

Rules of the Road for those Conducting Federally Funded or Regulated Research: Case Studies in Research Misconduct and Human Subjects

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Introduction

The materials that follow address three areas-misconduct in science, human subjects and privacy, and financial conflicts of interest. To help illustrate the application of the rules that pertain in each area, a number of hypothetical case studies are presented. You should read and be prepared to discuss each case study during the April 2 lecture.

The government regulates research under two authorities. First, it regulates research that it funds. How much does the federal government spend annually on research? *See Table 2.* Second, a federal agency can regulate research on products that fall within its jurisdiction. Thus, by way of example, the Food and Drug Administration asserts jurisdiction over clinical drug trials even though those trials are privately funded.

1. Misconduct

A. What is Research Misconduct?

The Public Health Service ("PHS"), which includes NIH, defines "research misconduct" as follows:

Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

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

Requirements for findings of research misconduct. A finding of research misconduct made under this part requires that-

- (a) There be a significant departure from accepted practices of the relevant research community;
- (b) The misconduct be committed intentionally, knowingly, or recklessly; and
- (c) The allegation be proven by a preponderance of the evidence.

42 C.F.R. § 93.104.

In contrast to federally funded research, clinical research that falls within the jurisdiction of the Food and Drug Administration is governed by its rules concerning the responsible conduct of clinical drug trials at 21 C.F.R. pt. 312, clinical device trials at 21 C.F.R. pt. 812, its rules for financial conflicts of interest at 21 C.F.R. pt. 54, and its human subjects and Institutional Review Board ("IRB") rules at 21 C.F.R. pts. 50 and 56, respectively. While the FDA's rules on financial conflicts and human subjects are compatible with those of its sister PHS agencies (*e.g.*, NIH, SAMHSA, CDC), its rules on misconduct are entirely different. Specifically, PHS has long held that scientific or research misconduct necessarily involves an "intent to deceive." However, FDA takes the position that, as far as it is concerned, negligently conducted research is sufficient to warrant sanction. As a result, there is no formal FDA definition of misconduct and FDA reserves the right to disqualify a researcher from receiving investigational new drugs if the researcher "has repeatedly or deliberately failed to comply with [FDA's rules] or has submitted to FDA or to the sponsor false information in any required report . . ." 21 C.F.R. § 312.70. Why do you think that the agencies take such different views?

B. How Common is Research or Scientific Misconduct?

One of the most enigmatic questions, at least in the 1980s, was the following: how common is scientific misconduct? There was a perception that scientific misconduct, at least in the biomedical sciences, was common, that scientists were less than fully honest, and that research institutions and government funding agencies were either unable or unwilling to stem the tide. This perception was being fueled by scandals which were unfolding faster than campaign cash and appearing as headlines in our major newspapers. The pundits were predicting that what we were seeing was the tip of the proverbial iceberg. At the same time, Daniel Koshland, then editor of SCIENCE, professor of biochemistry at Berkeley, and an heir to the Levi Strauss fortune, calmly predicted in a SCIENCE editorial that "99.9999% of reports are accurate and truthful." Koshland, D. E., *Fraud in Science*, 235 SCIENCE 141 (1987).

Both the doomsayers and cheerleaders had one thing in common-their predictions were not based on any data. Koshland's 99.9999% purity figure, for instance, was not the result of any searching study, but rather appears to have been a take-off on the old Ivory Soap

commercials, *i.e.*, "Ivory Soap is 99.94% pure." Notwithstanding, the dearth of data, when you have predictions going in every which direction, the odds are that one is going to approximate reality and Koshland's appears to be it.

Statistics collected over the past few years by the Office of Research Integrity ("ORI"), an agency within the United States Department of Health and Human Services, reveals that the incidence of misconduct in PHS funded studies is relatively low. Specifically, from January 1 through August 1, 2003, ORI closed 12 cases: in 8 there was a finding of no misconduct and in 4 there was a finding of misconduct. The year-to-year figures reported by ORI are as follows:

Table 1
Research Misconduct Cases By Year

YEAR	New Cases Opened by Institutions	Cases with OIR Finding of Misconduct ¹
2018	N/A	14
2017	N/A	8
2016	N/A	7
2015	N/A	14
2014	N/A	13
2013	N/A	11
2012	N.A.	13
2011	N/A	13
2010	N/A	7 or 8 or 9 ²
2009	31	11
2008	17	13
2007	14	10
2006	86	15
2005	92	8
2004	81	8
2003	105	12
2002	83	13
2001	72	14
2000	62	6
1999	63	13
1998	54	9
1997	64	14
1996	70	17
1995	81	24
1994	64	11
1993	77	No Data
Average Per Year	65.65	11.96 (Std. is 3.77)

The ORI statistics are limited to PHS-funded biomedical research and further, those that I

¹ Data for Years 2011-2016 are at http://ori.dhhs.gov/case_summary (last viewed Oct. 17, 2016); data for Years 2017 and 2018 were abstracted from the Federal Register.

