Findings and Consequences of Research Misconduct

DEFINING RESEARCH MISCONDUCT

Any institution that applies for or receives Public Health Services (PHS) support for biomedical or behavioral research, research training or activities related to that research or research training are subject to ORI's guidelines defining and enforcing research misconduct. Activities applicable to ORI guidelines include:

- "Grant applications or proposals;
- Research training or activities related to that research or research training and training programs;
- Activities related to research or research training, such as the operation of tissue and data banks or the dissemination of research information;
- Plagiarism of research records produced in the course of PHS supported research, research training or activities related to that research or research training." (DHHS 2005)

ORI defines "research misconduct" as:
"…fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

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

"To be considered research misconduct, actions must:

- represent a "significant departure from accepted practices";
- have been "committed intentionally, or knowingly, or recklessly"; and
- be 'proven by a preponderance of evidence.'"

CONSEQUENCES OF MISCONDUCT

Findings of research misconduct may result in debarment or a voluntary exclusion agreement. In 2005 ORI received 265 allegations of research misconduct; only eight resulted in either a Voluntary Exclusion Agreement or debarment (Weiss). Individuals and institutions may be disbarred or excluded. Debarred individuals or institutions may not participate in any research and supervisory roles involving Federal procurement or non-procurement transactions; debarments are government wide. Debarments are the result of an ORI investigation where ORI determines that there is reasonable evidence to

conclude that research misconduct has occurred. Voluntary Exclusion Agreements are often the result of an agreement between ORI and the alleged individual or institution in lieu of a full investigation; they are, metaphorically speaking, a plea of "No Contest". Excluded individuals or institutions may also be prohibited from participating in research involving Federal procurement and non-procurement transactions; however, sometimes individuals or institutions may only be prohibited from participating in advisory roles. Individuals and institutions who are debarred or enter into voluntary exclusion agreements are placed on ORI's public list PHS Administrative Action Bulletin Board for a period of three years. The FDA maintains a separate list of debarment or other administrative actions.

In two complete years of data available on the ORI website for Public Health Services (2006 – 2007),[1] ORI during its oversight review for the U.S. Public Health Services found reasonable evidence to warrant administrative action regarding research misconduct in twenty-four cases. Twenty-one of the twenty-four closed investigations involved data falsification and/or fabrication. One of those twenty-one cases involved the use of images as data. In that case, the investigator, a doctoral student, darkened with a marking device multiple sections of the image including the original autoradiographical film. One of the twenty-four cases involved data destruction and falsification of records to hide the data destruction. One other case involved mail fraud, criminally negligent homicide, and making false statements. In years 2006 and 2007, fifteen of the twenty-four closed investigations involved some kind of student—doctoral students, graduate students, postdoctoral students, medical residents, and even one undergraduate student. Nine of the twenty-four closed investigations involved researchers in other categories.

Consequences for research misconduct depend upon the severity of the misconduct. In the aforementioned years, fifteen closed investigations resulted in a Voluntary Exclusion Agreement and eight in debarment. One individual was excluded for two years, three individuals were excluded for five years, and two individuals were excluded permanently/lifetime; the remaining nine were excluded for three years. Eight individuals were debarred ranging from three to five years. The most severe of those, the criminally negligent homicide, entailed a seventy-one month imprisonment, payment of restitution of over $690,000, and a lifetime government-wide debarment from "participating in any and all Federal agency transactions to protect the public interest overall". At minimum four—three students and one professor—of the twenty-four closed investigations required the retraction of a published manuscript even if it involved multiple co-authors; one required that data be corrected in the published manuscript.

Individuals who are excluded may sometimes continue to participate in federally funded research. In those cases the individual may not be a PI and the PI or other supervisory authority must submit to ORI a Supervisory Plan designed to ensure the scientific integrity of research conducted by the excluded individual before that individual can participate in the research.

[1] Detailed data for 2005 is no longer available as of January 2008.

