

# The Office of Research Integrity Perspective on Retractions

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Office of Research Integrity  
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# Office of Research Integrity

- **Division of Investigative Oversight.**
  - Responds to allegations of scientific misconduct which includes fabrication, falsification and plagiarism.
- **Division of Education and Integrity.**
  - Activities and programs to teach the responsible conduct of research, research on research misconduct, assurance program.
- **Research Integrity Branch, OGC.**
  - Legal issues and litigation.

# PHS Regulations 42 C.F.R Part 93



**Federal Register**

Tuesday,  
May 17, 2005

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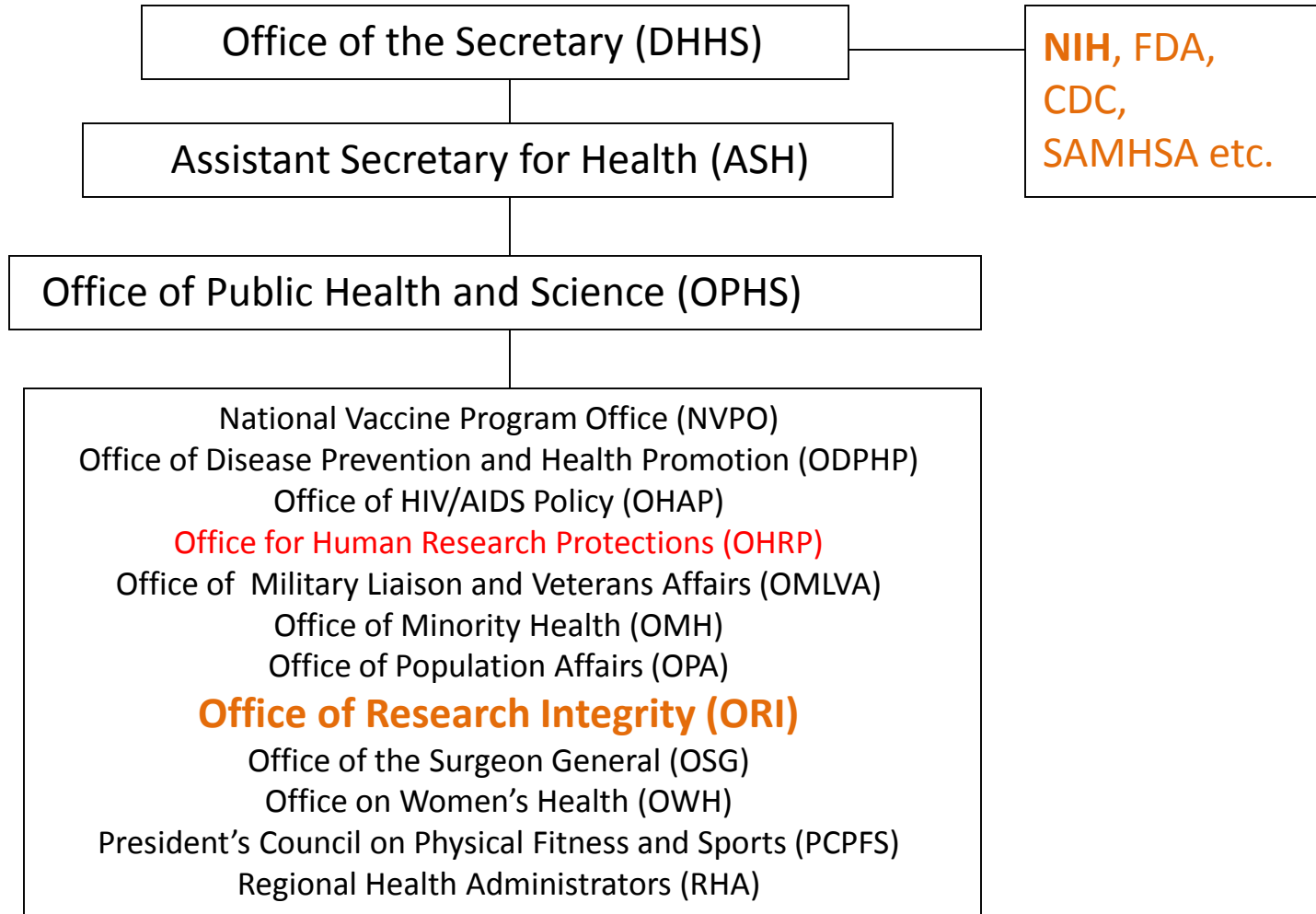
**Part III**

**Department of  
Health and Human  
Services**

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42 CFR Parts 50 and 93  
Public Health Service Policies on  
Research Misconduct; Final Rule