² ORI reports this number as 7 in its case summaries, 8 on its website, and 9 in its 2010 Annual Report; we used 8.

have reported in the "inquiry" and "investigation" columns, above, do not take into account inquiries and investigations undertaken at NIH's intramural program. The final column, though, is all-inclusive.

If we are interested in ascertaining the frequency of misconduct, these numbers provide only the "numerators." The denominators are the number of individuals, from year to year, who work on PHS funded research projects. This number is difficult to ascertain, but we can derive certain approximations. Specifically, in FY 2017, NIH made 52,229 awards (*i.e.*, research grants, training grants, fellowships, R&D contracts, and other forms of awards) for \$ 28.4 billion (or slightly more than \$554,496 per award per year).³ There are over 300,000 folks doing research under these NIH grants. Thus, the frequency of confirmed misconduct is about 0.004% or 99.996% free of confirmed misconduct. <https://report.nih.gov/fundingfacts/fundingfacts.aspx> (last visited on March 23, 2019).

The frequency of misconduct in NSF funded research also appears to be low. Interestingly, though, in early 2000s there was a spate of misconduct in physics research which made headlines. According to a report in AAAS Insight, "[t]he sham 'discovery' of elements 116 and 118 seems to be a case of scientific misconduct, according to officials at Lawrence Berkeley National Laboratory (LBL), who have dismissed a scientist for fabricating data."
<http://www.academicpress.com/insight/07152002/grapha.htm> (July 15, 2002).⁴ See NY TIMES (May 21, 2002) (reporting on possible misconduct at Bell Labs, Lucent Technologies).

³ The average number of awards increased by slightly less than 6% when compared to the prior fiscal year, while the amount of the average award increased by about 7%. See <<http://grants1.nih.gov/grants/award/trends/fund9202.htm>>.

⁴ The frequency of "misconduct" in FDA regulated research was documented much earlier and has tended to be much higher than in PHS or NSF-funded research owing to FDA's far less tolerant standards. See M. Shapiro & R. Charrow, *The Role of Data Audits in Detecting Scientific Misconduct: Results of the FDA Program*, 261 J. AMERICAN MEDICAL ASS'N 2505 (May 5, 1989); M. Shapiro & R. Charrow, *Scientific Misconduct in Investigational Drug Trials*, 312 NEW ENGLAND JOURNAL OF MEDICINE 731 (March 14, 1985).

2. Human Subjects

The rules regulating human subjects, define "research" and "human subject," as follows:

(d) *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

* * * *

(e)(l) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research:

- (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

(2) *Intervention* includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

(3) *Interaction* includes communication or interpersonal contact between investigator and subject.

(4) *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

(5) *Identifiable private information* is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

(6) *An identifiable biospecimen* is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

(1) *Research* means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and activities. For purposes of this part, the following activities are deemed not to be research:

- (1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
- (2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
- (3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
- (4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

45 C.F.R. § 46.102, as amended by 82 Fed. Reg. 7149 (Jan. 19, 2017).

3. Financial Conflicts

The Federal conflict of interest rules applicable to PHS funded research provide, in part, as follows:

(e)(1) Require that each Investigator who is planning to participate in the PHS-funded research disclose to the Institution's designated official(s) the Investigator's significant financial interests (and those of the Investigator's spouse and dependent children) no later than the time of application for PHS-funded research.

42 C.F.R. § 50.604(e), as adopted in 76 Fed. Reg. 53,256 (Aug. 25, 2011).

4. NIH Funding in General

NIH funding by year is as follows:

Table 2
NIH Budget (in thousands)

<i>Fiscal Year</i>	NIH Appropriation
1994	10,955,783
1995	11,299,522
1996	11,927,562
1997	12,740,843
1998	13,674,843
1999	15,629,156
2000	17,840,587
2001	20,458,556
2002	23,321,382
2003	27,166,715
2004	28,036,627
2005	28,594,357
2006	28,560,417
2007	29,178,504
2008	29,607,070
2009	30,545,098
2010	31,238,000
2011	30,916,345
2012	30,860,913
2013	29,315,822
2014	30,142,653
2015	30,311,349
2016	32,311,349
2017	34,300,999
2018	37,311,349
2019	39,312,000

Case Studies

Case I-The Mystery of the Missing Data (Misconduct) [Use Applicable PHS Rules]

Professor Powers ran a large laboratory at the University of East-West. There were, at any time, at least 10 post-doctoral students. One of those students, Harrison Green, was an intense young man bent on getting as many publications under his belt as possible during his two-year stay at the laboratory. Green was on an NIH training grant. During his first year, he had published a number of papers all in mediocre journals. Indeed, during that year he had submitted 6 articles for publication. None was earth shattering. Quantity appeared to be Green's primary objective.

