected for each set of MsbA crystals and for the EmrE crystals were processed with the same program, the structures reported in (*1*–*3*, *5*, *6*) had the wrong hand.

The error in the topology of the original MsbA structure was a consequence of the low resolution of the data as well as breaks in the electron density for the connecting loop regions. Unfortunately, the use of the multicopy refinement procedure still allowed us to obtain reasonable refinement values for the wrong structures.

The Protein Data Bank (PDB) files 1JSQ, 1PF4, and 1Z2R for MsbA and 1S7B and 2F2M for EmrE have been moved to the archive of obsolete PDB entries. The MsbA and EmrE structures will be recalculated from the original data using the proper sign for the anomalous differences, and the new Cα coordinates and structure factors will be deposited.

We very sincerely regret the confusion that these papers have caused and, in particular, subsequent research efforts that were unproductive as a result of our original findings.

GEOFFREY CHANG, CHRISTOPHER B. ROTH, CHRISTOPHER L. REYES, OWEN PORNILLOS, YEN-JU CHEN, ANDY P. CHEN

Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA 92037, USA.

References

1. G. Chang, C. B. Roth, *Science* **293**, 1793 (2001).
2. C. L. Reyes, G. Chang, *Science* **308**, 1028 (2005).
3. O. Pornillos, Y.-J. Chen, A. P. Chen, G. Chang, *Science* **310**, 1950 (2005).
4. R. J. Dawson, K. P. Locher, *Nature* **443**, 180 (2006).
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6. C. Ma, G. Chang, *Proc. Natl. Acad. Sci. U.S.A.* **101**, 2852 (2004).

Science 2001 Sept

Science 2005 May

Science 2005 Dec

doi:10.1016/S0022-2836(03)00587-4 J. Mol. Biol. (2003) 330, 419–430

JMB Available online at www.sciencedirect.com SCIENCE DIRECT®

Structure of MsbA from *Vibrio cholera*: A Multidrug Resistance ABC Transporter Homolog in a Closed Conformation

Geoffrey Chang

Department of Molecular Biology, CB-105, The Scripps Research Institute, La Jolla, CA 92037, USA

The spread of multidrug resistance (MDR) is a world health crisis that presents a significant challenge to the treatment of cancer and infection. MDR can be caused by a group of ABC (MDR-ABC) transporters that move hydrophobic drug molecules and lipids across the cell membrane. To gain insight into the conformational changes these transporters undergo when flipping hydrophobic substrates across the lipid bilayer, we have determined the structure of the lipid flippase MsbA from *Vibrio cholera* (VC-MsbA) to 3.8 Å. Structural comparison of VC-MsbA to MsbA from *Escherichia coli* reveals that the transporters share a structurally conserved core of transmembrane α-helices, but differ in the relative orientations of their nucleotide-binding domains (NBD). The transmembrane domain of VC-MsbA is captured in a closed conformation and the structure supports a "power stroke" model of transporter dynamics where opposing NBDs associate upon ATP binding. The separation of the α and β domains of the NBD suggests the possibility that their association could render them competent to bind ATP and gives further insight into the structural basis for catalytic regulation.

Keywords: multidrug resistance; integral membrane proteins; X-ray crystallography

Introduction

Multidrug resistance (MDR) is a rampant health problem and presents a major obstacle to the treatment of diseases and the development of effective therapeutics. In the treatment of cancer, for example, MDR has significantly limited the success of chemotherapy and results in a higher patient mortality rate. MDR can arise by the efflux of drug molecules by transporters that are located in the cell membrane. One of these, the human P-glycoprotein (human P-gp), can transport a diverse class of amphipathic drug molecules and lipids.[1] Several of these molecules are large and would require the transporter to undergo substantial structural rearrangements in order to accommodate their translocation. Exactly how MDR transporters structurally rearrange during transport is a fundamental question that remains to be answered. In an effort to understand the molecular architecture of ABC exporters, we have determined the structure of MsbA from the human pathogen *Vibrio cholera* (VC-MsbA).

MsbA belongs to one of the largest superfamilies of proteins characterized by a highly conserved adenosine triphosphate (ATP) binding cassette (ABC), which is also called a nucleotide binding domain (NBD).[2,3] All ABC transporters are composed minimally of two transmembrane domains (TMDs) and two NBDs. ABC transporters couple the energy of ATP hydrolysis to the import or export of a vast array of substrates that includes such diverse molecules as amino acids, ions, sugars, proteins, lipids, and drugs. While bacterial genomes encode genes for both classes of ABC transporter, in eukaryotes only exporters are found, which may be explained by an early evolutionary divergence between the two classes.[4] In humans, 46 ABC transporters have been identified to date, all of which are believed to encode exporters.[5] Several of these exporters are essential in cellular function and loss of their proper

doi:10.1016/j.jmb.2003.05.001 J. Mol. Biol. (2007) 369, 596

JMB Available online at www.sciencedirect.com ScienceDirect ELSEVIER

RETRACTION

Retraction of "Structure of MsbA from *Vibrio cholera*: A Multidrug Resistance ABC Transporter Homolog in a Closed Conformation" [J. Mol. Biol. (2003) 330 419–430]

Geoffrey Chang

This article has been retracted at the request of the authors.

The recently reported structure of Sav1866[4] indicated that our MsbA structures[1–3] were incorrect in both the hand of the structure and the topology. Thus, our biological interpretations based on the inverted models for MsbA are invalid.

An in-house data reduction program introduced a change in sign for anomalous differences. This program, which was not part of a conventional data processing package, converted the anomalous pairs (I+ and I−) to (F− and F+), thereby introducing a sign change. As the diffraction data collected for each set of MsbA crystals[1–3] were processed with the same program, the structures reported had the wrong hand.

The error in the topology of the original MsbA structure was a consequence of the lower resolution of the data as well as breaks in the electron density for the connecting loop regions. Unfortunately, the use of the multicopy refinement procedure allowed us to obtain reasonable refinement values for the wrong structures.

The Protein Data Bank (PDB) file 1PF4 has been moved to the archive of obsolete PDB entries. The structures will be recalculated from the original data using the proper sign for the anomalous differences, and the new Cα coordinates and structure factors will be deposited.

We sincerely regret the confusion that these papers have caused and, in particular, for subsequent research efforts that were unproductive as a result of our original findings.

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1. Chang, G. (2003). Structure of MsbA from Vibrio cholera: a multidrug resistance ABC transporter homolog in a closed conformation. *J. Mol. Biol.* **330**, 419–430.
2. Chang, G. & Roth, C. B. (2001). Structure of MsbA from E. coli: a homolog of the multidrug resistance ATP binding cassette (ABC) transporters. *Science*, **293**, 1793–1800.
3. Reyes, C. L. & Chang, G. (2005). Structure of the ABC transporter MsbA in complex with ADP.vanadate and lipopolysaccharide. *Science*, **308**, 1028–1031.
4. Dawson, R. J. & Locher, K. P. (2006). Structure of a bacterial multidrug ABC transporter. *Nature*, **443**, 180–185.

DOI of original article: 10.1016/S0022-2836(03)00587-4
E-mail address of the corresponding author: gchang@scripps.edu

Proc Natl Acad Sci U S A. 2004 March 2; 101(9): 2852–2857. PMCID: PMC365709
Published online 2004 February 17. doi: 10.1073/pnas.0400137101.

Biophysics

This article has been retracted

Structure of the multidrug resistance efflux transporter EmrE from *Escherichia coli*

Che Ma and Geoffrey Chang*

Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, CB-105, La Jolla, CA 92037
* To whom correspondence should be addressed. E-mail: gchang@scripps.edu.
Communicated by Douglas C. Rees, California Institute of Technology, Pasadena, CA, January 7, 2004

Received November 13, 2003.

This article has been retracted. See Proc Natl Acad Sci U S A. 2007 February 27; 104(9): 3668.
This article has been cited by other articles in PMC.