# Organizational Structure



# Public Health Service (PHS)

- **National Institutes of Health (NIH)**
- The Centers for Disease Control and Prevention (CDC)
- The Food and Drug Administration (FDA)
- The Substance Abuse and Mental Health Services Administration (SAMHSA)
- The Health Resources and Services Administration (HRSA)
- The Agency for Healthcare Research and Quality (AHRQ)
- The Agency for Toxic Substances and Disease Registry (ATSDR)
- The Indian Health Service (IHS)

# Definition of Research Misconduct- F/F/P

- **Research misconduct** means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.
  - *Research misconduct does not include honest error or differences of opinion.*

# F/F/P

- Fabrication: making up data or results and recording or reporting them.
- Falsification: 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: the appropriation of another's ideas, processes, results, or words without giving appropriate credit.

# Findings require:

- There be a significant departure from accepted practices of the relevant research community.
- The misconduct be committed intentionally, knowingly, or recklessly.
- The allegation be proven by a preponderance of the evidence (more than 50% likely).



# Falsification vs. Research Misconduct

- Proving research misconduct requires two steps
  - Demonstrating the data are false
  - Determining who is responsible for the falsification
    - Who did it?
    - Is it significant?
    - Can honest error be ruled out?

# Not Research Misconduct

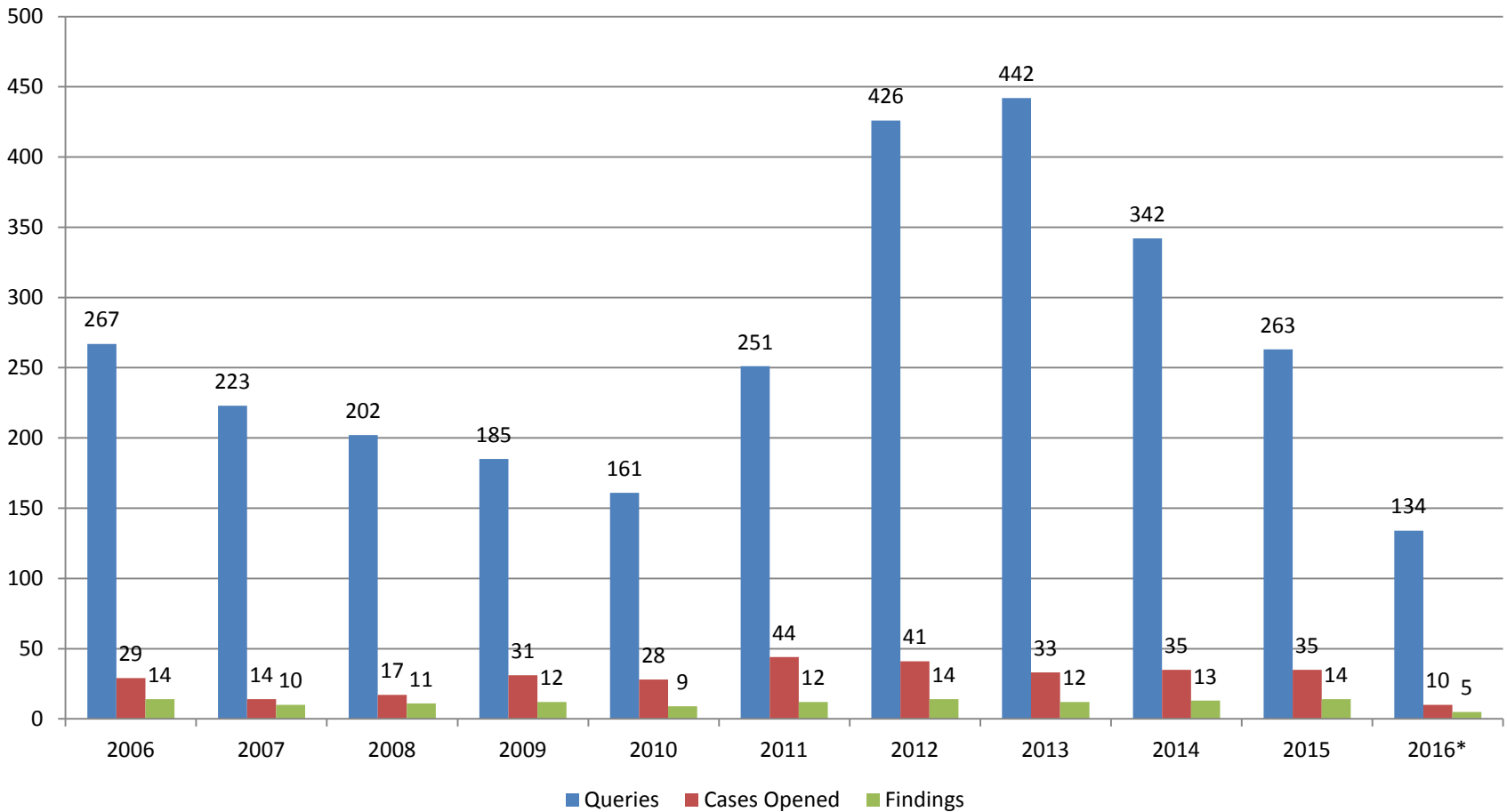
- Honest error or differences of opinion
- An inability to reproduce results
- Conflict of interest
- Intellectual property
- Employment issues (**termination\***, promotion, salary...)
- Disputes over work space, equipment
- Sexual harassment, criminal activities, discrimination
- Other regulatory violation (FDA)