Recently, he had been attempting to develop a new anti-sense technique that would more easily enable one to shut down the expression of a particular gene. At first, Green was having difficulty getting his technique to work. As a result, he had gone 5 months without generating publishable data. Suddenly, during a laboratory meeting, Green announced that he had gotten his technique to work and produced data showing a statistically significant reduction in the amount of the target protein expressed by cells that had been subjected to his new technique. Specifically, during his presentation, he set out data from a series of 29 experiments using independent controls (15 experiments) and treatments (14 experiments). His data, as presented during the lab meeting, are set out in Attachment 1. Although the results were not spectacular, they were, in Powers' opinion, worthy of publication. Green indicated that he would set about writing up his results immediately.

That evening, while in the laboratory near where Green worked, Powers received a telephone call giving her directions on how to get to a social event planned for the next evening. She needed some paper to take down the directions and without thinking, she reached into a trashcan and pulled out some crumpled paper; she took down the directions on the reverse side of the paper.

About a week later, Powers was going through her pockets and found the crumpled up paper with the directions. She was about to toss it out when she noticed that there were data on the other side. The data appeared to be almost identical to those presented by Green and indeed, she recognized the writing as belonging to Green. She studied the data and remembered that the compilation that Green had presented during the lab meeting had one more control than treatment, whereas these data had an equal number. She pulled out Green's loose-leaf notebook and compared the two. She immediately noticed that the scratch paper had an extra data point that Green had apparently deleted from the treatment group. With that extra data point included Green's results appeared no longer to be statistically significant. Indeed, this very fact was noted on the scratch paper: "p > .05. No Good."

The next day, Powers asked Green why he had deleted the data point. Green responded

that it was an outlier and had been deleted because he had botched the experiment that day and felt justified in tossing the point out. Green said that the statement "no good" indicated that he had botched an experiment. Powers asked to see the raw data for that experiment. Green got out his notebook and leafed through it. The raw data for the other 29 experiments (15 control and 14 treatment) were present. The raw data page for the discarded experiment was missing. Green had no explanation.

That evening, while pondering what to do, Powers reanalyzed Green's data and found, much to her surprise, that Green had miscalculated the t value the first time around and that even including the discarded treatment value of 109, Green's original results were actually statistically significant at the .05 level.

What should Powers do, if anything? If you were a university administrator judging the case, how would you resolve it?

**Case II-Revenge of the Disgruntled
Post-Doc (Misconduct)
[Use Applicable PHS Rules]**

Felicity Frank had been a professional post-doc, having spent five years in John Mulligan's laboratory. During her first few years at the lab, Frank had helped Mulligan write a number of successful NIH grant applications. Moreover, Mulligan and Frank had, at one point, been lovers. However, their personal relationship soured and pretty soon that began to affect their professional relationship. One day, Mulligan announced that he thought it would be a good idea if Frank looked for a tenure track position. Frank, who wasn't particularly interested in leaving the lab, paid no attention to Mulligan's suggestion. Frank had noticed, though, that Mulligan had been submitting grant applications without Frank's assistance and further, that Frank was not included in the budgets for these applications.

One day, Mulligan handed Frank a letter which read as follows:

As we have discussed, it is critical for your career development that you obtain a tenure track position at a major research university. Your ability to do so is likely to be adversely affected if you remain in this lab as a post doc for much longer. Accordingly, I have decided, after consulting with the Dean, not to renew your contract. As you know, your contract is due to expire at the end of next month.

Sincerely yours,

John Mulligan, Ph.D.

Frank was furious. She tried to discuss the matter with Mulligan, but he refused to talk to her. That evening, she returned to the laboratory and photocopied all of the grant applications that Mulligan had submitted after their relationship had soured. None of those applications included Frank. During the next few weeks, she examined each application in detail. Finally, in one application she noticed that the 300-word method section for one of the proposed experiments was a verbatim copy of the method section that she had written for one of her articles. The method section in the application did not reference the article. In that article, Frank was the first author, Martin and Goldstein, other researchers in the lab, were the second and third authors, respectively, and Mulligan was the last author. Frank had developed the method and had written up the entire paper. Although Mulligan did no work on the paper, he was included as the senior author because it was custom to include the head of the lab on all papers generated by researchers in that lab.

Frank also noticed that in discussing another proposed experiment, the application contained the following statement: "We have already run some of these experiments on rabbits and they demonstrate that our method is viable." Frank remembered that at the time the application was submitted, Mulligan had been unable to get the rabbit experiment to work. However, two weeks before the study section met, he had succeeded in getting the experiment to work.

The next day, Frank files with the dean charges of scientific misconduct against Mulligan. The dean convenes an inquiry panel. You are a member of that panel. How would you resolve this case?