ABSTRACT

Other Sections

Multidrug resistance efflux transporters threaten to reverse the progress treating infectious disease by extruding a wide range of drug and other cytotoxic compounds. One such drug transporter, EmrE, from the small multidrug resistance family, utilizes proton gradients as an energy source to drive substrate translocation. In an effort to understand the molecular structural basis of this transport mechanism, we have determined the structure of EmrE from *Escherichia coli* to 3.8 Å. EmrE is a tetramer comprised of two conformational heterodimers related by a pseudo two-fold symmetry axis perpendicular to the cell membrane. Based on the structure and biochemical evidence, we propose a mechanism by which EmrE accomplishes multidrug eff ges between two heterodimers with pro ity and compact size, the structure of Em standing the general structural ba fflux systems.

PNAS 2004 March

Retracted on 2007 Feb

Retractions

BIOPHYSICS. For the article "Structure of the multidrug resistance efflux transporter EmrE from *Escherichia coli*," by Che Ma and Geoffrey Chang, which appeared in issue 9, March 2, 2004, of *Proc Natl Acad Sci USA* (101:2852–2857; first published February 17, 2004; 10.1073/pnas.0400137101), the authors wish to note the following: "We have recently discovered that the structure was determined in the incorrect hand. An in-house data reduction program introduced a change in sign for anomalous differences. This program, which was not part of a conventional data processing package, converted the anomalous pairs (I+ and I−) to (F− and F+), thereby introducing a sign change that resulted in the structure being reported in the wrong hand. The Protein Data Bank file (PDB ID code 1S7B) has been moved to the archive of obsolete PDB entries. The structures will be recalculated from the original data, using the proper sign for the anomalous differences, and the new Cα coordinates and structure factors will be deposited. We sincerely regret any confusion that this error may have caused and, in particular, we regret that subsequent research efforts might have been unproductive as a result of our originally published findings. We therefore wish to retract this article."

Che Ma
Geoffrey Chang

www.pnas.org/cgi/doi/10.1073/pnas.0700711104

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Home > Science Magazine > E-Letters

E-Letter responses to:

n-week:
Greg Miller
SCIENTIFIC PUBLISHING: A Scientist's Nightmare: Soft
Five Retractions
Science 2006; 314: 1856-1857 [Summary] [Full text] [

PUBLISHED E-LETTER RESPONSES:

A Rough Time
Jay Pravda M.D. (23 March 2007)

A Rough Time

Jay Pravda M.D., Medical Research *Inflammatory Disease Research Center*

I am amazed that research that co for publication or not funded. Had have taken 5 years to correct this ramifications.

Respond to this E-Letter: Re: A Rough Time

It is not possible for reviewers to c possible to submit every research science has to identify and correct when subsequent contradictory (an funded to begin with.

Reviewers should realize that new tentatively wrong. The final outcom replicate the same work. This is an rough time" (*1*) regardless of the c

Perhaps groundbreaking results sh publication and not years later afte

Reference

1. G. Miller, *Science*, 314, p. 1856(

E-Letters: Submit a response

A Sign, a Flipped Structure, and a Scientific Flameout of Epic Proportions

update: fixed some typos, thanks to t

One of the most spectacular flameou short letter (barely over 300 words lor issue of 2006, Geoffrey Chang, a crys articles, a Nature article, a PNAS artic years of work was destroyed, appare data-processing program.

Geoffrey Chang was one of the young Institute, La Jolla. Winner of a slew of name solving the crystal structure of arguably the most difficult type of prot nature of the trans-membrane surfac

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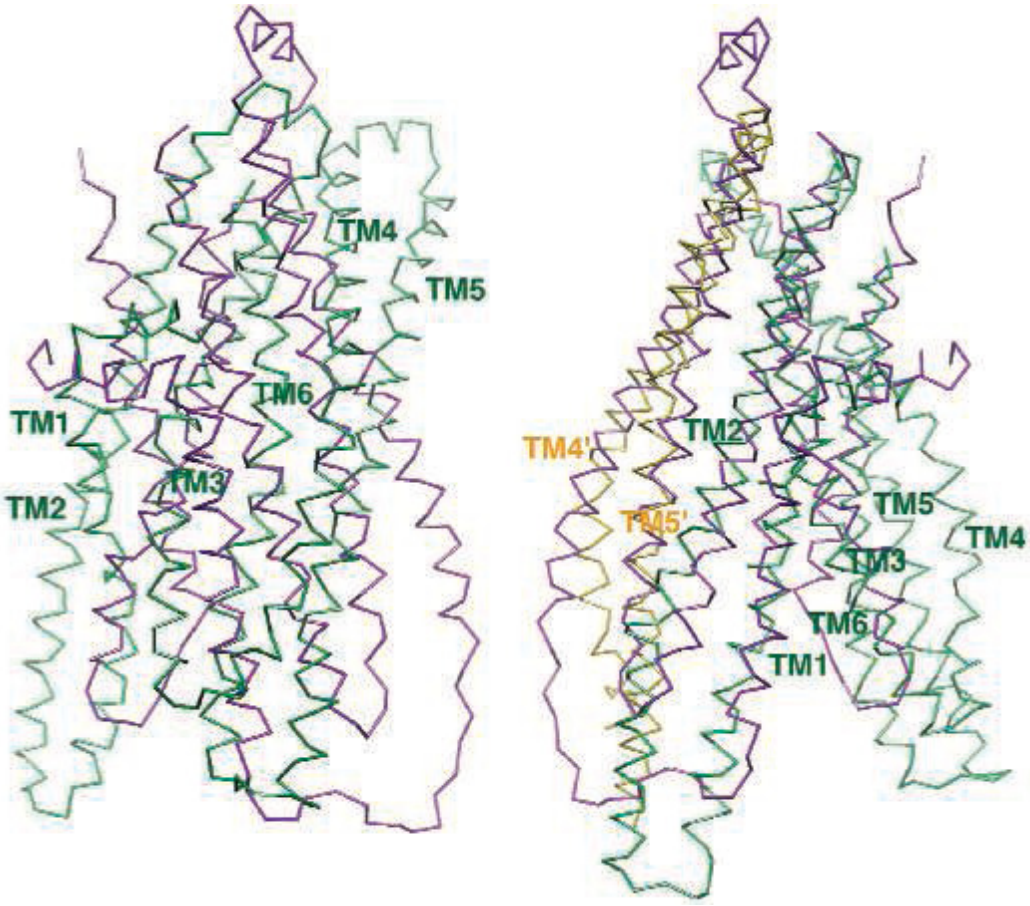
By Andrea Gawrylewski

Retractions unsettle structural bio

Recent findings upend conclusions from five highly-cited papers

[Published 4th January 2007 03:08 PM GMT]

Scientists from the Scripps Research Institute led by Geoffrey Chang have retracted three highly-cited papers (1, 2, 3) in *Science* on ATP binding cassette transporters, stating that new findings by another group invalidated their proposed structure and biology of the transporters. Two more retractions will appear in upcoming issues of the *Journal of Molecular Biology* and *Proceedings of the National Academy of Science*. The retracted papers span more than five years of work.