**\*Whistleblower protection**

# Plagiarism (for ORI) is narrowly defined!

- “. . .the **theft or misappropriation** of intellectual property and/or substantial unattributed textual copying of another’s work.” (ORI Newsletter, 15(4), p. 4 Sept 2007)
- *It does not include:*
  - Authorship or credit disputes
  - Self plagiarism
  - Collaborative disputes
  - Modest amounts of boiler plate/methods description
- Plagiarism of ideas is extremely difficult to prove.

# ORI Stats: Queries, Open Cases and Findings



\*Jan-June

# Allegations

- ORI does not “look” for misconduct, but responds to allegations.
- Allegations come from institutions, journal editors, grant reviewers (through NIH), co-authors, other agencies, colleagues and can be anonymous.
- Once you make an allegation, and become a complainant:
  - Be patient! It takes a while.
  - Maintain confidentiality.
  - ORI does not comment on open cases.
  - In cases of no misconduct ORI makes no comment.

# Public Allegations

- If a respondent is alerted to the potential allegations prior to the institutions involvement, data can be destroyed. These data are critical to prove research misconduct occurred, as per the requirements for a finding of research misconduct described in the regulation §93.104.

# Sequestration

§ 93.305 Responsibility for maintenance and custody of research records and evidence.

An institution, as the responsible legal entity for the PHS supported research, has a continuing obligation under this part to ensure that it maintains adequate records for a research misconduct proceeding. The institution must—

(a) Either before or when the institution notifies the respondent of the allegation, inquiry or investigation, promptly take all reasonable and practical steps to obtain custody of all the research records and evidence needed to conduct the research misconduct proceeding, inventory the records and evidence, and sequester them in a secure manner, except that where the research records or evidence encompass scientific instruments shared by a number of users, custody may be limited to copies of the data or evidence on such instruments, so long as those copies are substantially equivalent to the evidentiary value of the instruments;

# Assessment

- DIO assesses the allegation(s) for PHS jurisdiction:
  - Research must be supported by, or involve an application for, **PHS funds**.
  - Research must meet the **definition of scientific misconduct** set forth in PHS regulation (42 C.F.R. Part 50, Subpart A).
  - Allegation must contain **sufficient information** to proceed with an inquiry.
  - **Referral to institution** (RIO) for assessment, inquiry or investigation.



# Two Common Misconceptions

- ORI is (not) part of NIH
  - ORI is in the Office of the Assistant Secretary of Health (OASH) and the recommendation to make a finding goes to the ASH.
- ORI does (not) conduct investigations
  - ORI conducts oversight of investigations done at the institution where the alleged misconduct occurred.

# Jurisdiction

- Determining jurisdiction early on is important, because a finding would be overturned on appeal if not properly assessed.
- Determining funding jurisdiction is not straightforward when a respondent has multiple sources of funding.
- Respondents will deny that a project involved PHS funding, despite acknowledgement in publication.

# Inquiry

- A preliminary evaluation of the available evidence, testimony of respondent and complainant.
- Determine whether there is sufficient evidence of possible scientific misconduct to warrant an investigation.

Purpose of inquiry is **NOT** to reach a final conclusion about whether misconduct occurred or who was responsible.

# Investigation

- Explore the allegations in detail.
- Examine the evidence in depth. Includes all relevant materials such as lab notebooks, electronic notebooks, hard drives, email records, core facility records, purchasing records....
- Interview relevant witnesses.
- Consult with experts

Investigation reaches a final conclusion about whether misconduct occurred and who was responsible.