Case III-The Case of the Repressed Researcher (Human Subjects)

Elizabeth Soarer was a star experimental psychologist at the University of Western Technology focusing on the way in which an individual's memory can be inadvertently influenced by irrelevancies--both visual and linguistic. Her seminal work involved a video of a car crash in which subjects were asked various questions about the accident. Half of the subjects were asked how fast the car was going as it passed the red barn; the other half were not asked that question. Two weeks later, the subjects were called in and asked questions about what they remembered about the video. One question was whether they had seen a red barn. The overwhelming majority of those who were asked about the red barn two weeks earlier, answered in the positive. There was no red barn. The overwhelming majority in the control group answered that question correctly.

Recently, Soarer has shifted her attention to the reliability of repressed memory among young adults, who suddenly accuse a parent of having molested them when they were much younger. Soarer enlisted the help of a journalism professor (Winchell) at another state university to help her. The two focused on a particular case in which an adult in her twenties suddenly remembered having been molested by her father when she much younger. These memories were recalled after she had been interviewed by a clinical psychologist, I. M. Young, who specializes in repressed memories. The psychologist wrote up his findings using pseudonyms. Both Soarer

and Winchell smelled a rat. Scouring the records, they found that during a presentation at a psychology conference, Young let slip the name of the town in California where the molestation allegedly took place. With the help of a private detective, Soarer and Winchell were able to find a couple from that town with a daughter of the appropriate age who had gone through a messy divorce. They interviewed the father who confirmed that his daughter was the one whose memory was magically restored. When Soarer and Winchell sought an interview with the daughter, she not only refused, but filed a complaint with each professor's IRB alleging that neither had IRB approval and that interviews were being conducted without informed consent.

How would you resolve this case?

Case IV-The Case of the Compromised Collaboration (Human Subjects)

Kevin Motely entered Greater Ascension Treatment Center and Hospital ("GATC") as an outpatient for a routine screening colonoscopy. During the procedure, Kevin's physician detected a polyp, which he removed and sent off to pathology. The polyp was benign. However, unbeknownst to Motely or his physician, the chief pathologist, Gregor Van Husen, stored the unused portion of the polyp along with each patient's basic information-Name, Address, DOA, DOB, Zip Code, age, race, religion, and insurer.

A few months later, Van Husen, who is an amateur epidemiologist, obtained IRB approval to conduct a prospective study of colonoscopy patients. Under the approved protocol, he contacted each patient who has had a benign polyp removed to find out whether the patient would be interested in participating in a prospective study of eating habits and the development of future polyps, both benign and otherwise. If a subject were interested, he or she would be given a lengthy informed consent form which described the study. Specifically, the IRB-approved informed consent form, in pertinent part, contained the following:

This study poses no medical risks to you. You will be asked to complete a questionnaire containing questions about your eating and life style habits, medical history, and ancestry. Each year, someone from the study will contact you and ask if you have had a colonoscopy during the year, and if so the results. The person contacting you will also ask about your eating and life style habits during the year. The information that we obtain will be confidential and the results will be published only in the aggregate.

After about two years, Van Rusen found some interesting trends, but nothing really worth publishing. He was somewhat disappointed.

One Saturday, while mulling over what to do with all of his data, he decided that it would be interesting to run some basic genetic screens on the polyp samples that he collected. Van Husen, however, was not a bench scientist. He called his good friend, Arthur Crickson, who had done a fair amount of gene screenings. Crickson was a professor at nearby North Eastern Research and Development Center, part of Tech U. During the next nine months, Crickson and Van Husen ran various screens on the tissue samples. The results were, in Crickson's view, earth shattering. Crickson had located a gene in those samples with Mediterranean ancestry that correlated remarkably well with the development of polyps; the results were even more startling because they were relatively insensitive to diet or life style.

How would you resolve this case?

Case V-The Problem of the Prolific Professors (Misconduct)

Dr. William Peters is a well-respected researcher in biophysics. Originally trained as a theoretical physicist, Peters learned biology on his own, more than 30 years ago, while a graduate student. Since then he has pioneered many innovations in the field. Peters has always had difficulty aiming his publications at the "right" audience. Much of his work, whether it is theoretical or empirical, can be written for at least two audiences. As a general rule, biologists will not understand the physics laden component of his research, while physicists have difficulty grasping the more technical biological component of his work. Frequently, Peters finds that the best way to solve this problem is to write for a general science audience, publishing in journals like NATURE or SCIENCE. Occasionally, however, he attempts to address multiple audiences.

Recently, he and his colleague, Robert Roberts, completed an experiment that yielded surprising results. Given the likely impact of the experiment, Peters submitted the article reporting on the experiment to a general science journal, similar to NATURE or SCIENCE. Unbeknownst to Peters, his co-author, Roberts, had submitted a similar article to a physics journal. Consistent with past practices, both of their names were included as authors on each of the two submissions. However, neither was aware of the other's submission, until both articles had been accepted. Part of the confusion stemmed from the fact that Roberts was on sabbatical in Australia.