CAUSES OF MISCONDUCT

Science, as a field, rests on the foundation that the methods described in the research are accurate. One may disagree with the conclusions, the methodology, the assumptions within the research, etc. but everyone must be able to assume that the data and the procedures are presented accurately. Science is self-correcting in the sense that falsifications will eventually be corrected via ongoing research (Goodstein 2002). Goodstein identifies three motives, or risk factors, commonly present in research misconduct:

> "…the perpetrators (1) were under career pressure, (2) knew, or thought they knew, what the result would be if they went to all the trouble of doing the work properly, and (3) were in a field in which individual experiments are not expected to be precisely reproducible."

Publication keyed to positive outcomes creates an environment prone to career pressure driven misconduct. Research misconduct resulting from the second risk factor is a transgression against the scientific method in addition to the body of knowledge. "Perpetrators think they know how an experiment would come out if they did it properly, and they decide against going to all the trouble of doing it right" (Goodstein 2002). The third risk factor is rarely a motivation in and of itself; rather it is a risk factor for why egregious research misconduct—fabrication, falsification, and deliberate data misrepresentation—occurs more prevalently in the biomedical and related sciences where replication and repetition is pronouncedly more difficult. Discovering research misconduct in these areas usually comes about by a colleague's reporting it, a later admission of guilt, or secondary experiments reliant upon that research does not perform as expected (Goodstein 2002).

EXAMPLE CASES:

UAB: *The BCX-34 and BioCryst Case*

UAB has been teaching research integrity courses since the mid 90's; we are working to develop methods to more accurately evaluate the efficacy of these programs.

A case of misconduct at UAB occurred in the late 90's involving UAB President J. Claude Bennett and the pharmaceutical manufacturer BioCryst. UAB was contracted to conduct a Phase III double-blind, randomized, placebo controlled trial of the topical formulation of BCX-34, which was being billed as a potential treatment for psoriasis associated with cutaneous T-cell lymphoma. Dr. W. Mitchell Sams Jr., chairman of the dermatology department at UAB and an expert on T-cell lymphoma, was to conduct the double blind study of BCX-34's efficacy. Renee Peugeot, a nurse, was later hired to assist with the study. Peugot is the wife of Harry Snyder Jr., the scientist overseeing the study for the company.

The UAB BioCryst BCX-34 case involved image manipulation in addition to multiple other instances of research misconduct. Peugeot in early study trials traced lesions very loosely making them appear larger than the very tight tracings she performed in later trials, a clear instance of image processing which, in the continuum between best practices and misconduct, falls on the side of misconduct. When numerical data related to lesion size was found to be missing from a patient's chart, and Peugeot was asked about the data, she wrote in a number claiming to have remembered it from an examination performed over a week earlier. This was judged to be an instance of data fabrication. Furthermore, Peugeot and Sams often disagreed, in front of patients, over the size and redness of lesions. It was Peugeot's assessments that were recorded on patient charts and not Sams's assessments, a biochemist and M.D. and the study leader.

Dr. William Cook, hired by UAB to be Snyder's boss, requested examination of the randomization schedule (the "code key" identifying control and experimental patients) after BioCryst made public announcements regarding BCX-34's positive efficacy in the early trials for FDA approval. Cook wanted to begin writing the scientific paper. He found that the data results did not match the information supplied to the FDA and NASDAQ. Cook then asked a study coordinator, a subordinate of Snyder, for the printed copy locked in a cabinet. Again the data results neither matched the public data nor the data results from the randomization charts supplied by Snyder. Snyder created a false randomization chart, a clear instance of data falsification as defined by ORI.

The FDA barred Sams for life from testing drugs due to his failure to properly supervise the studies. Peugeot and Snyder were found guilty in criminal court of conspiracy, mail fraud, and making false statements to the FDA.

Subsequent studies not performed by Sams, Peugeot, Snyder, or Bennett revealed that BCX-34 performed at least equally as well as the placebo in 30% of cases and the placebo outperformed BCX-34 in reducing lesions in 70% of cases.

Where did the reasoning go wrong?

The UAB BCX-34 case involves clear examples of data fabrication, falsification, and misrepresentation. Peugeot fabricated data by writing data onto patient charts not based upon clinical examinations. Snyder falsified data by creating alternate randomization schedules. Peugeot misrepresented data, if not falsified and fabricated data, by subjectively drawing lesions to give the impression of positive treatment outcomes.