# ORI Oversight Review

- **DIO reviews** the institution's report and evidence
  - Did institution provide adequate justification of how it reached its conclusions?
  - Is there more evidence that can affect the findings?
- **DIO analysis**
  - Reviews computer files, notebooks, grant applications, publications, slides, letters, memoranda, transcripts, summaries of interviews, etc.
  - Performs statistical and image analysis.
  - In depth internal discussions between DIO staff.
- **Legal review**
  - ORI attorneys (OGC) and DIO scientists review case.
  - Report/recommendations prepared for ORI Director.

# Case Closure

- ORI may determine that there is insufficient evidence to make a finding of research misconduct.
- ORI may agree with all or some of the findings made by an institution and may make additional findings.
  - ORI may negotiate a voluntary settlement with the respondent where the respondent accepts the imposition of PHS administrative actions without necessarily admitting the misconduct. Allows the respondent to negotiate.
  - If a settlement is not reached, ORI recommends a finding of research misconduct and the imposition of administrative actions to the Assistant Secretary for Health for final decision. A charge letter must be written, and the case goes to an administrative law judge.

# Administrative Actions

- Findings are not punitive
- Retraction or correction of published paper
- Require plan of supervision or monitoring
- Prohibit advisory service
- Debarment loss of receipt of federal funds
- **Finding is public**
- ORI does not have the authority to recover funds (NIH), impose criminal sanctions (DOJ) or take action at the institution level (HR or thesis committees).

# When ORI Makes a Finding

- ORI notifies the funding agency
- ORI notifies the editor and sends a copy of the *Federal Register* notice
  - If a voluntary settlement was negotiated, then a request from the respondent to correct or retract can be part of the actions, if appropriate.
  - If a charge letter was written, ORI can recommend a correction or retraction, if appropriate.

The journal makes the ultimate decision about whether or not to correct or retract a paper.



# Findings

- Research misconduct findings are published in the *Federal Register*, *NIH Guide to Grants and Contracts* and on the ORI website.
- Name of the respondent
- Institution where the misconduct took place
- Grant support
- Finding: detailed summary of the misconduct, and where it was reported
- Administrative actions
- Statements (in the case of a voluntary)

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Items: 2

- [Genetic tracing reveals a stereotyped sensory map in the olfactory cortex.](#)  
 1. **Zou Z, Horowitz LF, Montmayeur JP, Snapper S, Buck LB.**  
 Nature. 2008 Mar 6;452(7183):120. doi: 10.1038/nature06819. No abstract available.  
 PMID: 18322536  
[Similar articles](#)
- [Genetic tracing reveals a stereotyped sensory map in the olfactory cortex.](#)  
 2. **Zou Z, Horowitz LF, Montmayeur JP, Snapper S, Buck LB.**  
 Nature. 2001 Nov 8;414(6860):173-9. Retraction in: [Zou Z, Horowitz LF, Montmayeur JP, Snapper S, Buck LB.](#)  
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**RETRACTED ARTICLE**

Retraction notice

Nature. 2001 Nov 8;414(6860):173-9.

**Genetic tracing reveals a stereotyped sensory map in the olfactory cortex.**

Zou Z<sup>1</sup>, Horowitz LF, Montmayeur JP, Snapper S, Buck LB.

Author information

Retraction in

Genetic tracing reveals a stereotyped sensory map in the olfactory cortex. [Nature. 2008]

Abstract

The olfactory system translates myriad chemical structures into diverse odour perceptions. To gain insight into how this is accomplished, we prepared mice that coexpressed a transneuronal tracer with only one of about 1,000 different odorant receptors. The tracer travelled from nasal neurons expressing that receptor to the olfactory bulb and then to the olfactory cortex, allowing visualization of cortical neurons that receive input from a particular odorant receptor. These studies revealed a stereotyped sensory map in the olfactory cortex in which signals from a particular receptor are targeted to specific clusters of neurons. Inputs from different receptors overlap spatially and could be combined in single neurons, potentially allowing for an integration of the components of an odorant's combinatorial receptor code. Signals from the same receptor are targeted to multiple olfactory cortical areas, permitting the parallel, and perhaps differential, processing of inputs from a single receptor before delivery to the neocortex and limbic system.

Comment in

Findings of research misconduct. [NIH Guide Grants Contracts. 2014]

PMID: 11700549 DOI: 10.1038/35102506

[PubMed - indexed for MEDLINE]



Publication Types, MeSH Terms, Substances

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NIH Guide Grants Contracts. 2014 Aug 8:NOT-OD-14-115.