At that point, the two decided to modify the physics article to make it more physics oriented. Neither needed additional publications; they both had tenure. They were both concerned, however, that the general science article had lost some of its flair when the physics had been edited out so as to appeal to the more general audience. They therefore decided to permit both articles to be published even though the underlying data were identical and would appear simultaneously in both journals.

Soon after publication, the editors of both journals realized the similarity. Acting together, the editors wrote both Peters and Roberts scathing letters criticizing them for violating

the journals' policies against duplicative publication and demanding an apology from both. Peters and Roberts were both taken aback by the letters, but wrote the apology thinking that that would end the matter.

Unfortunately, the editor of the general science journal was still miffed. He called the federal agency that had funded the research and filed a formal misconduct charge against both Peters and Roberts. The agency refers the matter to the university for appropriate action. You are the Dean of the School of Arts and Sciences. What should you do?

Process for Resolving Allegations of Scientific Misconduct

(See 42 C.F.R. Part 93)

The process for resolving allegations of scientific misconduct in research funded under the Public Health Service Act (PHS Act) is a cooperative effort involving the institution that received the funding and the Department of Health and Human Services acting through its Office of Research Integrity (ORI). The process involves four discreet steps, the first two are undertaken by the awardee institution and the last two by ORI. Those steps are as follows:

1. Inquiry- To be completed by awardee institution within 60 days.

Under federal law, an awardee institution is required to initiate an inquiry into any allegation of scientific misconduct. The inquiry is a preliminary fact finding process and may be conducted by a committee or single individual. There are no federal requirements concerning the precise procedures to be used other than the following:

- a. Should be completed within 60 days
- b. Inquiry panel or person must have no conflict of interest and must possess requisite scientific expertise
- c. Must determine whether there is sufficient evidence to warrant further investigation
- d. Should gather and sequester all pertinent laboratory records
- e. Should provide minimum due process (*e.g.* , notification, opportunity to be interviewed).
- f. Must prepare written report
- g. Must treat matter as confidential

2. Investigation--To be completed by awardee institution within 120 days.

If, following the inquiry, there is sufficient evidence to indicate that misconduct may have been committed, the awardee institution is required to undertake an investigation. An investigation is a formal fact-finding process and as such, the institution is required to examine all available evidence. As with the inquiry, there are no obligatory procedures; the institution is free to adopt whatever procedures it deems appropriate. Most institutions use an inquisitorial model in which an *ad hoc* investigative committee is empanelled to interview the complainant, the respondent, and all other witnesses. The interviews are conducted behind closed doors and the transcripts are not shared with either the respondent or any witness. In contrast, a few institutions have adopted an adversary model in which the respondent is permitted to be present during the interviews and to question each witness. Whatever model is used, there are certain basic federal requirements, as follows:

- a. Must commence within 30 days after inquiry and should be completed within 120 days after it is commenced
- b. Investigation panel must be free of conflicts and have requisite scientific expertise
- c. Should examine all pertinent laboratory records and all witnesses
- d. Should provide minimum due process (*e.g.*, notification spelling out the charges to be investigated, the nature of the investigation, opportunity to be interviewed).
- e. Must treat matter as confidential
- f. Must prepare and submit to ORI a detailed written report setting out, among other things, the findings and sanctions, where appropriate

3. ORI Review

After receiving an investigative report from an institution, ORI reviews the report and decides whether it agrees or disagrees with the institution's findings. This paper review process can take from three months to more than one year. During the review, ORI may ask the institution for additional information, but it rarely conducts an investigation of its own. During the ORI review process, the institution should keep the matter confidential. In the event that ORI confirms the institution's finding of misconduct, the following occurs:

- a. ORI notifies respondent that it has confirmed the institution's finding of misconduct and that ORI has found that respondent committed misconduct in science. ORI indicates in the notice the additional sanctions that it will impose (*e.g.*, cannot sit on an NIH study section for three years, receive grant or contract funds for 3 years, retract certain papers);
- b. Respondent is given 30 days in which to appeal the ORI findings

- c. If respondent does not appeal, then the findings become final and are published in the Federal Register, are posted on the Web and appear in the NIH Guide to Grants and Contracts. More than 90 percent of the respondents who have been found by ORI to have committed misconduct elect not to appeal
- d. If respondent files an appeal with the Departmental Appeals Board, then the matter becomes public at that point.

ORI has only disagreed with an institution's finding of misconduct in one case. However, in the unlikely event that ORI fails to confirm the institution's finding of misconduct, ORI could conduct an investigation of its own or remand the matter to the institution for a new or supplemental investigation.

4. Departmental Appeals Board Hearing

As noted above, a respondent can appeal ORI's finding of misconduct to the Departmental Appeals Board (DAB). In the event that an appeal is lodged, an administrative law judge ("ALJ") conducts a trial-like hearing at which ORI attorneys act as prosecutors. ORI anticipates that the institution will assist it in preparing the government's case.