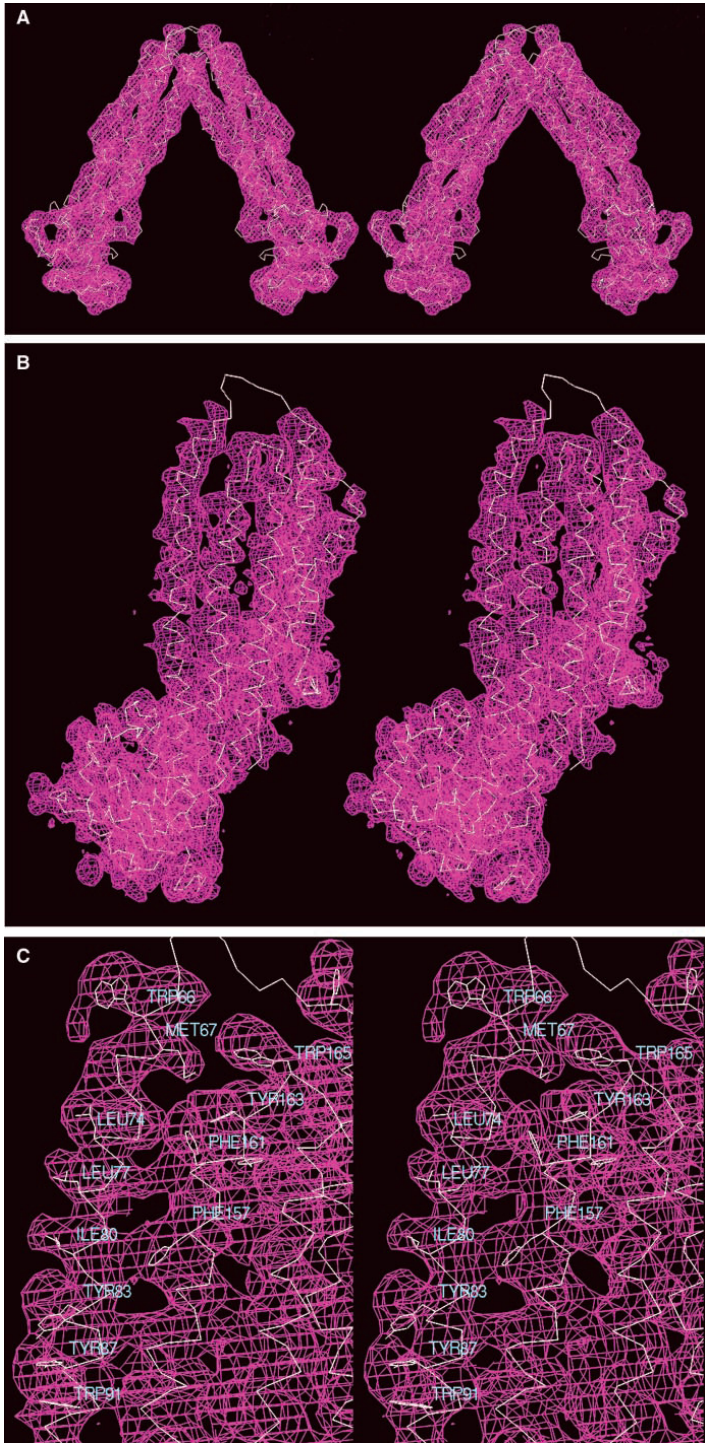
Flipping fiasco. The structures of MsbA (purple) and Sav1866 (green) overlap little (*left*) until MsbA is inverted (*right*).

Phases

= a program package for the processing and analyzing diffraction data from macromolecules.

"An in-house data reduction program introduced a change in sign for anomalous differences.

This program, which was not part of a conventional data processing package, converted the anomalous pairs (I+ and I-) to (F- and F+), thereby *introducing a sign change*."



" Iterative eightfold noncrystallographic symmetry averaging, solvent flattening/flipping, phase extension, and amplitude sharpening using in-house programs yielded electron density maps of excellent quality for tracing a polypeptide chain (Fig. 3) (*29*)."

29. The package PHASES was used for all phase calculations with multiple isomorphous and all anomalous scattering data.

The correct hand of the structure was established by observing the hand of the a-helices in the sharpened 4.5 □ electron density map and also confirmed when docking a fragment of the hisP to the NBD density.

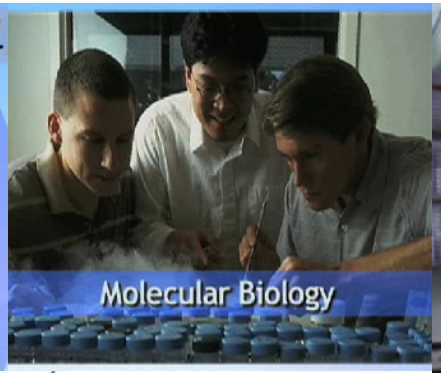
Eightfold non-crystallographic symmetry averaging, solvent fattening/fipping, phase extension, and amplitude sharpening were accomplished using locally written software (G. Chang, unpublished data) and yielded electron density maps that were of excellent quality for model building.

2006 September, Roger Dawson and Kasper Locher published their paper in *Nature*, presenting a new, highly-resolved structure of a homologous transporter, which illustrated an inherent flaw in Chang et al's research.

THE SCRIPPS RESEARCH INSTITUTE

1924

Ellen Browning Scripps



Geoffrey Chang

Associate Professor
Department of Molecular Biology
TSRI - 1999

Joint Appointments

The Skaggs Institute for Chemical Biology

Education

Ph.D., University of Pennsylvania, 1996

Awards & Activities

Presidential Early Career Award for Scientists and Engineers, Office of Science and Technology Policy of the White House.

Research Focus

Structural Biology Of Integral Membrane Proteins

The Nobel Prize in Physiology or Medicine 1972

"for their discoveries concerning the chemical structure of antibodies"

Gerald M. Edelman

The Nobel Prize in Chemistry 2002

"for the development of methods for identification and structure analyses of biological macromolecules"

Kurt Wüthrich

K. Barry Sharpless

The Nobel Prize in Chemistry 2001

"for his work on chirally catalysed oxidation reactions"

Summary

1. Structure of MsbA from E. coli: A Homolog of the Multidrug Resistance ATP Binding Cassette (ABC) Transporters. Science 2001 – 2006 Chang et al.
2. Structure of MsbA from Vibrio cholera: a multidrug resistance ABC transporter homolog in a closed conformation. JMB 2003 – 2007 Chang.
3. Structure of the multidrug resistance efflux transporter EmrE from Escherichia coli. PNAS 2004 – 2007 Ma et al.
4. Structure of the ABC Transporter MsbA in Complex with ADP·Vanadate and Lipopolysaccharide. Science 2005 – 2006 Reyes et al.
5. X-ray Structure of the EmrE Multidrug Transporter in Complex with a Substrate. Science 2005 -2006 Pornillos et al.

- The five retracted papers have been cited 729 times since their publication.

Prashant's pick

Plagiarism: copied text

Biology

- *In vitro* development of human germ line cells from embryonic stem cells
- Eventually develops into haploid motile, sperm-like cells

When Where and How?

- Published online (8th July, 2009) in Stem Cells and development without proof reading and copy editing!
- No problems with the science or conclusion of the paper
- On 21st July, 2009 paper was retracted
- Jae Ho Lee (Post-doc) was removed from the authorship
- Newcastle University is standing behind this group

Two copied paragraphs

Original text from 2007 review

and the emergence of postmigratory PGCs can occur spontaneously or be induced in EBs.

Using EBs, Geijsen et al. also suggested a spontaneous emergence of male PGCs from mouse ESCs in vitro [23]. Furthermore, the authors detected and isolated haploid cells from EBs, and showed that the injection of the cells into eggs resulted in the formation of blastocyst-like structures. Although the isolated cells did not resemble spermatozoa and analyses of further embryonic development was not completed, this study suggested that male PGCs arise from ESCs and spontaneously become postmeiotic cells that are capable of activating eggs.

Recently, Nayernia et al. reported not only the induction of male gametes from ESCs but also successful production of offspring [24]. These authors cultured mouse ESCs, which were transfected with a *Stra8* (stimulated by retinoic acid gene

Online version published in July, 2009

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Using EBs, Geijsen et al. also suggested a spontaneous emergence of male PGCs from mouse ESCs in vitro [7]. Furthermore, the authors detected and isolated haploid cells from EBs, and showed that the injection of the cells into eggs resulted in the formation of blastocyst-like structures. Although the isolated cells did not resemble spermatozoa and analyses of further embryonic development were not completed, this study suggested that male PGCs arise from ESCs and spontaneously become postmeiotic cells that are capable of activating eggs.