### Findings of research misconduct.

[No authors listed]

#### Comment on

Genetic tracing reveals a stereotyped sensory map in the olfactory cortex. [Nature. 2001]

Odor maps in the olfactory cortex. [Proc Natl Acad Sci U S A. 2005]

PMID: [25115028](#) PMID: [PMC4259757](#)

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PMCID: PMC4259757

## Findings of research misconduct.

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See the article "[Odor maps in the olfactory cortex](#)" in *Proc Natl Acad Sci U S A*, volume 102 on page 7724.  
See the article "[Genetic tracing reveals a stereotyped sensory map in the olfactory cortex](#)," in *Nature*, volume 414 on page 173.  
This article has been [cited by](#) other articles in PMC.

### Findings of Research Misconduct

**Notice Number:** NOT-OD-14-115

#### Key Dates

**Release Date:** August 7, 2014

#### Related Announcements

None

None

#### Issued by

Department of Health and Human Services ([DHHS](#))

#### Purpose

Notice is hereby given that the Office of Research Integrity (ORI) has taken final action in the following case:

Zhihua Zou, Ph.D., Harvard Medical School and Fred Hutchinson Cancer Research Center: Based on the reports of investigations conducted by Harvard Medical School (HMS) and Fred Hutchinson Cancer Research Center (FHCRC) and additional analysis conducted by ORI in its oversight review, ORI found that Dr. Zhihua Zou, former Postdoctoral Fellow, Department of Neurobiology, HMS, and former Staff

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- Findings of misconduct in science/research misconduct. [NIH Guide Grants Contracts. 2011]
  - Improving the scientific misconduct hearing process. [JAMA. 1997]
  - Findings of scientific misconduct. [NIH Guide Grants Contracts. 2004]
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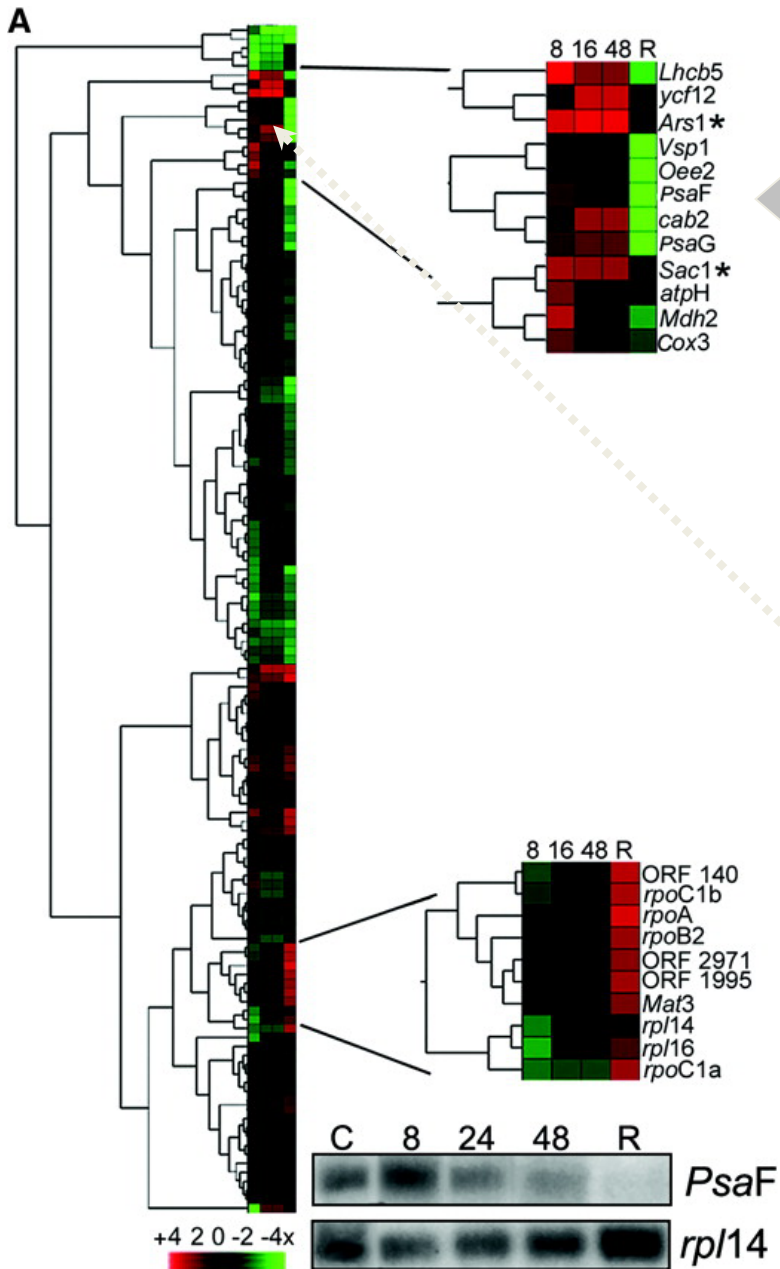
Findings of research misconduct.