At a DAB hearing, the burden of proof is on ORI to establish by a preponderance of the evidence that the respondent committed misconduct. DAB hearings normally last about five to ten days, and are conducted in the most convenient location (*e.g.*, city where the most witnesses reside, most records are located). It should be noted that DAB lacks subpoena power.

After the hearing is completed, the parties file proposed findings of fact and conclusions of law. The ALJ is supposed to issue a decision within 60 days of the last submission. The ALJ decision is only a "recommendation" and the Assistant Secretary for Health may review that decision and may modify it.

Attachment 1**CRUMBLED PAPER FOUND
BY DR. POWERS****PAGE PRESENTED AT
LABORATORY MEETING**

6/28/98
Compilation of Data

6/28/98
Compilation of Data

	Treatment	Control		Treatment	Control
	48	79		48	79
	54	85		54	85
	59	80		59	80
	62	105		62	105
	65	92		65	92
	59	76		59	76
	109	100		66	100
	66	100		55	100
	55	81		65	81
	65	89		49	89
	49	90		98	90
	98	72		65	72
	65	80		78	80
	78	32		12	32
	12	36			36
Mean		62.93	79.80		59.64
					79.80

T Test (2 tailed)

p>0.05 "No Good"

p= 0.00561

Attachment 2-Real Cases

I. Case Summary: Cokonis, Melanie

Findings of Research Misconduct and Administrative Actions

- 2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Findings of Research Misconduct AGENCY: Office of the Secretary, HHS. ACTION: Notice.

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

Melanie Cokonis, Southern Research Institute: Based on the report of an investigation conducted by Southern Research Institute (SRI) and additional analysis conducted by ORI in its oversight review, ORI found that Ms. Melanie Cokonis, former Research Technician, SRI, engaged in research misconduct in research supported by National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), contracts N01-AI-30047 (HHSN2722011000009C) and N01-AI-70042 (HHSN272200700042C), and National Human Genome Research Institute (NHGRI), NIH, grant U54 HG005034.

ORI found that the Respondent engaged in research misconduct by falsifying assay data that were submitted in reports to NIH. Specifically, ORI found that Respondent knowingly falsified data for cytoprotection assays with antiviral compounds and provided the false data for inclusion in reports submitted to NIH for contracts N01-AI-30047 and N01-AI-70042 and grant U54 HG005034. Respondent transferred raw data from 8X12 SoftmaxPro matrix files into spreadsheets and then falsified the numbers for cell control, virus control, drug cytotoxicity, drug only, and/or cells+ virus+ drug wells to make 206 assays appear to have been successfully performed when they were not.

Ms. Cokonis has voluntarily agreed for a period of three (3) years, beginning on May 29, 2014:

(1) to exclude herself from any contracting or subcontracting with any agency of the United States Government and from eligibility or involvement in nonprocurement programs of the United States Government referred to as "covered transactions" pursuant to HHS' Implementation (2 C.F.R Part 376 et seq) of OMB Guidelines to Agencies on Governmentwide Debarment and Suspension, 2 C.F.R. Part 180 (collectively the "Debarment Regulations"); and

(2) to exclude herself voluntarily from serving in any advisory capacity to PHS including, but not limited to, service on any PHS advisory committee, board, and/or peer review committee, or as a consultant.

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II. Case Summary: Chen, Li

Findings of Research Misconduct and Administrative Actions

- 2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Findings of Research Misconduct AGENCY: Office of the Secretary, HHS. ACTION: Notice.

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

Li Chen, Ph.D., Mount Sinai School of Medicine: Based on evidence and findings of an investigation report by Mount Sinai School of Medicine (MSSM) transmitted to the United States Department of Health and Human Services (HHS), Office of Research Integrity (ORI), in April 2010 and additional analysis conducted by ORI in its oversight review, ORI found that Dr. Li Chen, former Postdoctoral Fellow, Department of Gene and Cell Medicine, MSSM, engaged in research misconduct in research that was supported by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), grant R01 DK062972 and National Institute of General Medical Sciences (NIGMS), NIH, grant P20 GM075019 and was submitted in grant applications R01 DK074695 and R01 DK083286 to NIDDK, NIH, P20 GM075019 to NIGMS, NIH, and R01 NS062054 to the National Institute of Neurological Disorders and Stroke (NINOS), NIH.