We may ask two different questions: Why are these actions scientifically wrong? Why are these actions morally wrong? Here we are concerned with the latter question. T-cell lymphoma has no known cure. The BioCryst executives were claiming, based upon falsified data, that BCX-34 provided a potential cure for T-cell lymphoma, a deadly form of cancer. If the falsified data had not been discovered by Cook, BCX-34 may have been on the path towards FDA approval. The health of patients utilizing BCX-34 would have been highly compromised; patients may have forgone other treatments with positive

effects for BCX-34 with no positive effects. As medical professionals Peugeot, Snyder, and others violated their Hippocratic Oath of "do no harm"—their data falsification, fabrication, and misrepresentation entailed a potential for malfeasance. In presumed marketing of BCX-34, if awarded FDA approval, BioCryst would have violated the principle of truthfulness. Once exposed, the misrepresentation of BCX-34's efficacy would have undermined public confidence in medical testing, health professionals, researchers (some of whom, like Sams, perform dual functions as educators), and the broader scientific community whom the public views as impartial seekers of the truth. Medical professionals and researchers are stewards of public health.

Korea: ***Hwang Woo-suk's Cloning and Stem Cell Research***

One of the best known cases of research misconduct occurred in 2005; Hwang Woo-suk's fabricated and falsified data involving the cloning of eleven stem cell lines from 11 patients:

- Digital photographs of two stem cells had been manipulated to make it seem as though they were 11 stem cells from 11 patients cloned.[2]

- DNA comparison tests were misrepresented as comparing DNA from the donor and a cloned stem cell when they really compared DNA from the donor and an embryo from the donor.

- There were also problems with the human subjects practices:
  - not describing the consent process
  - consent forms of collaborators in the US were approved by the IRB but not signed
  - participants suffered side effects not listed in the consent form
  - graduate students enrolled as participants
  - describing methods other than those used
  - colleagues were coerced to donate oocytes and without IRB or equivalent approval

According to Donald Kennedy, editor-in-chief of *Science* as a consequence of this case journals now more closely scrutinize "high risk" papers—research that is of significant public interest, has unexpected or counterintuitive results.

Where did the reasoning go wrong?

In interviews, Dr. Woo-suk stated he firmly believed in the validity of the methods described in the research papers that were not methods actually employed and that one day the fabricated research would be validated by others in the field. His blind faith in the

[2] Refer to Wade article in the *New York Times* to see the images and the process used.

falsified procedures became more important than performing responsible research and the search for knowledge.

It stands to reason that the methods described in the research papers would be replicated by others in the search for patient specified cloned embryonic stem cell medical treatments. His reasoning was short-sighted as others would eventually come forth claiming that the methods described failed to produce cloned embryonic stem cells. Dr. Woo-suk's reasoning amounted to "the ends will justify the means" based upon a hope, not evidence and data.

His reporting falsified and fabricated data undermined public confidence in the scientific community, undermined the profession, and tainted the public's acuity of the ethics of researchers in a field that is itself ethically controversial in the public arena.

In coercing female colleagues to provide oocytes, Dr. Woo-suk violated their autonomy as subjects—i.e., they could not dissent from participating; they were not provided informed consent with the possibility dissenting prior to undergoing medical procedures. Furthermore, as colleagues and subordinates of Dr. Woo-suk, they couple be considered subjects with diminished capacity for autonomy and voluntariness. The procedures for acquiring oocytes entail the potential for long-term harm. The female colleagues reproductive capacity could have been negatively affected by a procedure not the result of their voluntary choice.

The line between researcher and subject was blurred. The IRB regulations differentiate between the two groups as the interests of one, the researcher, are sometimes mutually exclusive from the interests of the other, the subjects. Dr. Woo-suk placed a higher value on the research than the well-being of his female colleagues who simultaneously became subjects. In blurring the line between researcher and subject, the colleagues may have then felt a vested interest in the positive outcome of the research project thereby participating in research misconduct or at minimum not desiring to report the misconduct of another.

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