Recently, Nayernia et al. reported not only the induction of male gametes from ESCs but also successful production of offspring [8]. These authors cultured mouse ESCs, which were transfected with a *Stra8* (stimulated by retinoic acid gene 8)-reporter

yer, RA treatment, *Stra8*$^+$ cells for culture — I — IVF, morula-like, transplantation into testes

yer, RA treatment, *Stra8*$^+$ cells for culture — I — Transplantation into testes

S — Meiotic gene expression

otamine 1; *Stra8*, stimulated by retinoic acid gene 8; MSC, mesenchymal stem

h, human.
germ line.

development (e.g., *DDX4*, *DAZL*). Furthermore, cells expressing a meiotic marker gene, *SYCP3*, were identified in human EBs. Thus, this study suggested the possibility that human ESCs of both sexes may spontaneously enter the germ line and undergo meiosis.

NEED FOR FUTURE STUDIES

These studies collectively indicate that the derivation of mammalian germ cells, both female and male, is possible in vitro from pluripotent stem cells. These in vitro systems can be

transferred to surrogate mothers, seven five pups carrying the *Prm1*-reporter gene were derived, which apparently had growth abnormalities and died within 5 months after birth.

The ability of human ESCs to enter the germ line was examined by Clark et al. [10]. These authors generated EBs from female and male human ESCs and found using PCR or immunohistochemistry that some cells in EBs expressed marker genes specific to different stages of germ line development (e.g., *DDX4*, *DAZL*). Furthermore, cells expressing a meiotic marker gene, *SYCP3*, were identified in human EBs. Thus, this study suggested the possibility that human ESCs of both sexes may spontaneously enter the germ line and undergo meiosis.

In present study, we have developed a strategy for the establishment of germline stem cells from human embryonic stem cells which are able to enter and complete meiosis and produce sperm-like cells.

Ben's pick

Ohio University Engineering College Plagued with Plagiarism

"...some papers included words or even pages that had been copied from other research work or published books." VOA

(Tom), "says in one case more then 50 pages had been copies (sic), and another 14 pages, including typos." NPR

Plagiarism in Grad students' theses

- 2005 former student, Tom Matrka investigating dishonesty among colleagues, after dispute with advisor over thesis proposal
- reviewed by 2 university officials
- "rampant and flagrant plagiarism" (40 theses)
- most problems in literature review section
- some material appeared again and again
- many were students of Jay S. Gunasekera and Bhavin V. Mehta

Example

$$\dot{\varepsilon}_{ii} = 0. \tag{1.3}$$

During gross plastic deformation, the plastic components of strains are considerably larger than the elastic components; therefore, the elastic portion of the deformation is simply ignored. Since plastic deformation in metals always occurs without volume change, incompressibility will always apply. When incompressibility prevails, the displacement fields, which led to the associated strain components, is termed a compatible displacement field.

For upper bound analysis of plastic deformations, the instantaneous picture, rather than the relations between the initial and final shapes, is important. Thus, the displacement vector is replaced by a velocity vector, $\dot{U}_i$, describing the velocity of each point in the deforming body at any specific moment. With the velocity vector, components of the strain tensor become

$$\dot{\varepsilon}_{ij} = \frac{1}{2}\left[\frac{\partial \dot{U}_i}{\partial x_j} + \frac{\partial \dot{U}_j}{\partial x_i}\right]. \tag{1.4}$$

Compatibility and the law of incompressibility lead to the relation

$$\dot{\varepsilon}_{ii} = 0. \tag{1.5}$$

1.2.4. Instantaneous Yield Conditions

In metal forming operations, sufficient forces are imparted by a tool to cause the internal strains and stresses to surpass the elastic limit. The actual conditions that control the yielding are complicated and defy formulation, thus, many simplified rules such as maximum tensile load, maximum shear stress, etc. have been proposed as criteria to

determine when the plastic state is reached. One of the widely used criteria used to determine yielding, proposed by von Mises, states that plastic flow commences when a certain combination of the components of the stress deviatoric tensor reaches a characteristic value. In mathematical form, Mises criteria can be stated as

$$J_2 = \frac{1}{2} S_{ij} S_{ij} \le \frac{\sigma_0^2}{3}, \tag{1.6}$$

where J_2 is the second invariant of the stress deviator tensor, S_{ij} are the components of stress deviator tensor, and σ_0 is the yield strength in simple tension.

Consequently, for a complete solution, the components of the stress tensor must obey Mises' yield criterion throughout the entire domain. This restriction supplements the demand for force equilibrium as expressed by the differential equations of equilibrium. These are the restrictions imposed on the stress tensor σ_{ij}. Demands on the strains or strain rates were expressed separately in the form of compatibility or volume constancy. In reality, however, for any material, stresses and strains are introduced simultaneously as the workpiece is loaded. Hence, the components of the stress tensor are related to the components of the strain and strain rate tensors.

For large-scale plastic deformation in metals, the relations between the stresses and flow are very complex and not fully determined. When the factors such as strain hardening, strain rate effects, temperature changes, inhomogeneity, anisotropy, etc. are considered, it becomes clear that an exact relation may be unattainable.

The first approach to the plastic stress-strain relations was suggested by Saint-Venant [5], who proposed that the principle axis of strain increment coincided with the

The Defense...

- Most of the offending students came from other countries
  - limited english skills?
  - limited knowledge of rules of writing
- Gunasekera had previously taught in Australia and Sri Lanka, and was not familiar with US standards of citations
  - but problem goes back 20+ years!

Consequences

- Theses required to be rewritten or revoked
- former students defend theses again and re-enroll
- Ph.D students suspended until master's theses re-written
- a University committee recommended firing Gunasekera and another prof, Mehta
- Mehta left Ohio U
- Gunasekera stepped down from dept chair and lost "distinguished prof" title
- Gunasekera is suing Ohio U for defamation

Ongoing fallout

- as of 1/14/2010 – federal judge ordered that the university hold a public hearing where Gunasekera can attempt to clear his name
- problems not limited to mech eng dept
- Chair of Ac Honesty Hearing Committee approved a Ph.D. dissertation that contains plagiarism

Ed's pick

Scientific Misconduct: Chinese Researchers Debate Rash of Plagiarism Cases

Li Xiguang, Xiong Lei

Science 18 October 1996: Vol. 274. no. 5286, pp. 337 – 0 DOI: 10.1126/science.274.5286.337

Plagiarism - "use or close imitation of the language and thoughts of another author and the representation of them as one's own original work."

1995 *Random House Compact Unabridged Dictionary*

Accidental or Deliberate?

Does it matter?

Li Fubin Papers

- Published two papers identical to earlier papers
- Made up an additional 23 papers!
- Plagiarism!

Pan Aihua Paper

- Others point out Pan Aihua paper is 1/3 identical to another paper.
- Admits: “significant degree of identity in the wording”
- Not plagiarism (?): "because we have all the original data."