ORI found that the Respondent intentionally, knowingly, and recklessly fabricated and falsified data reported in four (4) publications, one (1) submitted manuscript, and four (4) grant applications:

- Chen, L., & Woo, S.L.C. "Complete and persistent phenotypic correction of phenylketonuria in mice by site-specific genome integration of murine phenylalanine hydroxylase cDNA." *Proc. Natl. Acad. Sci. U.S.A.* 102(43):15581-15586, October 2005 (hereafter referred to as "PNAS 2005")
- Chen, L., Thung, S.N., & Woo, S.L.C. "Metabolic Basis of Sexual Dimorphism in PKU Mice After Genome-targeted PAH Gene Therapy." *Mol. Ther.* 15:1079-1085, June 2007; Retracted in December 2010 (hereafter referred

to as "Mol. Ther. June 2007")

- Chen, L., & Woo, S.L.C. "Correction in Female PKU Mice by Repeated Administration of mPAH cDNA Using phiBT1 Integration System." *Mol. Ther.* 15:1789-1795, October 2007; Retracted in December 2010 (hereafter referred to as "Mol. Ther. Oct. 2007")
- Chen, L., & Woo, S.L.C. "Site-Specific Transgene Integration in the Human Genome Catalyzed by 0BT1 Phage Integrase." *Hum. Gene Ther.* 19:143-151, February 2008; Retracted in August 2010 (hereafter referred to as "HGT 2008")
- Chen, L., Roy, I., Prasad, P.N., & Woo, S.L.C. "Nanoparticle-Based Gene Therapy for Metabolic Disorders: Hepatic Delivery of Minicircle DNA for Complete Correction of Phenylketonuria." Submitted for publication in *Proc. Natl. Acad. Sci. U.S.A.* (hereafter referred to as the "PNAS 2008 manuscript")

- R01 DK074695, "Genome-targeted PAH Gene Integration in PKU Mice and Sexual Dimorphism," Savio LC. Wood, Ph.D., Principal Investigator (P.I.) (hereafter referred to as "R01 DK074695")
- P20 GM075019, "Growth, Differentiation & Genetic Alteration of Human ES Cells," Gordon M. Keller, Ph.D., P.I. (hereafter referred to as "P20 GM075019")
- R01 NS062054, "Nanoparticle-mediated Gene Therapy for PKU," Savio L. Woo, Ph.D., P.I. (hereafter referred to as "R01 NS062054")
- R01 DK083285, "Nanoparticle-Mediated Gene Therapy PKU," Savio L. Woo, Ph.D., P.I. (hereafter referred to as "R01 DK083285")

The Respondent fabricated figures reporting the chromosomal locations of integration sites, fabricated data reporting the use of polymerase chain reaction (PCR) to determine integration frequencies, falsified data representing the detection of chromosomal translocations in human cells, and fabricated figures by falsely reporting the results of High-Performance Liquid Chromatography (HPLC) assays. The Respondent also falsified experimental data for Lacz stained liver sections and for hematoxylin and eosin (H&E) stained liver sections.

Specifically, ORI finds by a preponderance of the evidence that the Respondent engaged in misconduct in science and research misconduct by intentionally, knowingly, and recklessly:

1. fabricating and/or falsifying nineteen (19) figures by falsely reporting that phenylketonuria (PKU) gene therapy experiments were successfully completed, when the available evidence shows the experiments were not performed; specifically the Respondent:

(a) fabricated figures where DNA sequencing was purportedly used to identify the chromosomal locations of integration sites for the PAH gene in mouse and human cells, reported in seven (7) figures:

(b)

- PNAS 2005, Figure 2A
- HGT 2008, Figures 3b and 3c
- R01 NS062054, Figures 3 and 20
- R01 DK074695, Figure 6
- R01 DK083286, Figure 17
- P20 GM075019, Figure 4

(c) fabricated data purportedly representing the use of PCR to determine integration frequencies for the phenylalanine hydroxylase (PAH) gene and the secreted embryonic alkaline phosphatase (SEAP) reporter gene, in mouse and human cells, reported in eleven (11) figures:

- PNAS 2005, Figures 2C and 38
- Mol. Ther. June 2007, Figures 2a and 5a
- Mol. Ther. Oct. 2007, Figures 2d and 5a
- HGT 2008, Figure 4
- R01 NS062054, Figure 4b and 10a
- R01 DK074695, Figure 7b
- R01 DK083286, Figure 2b

(d) falsified figures representing the detection of chromosomal tranlocations in human cells, purportedly determined by PCR in two (2) figures:

- HGT 2008, Figure 5a
- R01 NS062054, Figure 21a

2. fabricating the results of HPLC assays to show generally lowered blood levels of phenylalanine after PKU gene therapy and to show liver levels of BH4 when the Respondent did not have the HPLC data needed to support those claims; specifically the Respondent:

(a) fabricated serum phenylalanine graphs in:

- PNAS 2005, Figure 48; this false data also is presented in R01 DK074695, Figure 10b
- Mol. Ther. June 2007, Figure 1a; this false data also is presented in R01 DK074695, Figure 11
- R01 DK083286, Figure 3; this false data also is presented in Mol. Ther. June 2007, Figure 3, and R01 NS062054, Figure 7
- Mol. Ther. Oct. 2007, Figure 4a; this false data also is presented in R01 NS062054, Figure 9a
- PNAS 2008 manuscript, Figure 4