# What tools does ORI Use?

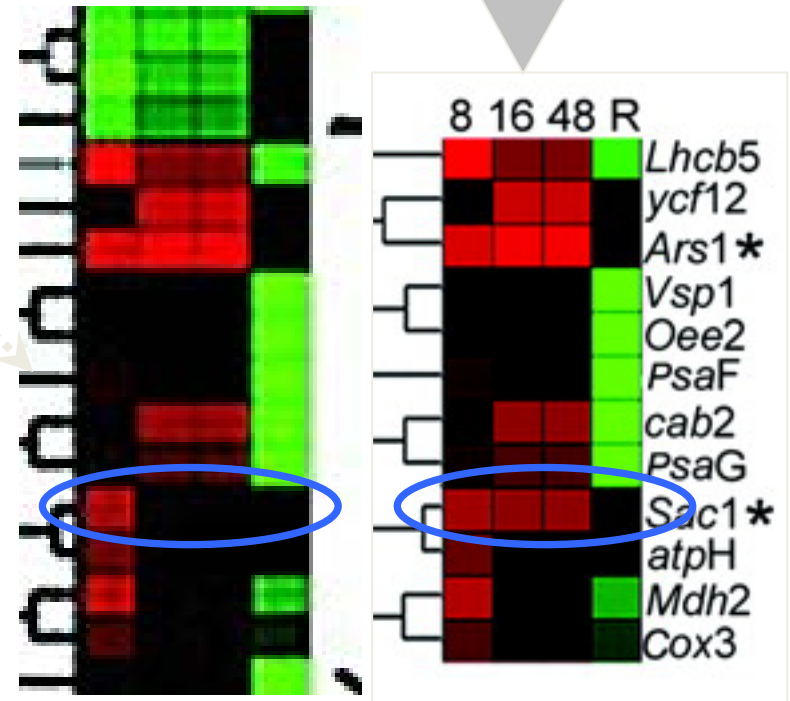
- iThenticate
- Photoshop tools
- Statistical Analysis
- Excel and PowerPoint functions
- Software to determine metadata associated with files and discover deleted files

# Surge in Image Manipulation

- **Technology:** Methods to acquire & present data displace review of raw data.
- **Opportunity:** Ease of manipulation: Very easy to manipulate image; community standards have not kept pace with use.
- **New methods for detection:** Facilitated by online publication, journal pre-screening images, new tools.




Author shows  
us what he wants  
us to see



**Note: \* denotes key metabolic gene**



# Forensic analysis: Text analysis with iThenticate



Document Viewer

**Glioblastoma 2013 article**

As of: August 4, 2014 10:50:21 AM EDT  
10,889 words - 273 matches - 79 sources

Jump to: Glioblastoma 2013 article - 62%

Similarity Index

62%

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phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR), 11 – 15 platelet derived growth factor receptor (PDGFR), 16 and Olig2. 17 Recently, a gene expression profiling of gliomas has shown that SHH signaling is active in a subset of gliomas. 18 This study further showed that SHH signaling is essential for glioma GIC self-renewal and GIC -initiated brain tumor growth. 18 It is postulated that the relatively homogeneous population of GICs, rather than the heterogeneous tumor cells, may reveal key mechanisms of tumor initiation and propagation of primary tumors and hence predict tumor prognosis, therapy, and drug response.

The

SHH signaling pathway is a key regulatory mechanism in neural development, and abnormal SHH signaling has been implicated in tumorigenesis in brain, such as

that of glioblastoma. 3, 19 – 21

The normal function of the SHH ligand in the SHH pathway is to serve as a morphogen, inducing proper differentiation in

embryo- genesis. 22 – 24

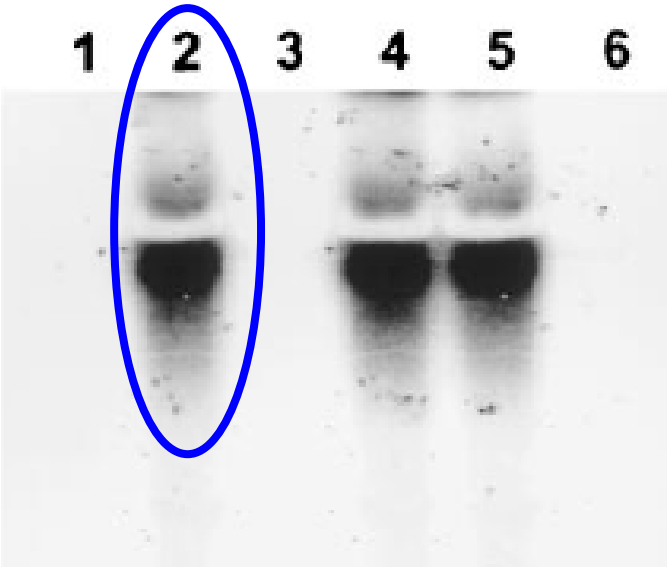
Genomic alterations of the SHH pathway have been shown to lead to the development of brain cancers. 25 Aberrant activation of the SHH pathway leads to an increase in cell survival and metastasis in cancer cells. Such aberrant activity includes inactivating mutations of Patched1 or Sufu as well as activating mutations of Smoothened (Smo). 26 – 28 The binding of the SHH ligand to its receptor, Patched, leads to the