CJ's pick

Published online August 31, 2009

PKNOX2 gene is significantly associated with substance dependence in European-origin women

Xiang Chen[a,1], Kelly Cho[a,1], Burton H. Singer[b,2], and Heping Zhang[a]

[a]Department of Epidemiology and Public Health, Yale University School of Medicine, Ne
Princeton University, Princeton, NJ 08544

Contributed by Burton H. Singer, August 1, 2009 (sent for review March 18, 2009)

Substance dependence is a complex environmental and genetic disorder that results in serious health and socioeconomic consequences. Many studies have reported and implicated genes associated with various substance dependence outcomes, including addiction to nicotine and addiction to alcohol. Using data from several genome-wide case-control studies, we conducted a genome-wide association study of a composite substance dependence phenotype derived from six individual diagnoses: addiction to nicotine, alcohol, marijuana, cocaine, opiates, or other drugs as a whole. We identified a strong (odds ratio = 1.77) and significant (*P* value = 7E-8) association signal with the PBX/knotted 1 homeobox 2 (PKNOX2) gene on chromosome 11 in European-origin women with the composite phenotype. Our findings also indicate that the associations are not as significant when individual outcomes for addiction are considered, underscoring the importance of considering multiple addiction types.

comorbidity | genetics of addiction | genomewide a

There is strong evidence that vulnerabili
pendence or addiction (drugs, alcohol,
complex trait with both genetic and environ
(1–3). Whether legal or illicit, substance abus
sought-after phenomena in many populati
serious health and socioeconomic consequ
Centers for Disease Control and Prevent
443,000 deaths were caused by cigarette sm
to second-hand smoke (4). In addition, alcoh
linked to attempted and successful suicide,
adolescents (5). Clearly, a better understand

Why data-sharing policies matter

Alan E. Guttmacher[a,1], Elizabeth G. Nabel[b], and Francis S. Collins[c]

[a]*National Human Genome Research Institute, National Institutes of Health, Bethesda, MD 20892;* [b]*National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD 20892;* and [c]*National Institutes of Health, Bethesda, MD 20892*

Data from biomedical research are more broadly available to the research community today than in the past. Technical developments, such as web-based databases, have played a role in this transition, but so has a fundamental shift in the view of who "owns" research data. The model of the investigator owning data has been increasingly replaced by one in which society owns data. Scien-

The interests of the investigator who places data in an accessible database also require protection. The major available protection is the guarantee of a period of exclusivity in submission of abstracts and publications for a number of months (usually 6 to 12). This exclusive period is assured by allowing data access only to end users who agree to abide by it. The investigator also frequently profits both from the value

cess, including a 12-month period of exclusivity.

A recent breach by a recipient investigator of the Data Use Certification led to the on-line publication by PNAS of a manuscript that should never even have been submitted (2). While both PNAS and the NIH will deal with this specific breach, it is the wider research community that must police itself and prevent inappropriate publication in the future.
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research miscon-
at the NIH design
alerting the re-
his issue and im-
ke breaches diffi-
sy to discover.
benefits the re-
society. We must
in protecting the
participants and
if this important

EDITORIAL

PNAS takes action regarding breach of NIH embargo policy on a PNAS paper

After the paper titled "PKNOX2 gene is significantly associated with substance dependence in European-origin women," by

agreed to retract their work in PNAS on September 9, 2009.

Although the scientific community is often viewed as self-correcting, the system failed for this paper. It appears hat not all of the coauthors were ware of the embargo agreement, and he referees and the editors did not now that a serious breach of scientific onduct and NIH policy had taken lace. This oversight does a disservice o the SAGE investigators on this National Human Genome Research nstitute-funded genetic study of addiction, the other investigators who bided by the NIH embargo, and the cientific community.

PNAS takes such breaches in conduct eriously and moved quickly and decively to address the situation. Because he NIH embargo had been broken and he PNAS paper published, neither action could be reversed. The editors and authors, after discussions with NIH and the SAGE principal investigators, agreed that the authors would retract their paper promptly, with a retraction notice appearing online and in print. The paper will not appear in the print edition of PNAS, which will contain only the retraction statement. The watermark "See Retraction Published September 9, 2009" has been added to the paper in PNAS Online, with a link to the retraction notice.

PNAS hopes that this case will emphasize the importance of maintaining the highest ethical standards regarding publication, and will assure the scientific community that sanctions will be levied for those whose actions, whether intentional or through oversight, contradict accepted research practices.

Randy Schekman, *Editor-in-Chief*

ld be addressed: Email:

icy on a PNAS paper. *Proc*
/pnas.0910317106.

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PNAS

Proceedings of the National Academy of Sciences of the United States of America

Retraction

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This Article

Published online before print September 9, 2009, doi: 10.1073/pnas.0910252106

PNAS October 6, 2009 vol. 106 no. 40 17241

Retraction to Chen et al.

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This Week's Issue

February 2, 2010, 107 (5)

From the Cover

- Reproductive strategies in baboons
- Metal template for a stable protein
- Mouse model for hereditary bone tumors
- Uncovering camouflage
- Intermolecular cooperation in g-protein

GENETICS, SOCIAL SCIENCES Retraction for "PKNOX2 gene is significantly associated with substance dependence in European–origin women," by Xiang Chen, Kelly Cho, Burton H. Singer, and Heping Zhang, which published online August 31, 2009, in *Proc Natl Acad Sci USA* (10.1073/pnas.0908521106).

The authors wish to retract this paper because its publication violates the Gene Environment Association Studies Genes and Environment Initiative Study of Addiction: Genetics and Environment (SAGE) dataset's embargo policy. The SAGE data access agreement states that investigators agree not to submit findings of the SAGE dataset(s) for publication until September 23, 2009. The authors sincerely apologize for this violation of SAGE policy.

Xiang Chen

Kelly Cho

Burton H. Singer

Heping Zhang

Retracted online September 6, 2009

SCIENTIFIC PUBLISHING

Paper Retracted Following Genome Data Breach

Here's a nightmare scenario: You go to the Web site of a leading journal, and there on your screen is a paper based on data you have painstakingly gathered but not yet had time to analyze.

That's what happened to psychiatrist Laura Bierut, who discovered last week that other researchers had broken an embargo on use of data she and her colleagues had deposited in dbGaP, the National Institutes of Health's (NIH's) database of genotypes and phenotypes. Bierut, a professor at Washington University in St. Louis in Missouri, and colleagues had collected the data as part of genetic studies of alcoholism and other addictions collectively known as SAGE (Study of Addiction: Genetics and Environment).

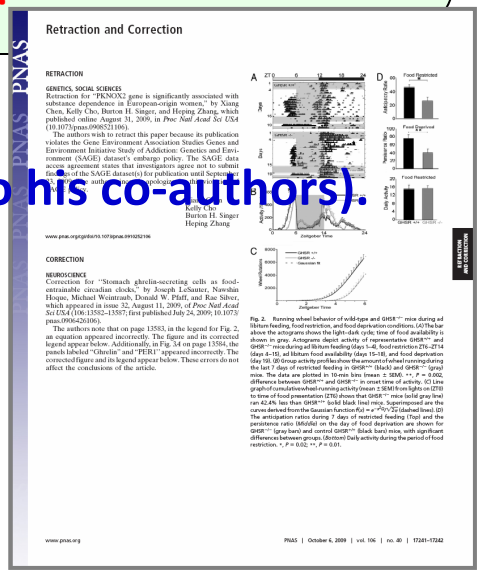
dbGaP was established in 2006 to facilitate sharing of the oceans of genetic data generated by federal grantees. Other scientists can submit papers based on the material after an embargo period of 9 to 12 months so those who generated the data can have first crack at analyzing them.

The SAGE embargo ends on 23 September. But on 31 August, a paper based on

Scooped. Another team broke the databa
and published a paper using Laura Bierut

- NIH database of genotype and phenotype (dbGaP)
- SAGE (Study of Addiction: Genetics and Environment)
- Policy: data embargo for 9-12 months
- This SAGE data embargo ended Sep. 23, 2009
- Chen et al. paper published online Aug. 31, 2009
- Submitted in March 2009
- Caught by the data generator!

Published by AAAS



Retraction and Correction

RETRACTION

GENETICS, SOCIAL SCIENCES

Retraction for "PKNOX2 gene is significantly associated with substance dependence in European-origin women," by Xiang Chen, Kelly Cho, Burton H. Singer, and Heping Zhang, which published online August 31, 2009, in *Proc Natl Acad Sci USA* (10.1073/pnas.0908521106).

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Kelly Cho
Burton H. Singer
Heping Zhang

www.pnas.org/cgi/doi/10.1073/pnas.0910252106

CORRECTION

NEUROSCIENCE

Correction for "Stomach ghrelin-secreting cells as food-entrainable circadian clocks," by Joseph LeSauter, Nawshin Hoque, Michael Weintraub, Donald W. Pfaff, and Rae Silver, which appeared in issue 32, August 11, 2009, of *Proc Natl Acad Sci USA* (106:13582–13587; first published July 24, 2009; 10.1073/pnas.0906426106).