(b) fabricated graphs for BH4 levels in:

- Mol. Ther. June 2007, Figure 5c; this false data also is presented in R01 NS062054, Figure Sc

3. falsely reporting the results of LacZ stained liver sections by reusing and relabeling an image and claiming that it represents different experiments; specifically, the same image was used to represent mice treated with a nanoplex gene delivery system in R01 NS062054, Figure 14b (right panel), and also to represent a wholly different experiment for mice treated with 10 injections of the phiBT1 integrase system alone in R01 NS062054, Figure 4c (right panel), and Mol. Ther. Oct. 2007, Figure 2b (D panel)

4. falsely reporting the results of H&E stained liver sections in R01 NS062054, Figure 6, by using the identical image to represent four (4) different experimental treatments of H&E stained liver sections; specifically the Respondent reused and relabeled one image to represent liver sections from mice that received either 1 or 10 injections, with or without the phiBT1 integrase plasmid.

The Respondent failed to take responsibility for the fabrication and falsification described in ORI's findings.

The following administrative actions have been implemented for a period of three (3) years, beginning on April 11, 2014:

(1) Respondent is debarred from any contracting or subcontracting with any agency of the United States Government and from eligibility for, or involvement in, nonprocurement programs of the United States Government referred to as "covered transactions" pursuant to HHS' Implementation (2 C.F.R. Part 376 et seq) of Office of Management and Budget (OMB) Guidelines to Agencies on Governmentwide Debarment and Suspension, 2 C.F.R. Part 180 (collectively the "Debarment Regulations"); and

(2) Respondent is prohibited from serving in any advisory capacity to PHS, including but not limited to service on any PHS advisory committee, board, and/or peer review committee, or as a consultant.

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III. Case Summary: Freeman, Helen

Findings of Research Misconduct and Administrative Actions

- 2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Findings of Research Misconduct AGENCY: Office of the Secretary, HHS. ACTION: Notice.

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

Helen Freeman, Ph.D., Harvard Medical School and Beth Israel Deaconess Medical Center: Based on an investigation conducted by Harvard Medical School (HMS) and Beth Israel Deaconess Medical Center (BIDMS) and additional analysis conducted by ORI in its oversight review, ORI found that Dr. Helen Freeman, former HMS Postdoctoral Fellow at BIDMS, engaged in research misconduct in research supported by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), grant R37 DK053477.

ORI found that the Respondent engaged in research misconduct by knowingly and intentionally falsifying three (3) figures and/or legends and one (1) supplemental movie legend in a manuscript submitted for publication to the journal *Nature* (Freeman, H.C., Kong, D., Sidman, R.L., & Lowell, B. "Inhibition of UCP2 Prevents Neurodegenerative Diseases in Mice.").

Specifically, ORI found that Respondent:

- . falsified Figure 6 and its legend in a manuscript submitted to *Nature* by claiming that the experiment represented histological and rotarod results from 5 week old *pcd3J^{-/-}* mice treated with saline or *pcd3J^{-/-}* - mice treated with genipin when the genotype, treatment conditions, numbers of mice used, and mice age were not as claimed; these falsified data also were presented to a colleague for use in related experiments
- . falsified Figure 4, Supplementary Figure 3, and Supplementary Movie 1 and/or its legends in a manuscript submitted to *Nature* by claiming that the knockout of UCP2 rescues the ataxic phenotype of *pcd3J^{-/-}* mice when she knew this to be false.

Dr. Freeman has voluntarily agreed for a period of three (3) years, beginning on May 6, 2014:

- (1) to have her research supervised if employed by an institution that receives or applies for U.S. Public Health Service (PHS) funding; Respondent agreed that prior to the submission of an application for PHS support for a research project on which the Respondent's participation is proposed and prior to Respondent's participation in any capacity on PHS-supported research, Respondent shall ensure that a plan for supervision of Respondent's duties is submitted to ORI for approval; the supervision plan must be designed to ensure the scientific integrity of Respondent's research contribution; Respondent agreed that she shall not participate in any PHS-supported research until such a supervision plan is submitted to and approved by ORI; Respondent agreed to maintain responsibility for compliance with the agreed-upon supervision plan;
- (2) that any institution employing her shall submit, in conjunction with each application for PHS funds, or report, manuscript, or abstract involving PHS-supported research in which Respondent is involved, a certification to ORI that the data provided by Respondent are based on actual experiments or are otherwise legitimately derived and that the data, procedures, and methodology are accurately reported in the application, report, manuscript, or abstract; and
- (3) to exclude herself voluntarily from serving in any advisory capacity to PHS including, but not limited to, service on any PHS advisory committee, board, and/or peer review committee, or as a consultant.

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