4	237 words / 2% - CrossCheck <a href="#">Brahma N. Singh. "Hedgehog Signaling Antagonist GDC-0449 (Vismodegib) Inhibits Pancreatic Cancer Stem Cell Characteristics: Molecular Mechanisms". PLoS ONE. 11/08/2011</a>	✕
5	206 words / 2% - Internet from 17-Apr-2012 12:00AM <a href="#">www.nature.com</a>	✕
6	188 words / 2% - CrossCheck <a href="#">Q. Xu. "Hedgehog Signaling Regulates Brain Tumor-Initiating Cell Proliferation and Portends Shorter Survival for Patients with PTEN-Coexpressing Glioblastomas". Stem Cells. 12/01/2008</a>	✕
7	178 words / 2% - Internet from 06-May-2013 12:00AM <a href="#">www.ncbi.nlm.nih.gov</a>	✕
8	147 words / 1% - Internet from 07-Feb-2014 12:00AM <a href="#">experts.kumc.edu</a>	✕
9	116 words / 1% - CrossCheck <a href="#">Dara Nalls. "Targeting Epigenetic Regulation of miR-34a for Treatment of Pancreatic Cancer by Inhibition of Pancreatic Cancer Stem Cells". PLoS ONE. 08/31/2011</a>	✕
10	114 words / 1% - Internet from 08-Jan-2011 12:00AM <a href="#">www.biomedcentral.com</a>	✕
11	99 words / 1% - Publications "Reports from Norris Cotton Cancer Center Add New Data to Research in Glioblastomas (Report)", Biotech Week, August 24 2011 Issue	✕
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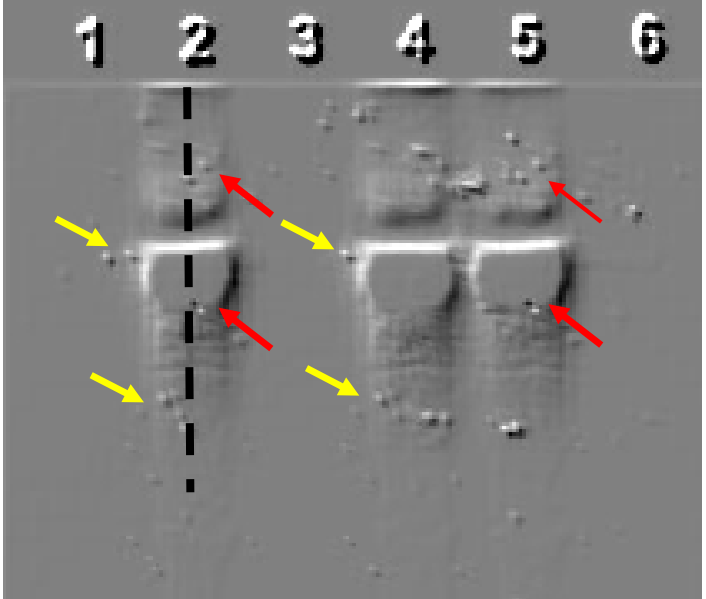
# Embossing – reveals borders in background or edges



Original Data



Published Data



Embossed

# Excel Can Show Relationship Between Cells

Excel spreadsheet showing data relationships between columns. The spreadsheet has columns A through I. Column A lists amino acids, B through E show measurement values for four experiments (#1-#4), and F through I show values for four experiments (Expt'l 1-4). Blue arrows point from the values in columns F through I back to the corresponding values in column E, illustrating the relationship between the data points. A red box with the text "Use 'Audit' Function" and a red arrow points to the "Audit" icon in the Excel ribbon.