The authors note that on page 13583, in the legend for Fig. 2, an equation appeared incorrectly. The figure and its corrected legend appear below. Additionally, in Fig. 3*A* on page 13584, the panels labeled "Ghrelin" and "PER1" appeared incorrectly. The corrected figure and its legend appear below. These errors do not affect the conclusions of the article.

www.pnas.org

PNAS | October 6, 2009 | vol. 106 | no. 40 | 17241–17242

- Zhang signed the data-sharing agreement (unbeknown to his co-authors).
- Paper never made it to the printer.
- BUT the retraction did (Oct 6, 2009)!
- PNAS may modify the author checklist.
- Zhang may be further sanctioned by NIH.

Baggi's pick

Even Retracted Papers Endure

KATHERINE UNGER AND JENNIFER COUZIN

www.sciencemag.org

SCIENCE VOL 312 7 APRIL 2006

Even Retracted Papers Endure

Like ghosts riffling the pages of journals, retracted papers live on. Using Thomson Scientific's ISI Web of Knowledge and Google Scholar, Science found dozens of citations of retracted papers in fields from physics to cancer research to plant biology.

Seventeen of 19 retracted papers co-authored by German cancer researcher Friedhelm Herrmann have been cited since being retracted, in some cases nearly a decade after they were pulled. Together, two of those papers were cited roughly 60 times. Examination of one Nature paper by former Bell Labs physicist Jan Hendrik Schön, published in 2000 and retracted in 2003, revealed that it's been noted in research papers 17 times since, although the drop-off after retraction was steep: Prior to being pulled, the paper was cited 153 times.

It's "quite embarrassing," says Richard Smith, former editor of the British Medical Journal, of references to retracted publications. "If people cite fraudulent articles, then either their research is going to be thrown off or something will be wasted," says Paul Friedman, a former dean at the University of California, San Diego, who oversaw an investigation into papers by radiologist Robert Slutsky in the mid-1980s.

In some cases, citations are "negative": The paper is cited precisely because it was retracted, and the retraction duly noted in the text. But those familiar with postretraction citation consider that rare. "It almost never happens," says Drummond Rennie, a deputy editor of the Journal of the American Medical Association. Spot checks of 10 papers that cite withdrawn publications found no negative citations.

Instead, scientists often don't know that the work they are citing has been retracted. Lon Kaufman, a cell biologist at the University of Illinois, Chicago, was surprised to learn from Science that his 1999 article in The Plant Journal cited

Afterlife. This Science paper was retracted nearly 7 years ago, but that hasn't stopped other researchers from citing it.

Retracted papers continue being cited

- Many retracted papers continue to be cited
  - after retraction citations sharply decrease but difficult to "prevent" it from happening
  - some citations are "negative"
  - negative post-retraction citations are rare

- Friedhelm Herrmann (German cancer researcher):
  - 17 of his 19 retracted papers cited since retraction
  - some after 10 years
  - two were cited > 60 times

- Jan Hendrik Schon (German physicist):
  - 2 of his retracted *Nature* papers have been cited
  - 17 times after vs. 153 times before retraction

Know before you cite

- Research is not credible if fraudulent paper is cited:
  - Paul Friedman (former dean at UCSD): "If people cite fraudulent articles, then either their research is going to be thrown off or something will be wasted"

- Scientists often unaware that they are citing a retracted paper:
  - Lon Kaufman (cell biologist at University of Illinois, Chicago) was **unaware** that his 1999 *Plant Journal* article cited a *Nature* paper retracted in 1998

  - Michael Croft (immunologist at La Jolla Institute) **had no idea** that his 2003 article in *Nature Reviews Immunology* cited a *PNAS* paper co-authored by Herrmann retracted in 1997

How to prevent retracted papers from enduring

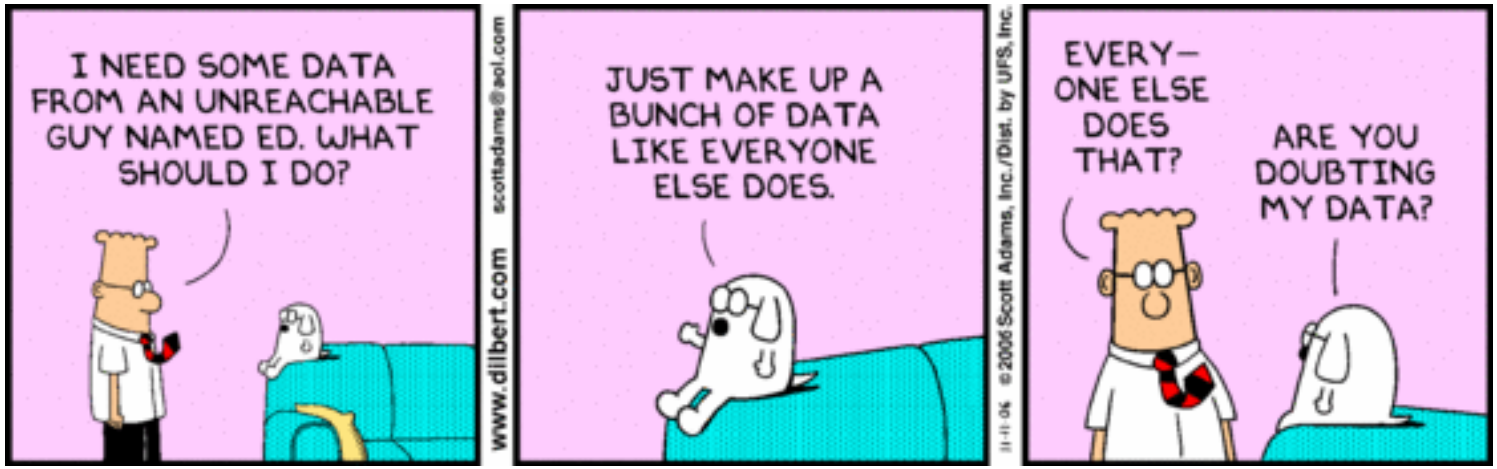
- **Online retraction notices not efficient:**
  - Biochemist Hans Vogel learned that his 2005 *Biochemistry* article cited a paper retracted from *Cell* 4 months earlier
  - Vogel's paper was submitted before retraction was issued: "I would have probably cited it again."

- **Possible solutions:**
  - Journals should purge the literature of retracted data
  - when a retraction is issued journals should alert those who previously cited the work

- **Journal editors say they don't have resources to do so:**
  - A journals' director: "Checking every citation in submitted paper is impossible; reviewers and publishers do not look up every reference."

- **Reviewers closely familiar with a given field ought to recognize "a suspicious name" in a citation**

- **Publicity may be one of the best tools to keep track of retracted papers**



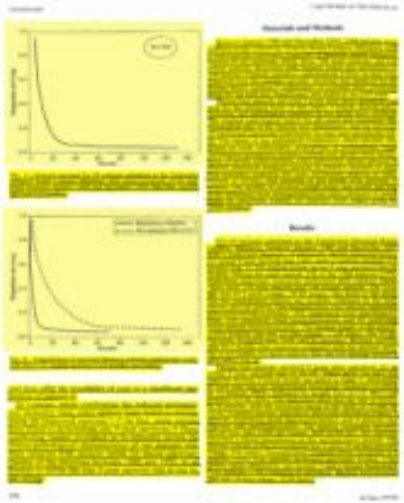
http://www.dilbert.com/fast/2006-11-11/

Mark's pick

Authors, journal editors respond to possible cases of plagiarism identified by UT Southwestern Medical Center

- eTBLAST – analyzes random abstracts from Medline
  - 70,000 highly similar citations
  - Small sample → 207 article pairs with signs of plagiarism
  - 162 questionnaires sent to authors and editors
    - 83 submissions reviewed, 46 retracted (55.4%)
  - ~50% of duplications have not been reviewed
- Before questionnaires:
  - Original authors
    - 93% did not know of duplications
  - Duplicate authors (only 60 replies)
    - ~25% deny wrongdoing
    - ~17% unaware of being an author
- 174 responding journal editors
  - 11 never had to handle potential plagiarism
  - 12 not going to pursue plagiarism complaint

Carcinoma of the Pancreas: Resection Outcome at the University Hospital Kuala Lumpur



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PNAS

Proceedings of the National Academy of Sciences of the United States of America

PKNOX2 gene is significantly associated with substance dependence in European-origin women

Xiang Chen[a,1], Kelly Cho[a,1], Burton H. Singer[b,2] and Heping Zhang[a,2]

+ Author Affiliations

[1]X.C. and K.C. contributed equally to this work.

Contributed by Burton H. Singer, August 1, 2009 (sent for review March 18, 2009)

Abstract

Substance d
results in se
reported and
outcomes, ir
from several
association s
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significant (A
2 (PKNOX2)
composite pl
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Footnotes

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or singer@pr

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The authors

CiteULike

This Article

Published online before print August 31, 2009, doi: 10.1073/pnas.0908521106

» Abstract
Full Text (PDF)
A retraction has been published

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Author: Cottone et al.
Published: November 9, 2009

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February 2, 2010, 107

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This article has been retracted

Science 16 January 2004:
Vol. 303. no. 5656, pp. 371 - 373
DOI: 10.1126/science.1089509

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REPORTS

A New Strategy for the Synthesis of Glycoproteins

Zhiwen Zhang,[1] Jeff Gildersleeve,[1] Yu-Ying Yang,[1] Ran Xu,[1] Joseph A. Loo,[2] Sean Uryu,[1] Chi-Huey Wong,[1] Peter G. Schultz[1]*

Posttranslational modifications of proteins regulate many biological processes, including metabolism, signal transduction, and gene expression. The synthetic challenges associated with generating homogeneous populations of selectively modified proteins, however, have hindered detailed studies of the effects of these modifications on protein structure and function. Here, we report an approach to the cotranslational synthesis of selectively glycosylated proteins in which the modified amino acid is genetically encoded. We show that myoglobin containing ß–*N*-acetylglucosamine (GlcNAc)–serine at a defined position can be expressed in *Escherichia coli* in good yield and with high fidelity. The ß-GlcNAc moiety can be recognized by a saccharide-binding protein, or subsequently modified with a galactosyltransferase to build more complex carbohydrates. This approach should be generally applicable to other posttranslational modifications such as protein phosphorylation, acetylation, and methylation.

[1] Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.
[2] Department of Biochemistry and Biological Chemistry, University of California at Los Angeles, 405 Hilgard Avenue, 402 Paul D. Boyer Hall, Los Angeles, CA 90095, USA.

* To whom correspondence should be addressed. E-mail: schultz@scripps.edu

See Retraction Published September 9, 2009

PKNOX2 gene is significantly associated with substance dependence in European-origin women

Xiang Chen[a,1], Kelly Cho[a,1], Burton H. Singer[b,2], and Heping Zhang[a,2]

[a]Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT 06520-8034; and [b]Office of Population Research, Princeton University, Princeton, NJ 08544

Contributed by Burton H. Singer, August 1, 2009 (sent for review March 18, 2009)

Substance dependence is a complex environmental and genetic dis- dependence phenotype that may not be apparent when individ-

T Regulatory Cells in Long-Term Stable Transplant
e in Rhesus Macaques Induced by Anti-CD3
oxin and Deoxyspergualin[1]

siedu,* Karen J. Goodwin,* Gansuvd Balgansuren,* Stacie M. Jenkins,*
Bas-Bernardet,* Uuganbayar Jargal,* David M. Neville, Jr.,† and
omas[2]*

(Tregs) are implicated in immune tolerance and are variably dependent on IL-10 for in vivo function. Brief
ainment of multiple nonhuman primates (NHP) with anti-CD3 immunotoxin and deoxyspergualin has induced
rejection-free tolerance to MHC-mismatched allografts, which associated with sustained elevations in serum
y, we demonstrate that resting and activated PBMC from long-term tolerant NHP recipients are biased to
of IL-10, compared with normal NHP PBMC. Although IL-10-producing CD4+ Tregs (type 1 regulatory cells
) were undetectable (<0.5%) in normal rhesus monkeys, 7.5 ± 1.7% of circulating CD4+ T cells of tolerant
expressed IL-10. In addition to this >15-fold increase in Tr1/IL-10 Tregs, the tolerant monkeys exhibited a
ase in CD4+CD25+ Tregs, 8.1 ± 3.0% of CD4 T cells vs 2.8 ± 1.4% in normal animals ($p < 0.02$). The frequency
-10+ cells was elevated 5-fold in tolerant vs normal NHP (1.8 ± 0.8% vs 0.5 ± 0.2%). Rhesus CD4+CD25+
memory phenotype, and expressed high levels of Foxp3 and CD
Tregs proliferated poorly after activation and suppressed proliferation of CD4+CD25− effector T cells, ex-
properties similar to rodent and human CD4+CD25+ Tregs. Depletion of CD4+CD25+ Tregs restored
antidonor responses in tolerant NHP. Our study demonstrates an important role of Treg populations in
olonis, suggesting that these mechanisms may contribute to maintaining peripheral tolerance. *The Journal of*
. 175: 8060–8068.

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oda, MD 20892

December 28, 2004. Accepted for publication October

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d Juvenile Diabetes Research Foundation Grant 4-2004-364.

and reprint requests to Dr. Judith M. Thomas, Department
ansplant Immunology, University of Alabama, Birming-

this paper: Treg, regulatory T cell; Tr1, type 1 regulatory
DSG, 15-deoxyspergualin; IT, immunotoxin; NHP, rhesus
ate dehydrogenase.