	A	B	C	D	E	F	G	H	I
1	Measurement	#1	#2	#3	#4	Expt'l 1	Expt'l 2	Expt'l 3	Expt'l 4
2	Taurine	55	56	51	39	63	66	20	27
3	Aspartate	2	2	2	1	2	12	3	2
4	Threonine	120	135	86	73	125	122	100	61
5	Serine	130	85	110	51	56	60	63	40
6	Asparaganine	25	23	60	32	59	63	59	45
7	Glutamate	6	5	0	0	5	14	31	29
8	Glutamine	645	398	485	688	700	624	610	477
9	Proline	61	52	43	85	53	61	20	25
10	Glycine	6	12	10	11	3	18	10	4
11	Alanine	152	163	100	114	150	145	125	115
12	Citrulline	1	2	5	1	2	17	0	4
13	Valine	112	125	141	86	100	102	07	79
14	Cystine	1	0	2	1	2	17	11	8
15	Methionine	63	58	45	89	45	54	34	27
16	Isoleicine	50	52	56	54	52	60	27	16
17	Leucine	162	98	100	75	125	124	73	52
18	Tyrosine	65	31	52	19	63	70	41	26
19	Phenylalanine	65	85	51	52	63	70	56	46
20	Tryptophan	10	12	16	18	12	25	22	20
21	Ornithine	5	5	2	2	2	17	7	3
22	Lysine	125	103	188	145	156	151	106	90
23	Histidine	30	36	35	12	31	42	10	7
24	Arginine	142	152	96	145	143	139	139	139


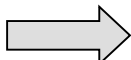
# Why sequester electronic information?

- Hard drives – original files are useful
  - PowerPoint – can show origin of material
  - Excel – can show how numbers were derived
  - Photoshop- shows how images were manipulated
  - Word- metadata to show when files were changed
- Email
  - Demonstrates who sent what
  - Has attachments that were not saved to drive
  - Helps establish timeline
  - The gotcha! email (very elusive)

# Interpretation of Analysis

- It is one thing to notice an anomaly, it is another to demonstrate research misconduct
  - iThenticate: it is not enough to pick a threshold for amount of plagiarized material, the type of plagiarized material must be analyzed.
  - Photoshop: It is not enough to demonstrate inconsistencies, the significance must be demonstrated.

# Is Manipulation a Falsification?

- Detection of manipulated image/data is one aspect
- Must understand and interpret what is found
  - Manipulation  Falsification
  - Falsification  Research Misconduct
- Requires Inquiry and/or Investigation
  - Who did it?
  - Is it significant?
  - Can you rule out honest error? Intent?

# Our Responsibilities (I)

- Laboratory: Perform and report research accurately.
- Mentor: Provide environment conducive to ethical research, check raw data.
- Institution: Create environment that does not tolerate research misconduct, has mechanisms in place to investigate, protect whistleblowers.

# Our Responsibilities (II)

- Journals: Publish accurate data.
- ORI: Protect federal funds, correct the literature.
- The different goals and standards of the parties makes it difficult to come up with a policy that reconciles all the issues.



# Peer Review vs. Detection of Misconduct

- Is it the job of reviewers to look for F/F/P?
- Possible screening (not trivial)
  - Ask for raw data
  - Use plagiarism detection software
  - Analyze images
- Recognition of a problem (not obvious)
  - Does author's response satisfy reviewers or raise more questions?
  - Does author attempt to negotiate?
  - Are there similar problems in other papers (pattern)?

# When a journal receives allegations about a manuscript or publication:

- Handle it internally.
- Communicate with the corresponding author/department chair.
- Contact the institutional RIO.
- Refer the allegations to ORI.

# Outcomes?

- Communicating with author or chair may lead to correction of issues with current submission, but does not address if there are larger problems.
- Communicating with the institution, who is freer to communicate can get access to relevant information sooner rather than wait for ORI decision and begins the RM process.
- Communicating with ORI means the journal becomes a complainant and is not given any information until the case is closed.

# When to Retract?

- Articles may be retracted at anytime at the discretion of the editor.
- A correction may resolve the problem.
- Early retractions do not inform of misconduct issues.
- Sometimes an expression of concern is more appropriate if it is known that there are problems with the data and more time is needed to resolve the issue.
- No mention of ORI should be made if ORI has not made a finding.

# What Should a Retraction Say?

- Balance between too much and not enough information.
- Range of options from
  - This paper was retracted.
  - The data are unreliable.
  - Misconduct occurred.
  - Misconduct occurred on the part of respondent.
- Wording of retraction is up to journal, but increase in litigation may play a role.

# Thanks!

- ORI: slides, discussions
- Conference organizers
  
- Contact us:

[www.ORI.dhhs.gov](http://www.ORI.dhhs.gov)

240-453-8800

[askORI.hhs.gov](mailto:askORI@hhs.gov)