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0022-1767/05/$02.00

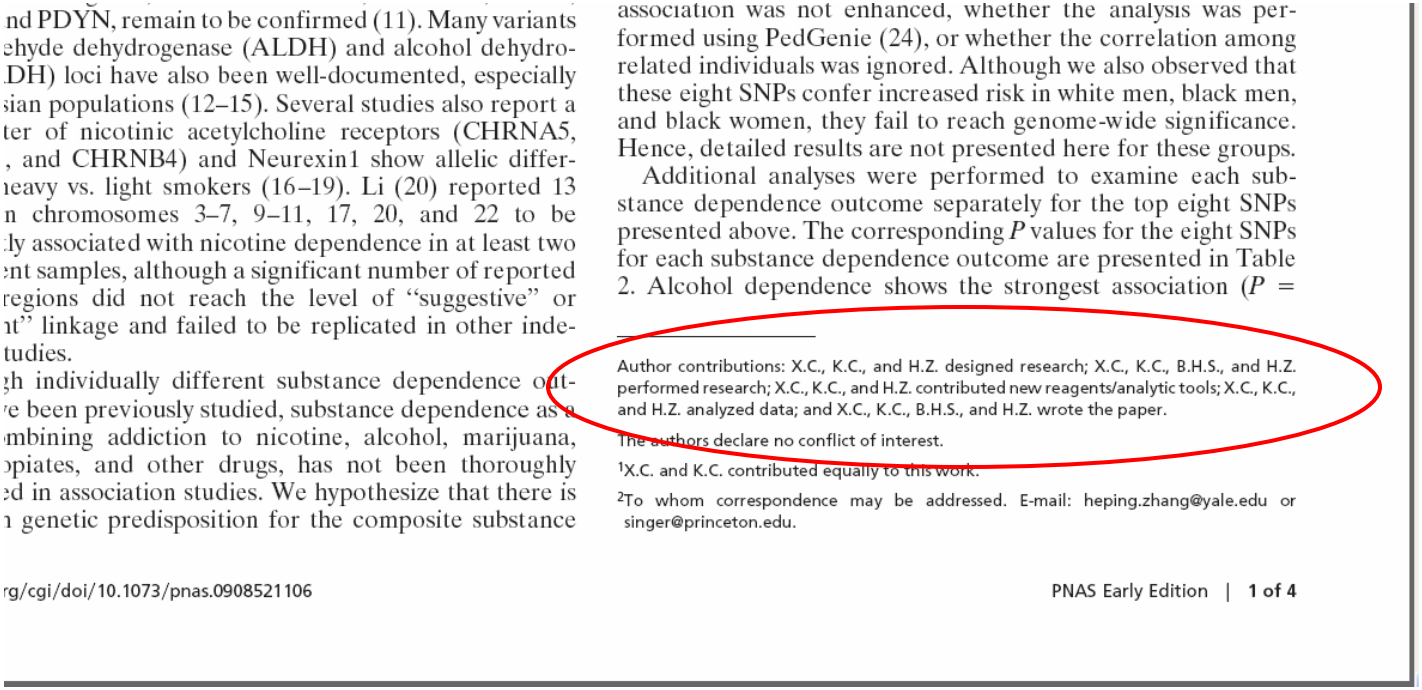
PEER-REVIEWED | PUBLISHED | 2005

GENETICS

SOCIAL SCIENCES

That's why we have these 'new' polices:

- Web-based supplemental data submission required.
- "data not shown" not allowed by high-profile journals.
- Author contribution statement required.



nd PDYN, remain to be confirmed (11). Many variants
ehyde dehydrogenase (ALDH) and alcohol dehydro-
DH) loci have also been well-documented, especially
ian populations (12–15). Several studies also report a
ter of nicotinic acetylcholine receptors (CHRNA5,
, and CHRNB4) and Neurexin1 show allelic differ-
eavy vs. light smokers (16–19). Li (20) reported 13
n chromosomes 3–7, 9–11, 17, 20, and 22 to be
ly associated with nicotine dependence in at least two
nt samples, although a significant number of reported
regions did not reach the level of "suggestive" or
t" linkage and failed to be replicated in other inde-
tudies.
gh individually different substance dependence out-
e been previously studied, substance dependence as a
mbining addiction to nicotine, alcohol, marijuana,
piates, and other drugs, has not been thoroughly
d in association studies. We hypothesize that there is
genetic predisposition for the composite substance

association was not enhanced, whether the analysis was performed using PedGenie (24), or whether the correlation among related individuals was ignored. Although we also observed that these eight SNPs confer increased risk in white men, black men, and black women, they fail to reach genome-wide significance. Hence, detailed results are not presented here for these groups.

Additional analyses were performed to examine each substance dependence outcome separately for the top eight SNPs presented above. The corresponding *P* values for the eight SNPs for each substance dependence outcome are presented in Table 2. Alcohol dependence shows the strongest association (*P* =

Author contributions: X.C., K.C., and H.Z. designed research; X.C., K.C., B.H.S., and H.Z. performed research; X.C., K.C., and H.Z. contributed new reagents/analytic tools; X.C., K.C., and H.Z. analyzed data; and X.C., K.C., B.H.S., and H.Z. wrote the paper.

The authors declare no conflict of interest.

[1]X.C. and K.C. contributed equally to this work.

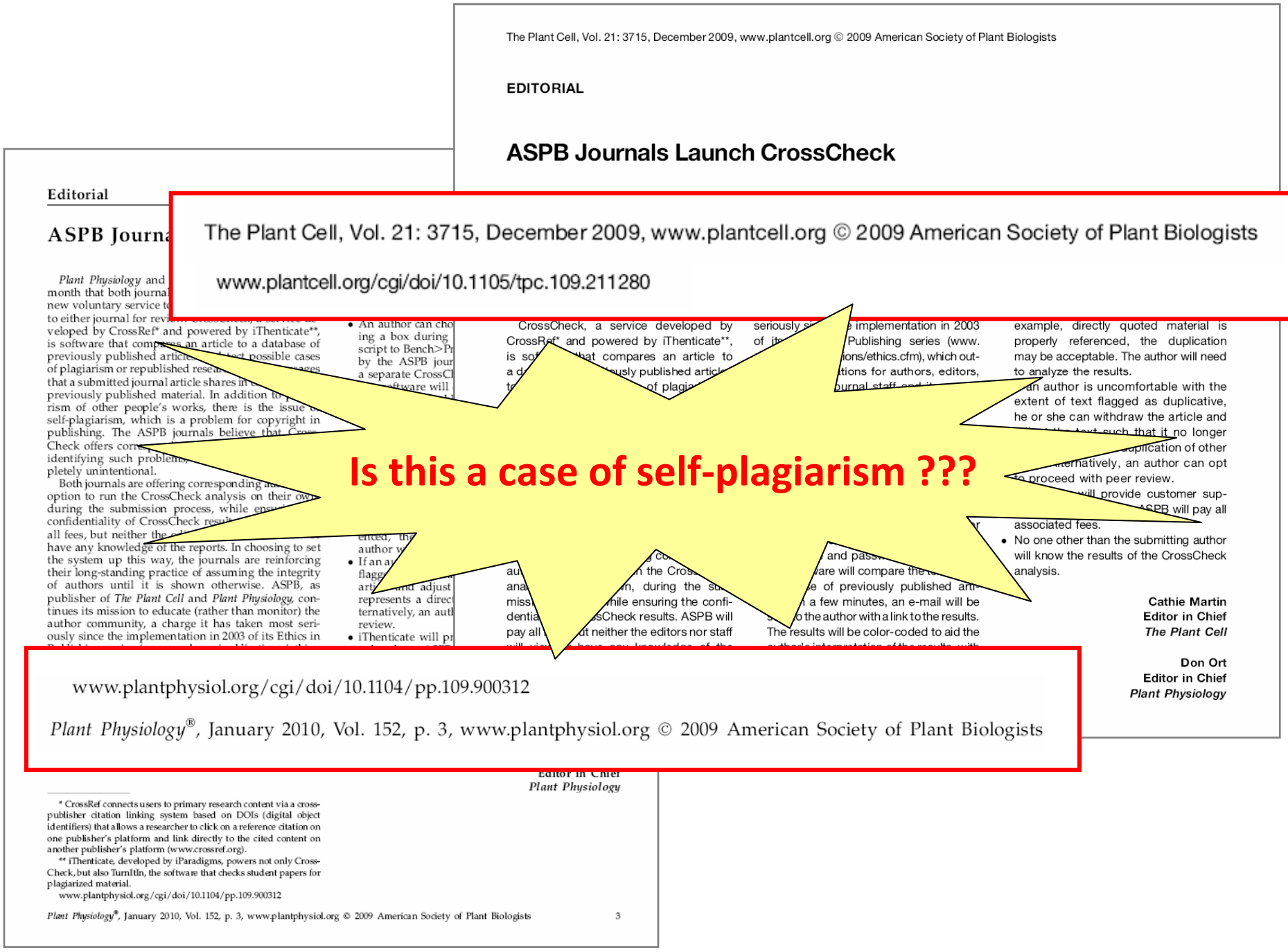
[2]To whom correspondence may be addressed. E-mail: heping.zhang@yale.edu or singer@princeton.edu.

g/cgi/doi/10.1073/pnas.0908521106

PNAS Early Edition | 1 of 4

What do all these mean
to researchers and/or mentors ?

- Misconduct:
  - Data record, lab notebook etc
  - Lab/peer discussion
  - Check your own data (human/computer errors etc)
- Plagiarism:
  - Not OK to copy other's sentences (not even in Methods!).
  - Not OK for "self-plagiarism" either.
  - Not OK to use 2nd-hand references (read what you cite).
  - Not to "believe" everything you read: Just because it was published doesn't mean the data or the interpretation is "correct".
- The peer-review system…



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