Responsible Conduct in Research: Research Misconduct

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Objectives

• Introduce the concept and issues surrounding research misconduct

• Review of case studies on research misconduct allegations

• To better understand the regulations and Tulane University policies and procedures applicable to research misconduct
Background

- Prior to World War II, little public funding of research existed.
- Today, public funds support 1/3 of all research and development in the United States and half of all basic research.
- As public funding for research has grown, interest by the public, through its elected officials, has resulted in increased regulation and oversight of research.
Background (continued)

• According to the Federal Office of Research Integrity (“ORI”), in general terms, Responsible Conduct in Research (“RCR”) is good citizenship applied to professional life.

• Researchers who conduct and report their work honestly, accurately, efficiently, and objectively can achieve RCR.
What is research misconduct?

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.

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.
Plagiarism:
the act of presenting another's work or ideas as your own.
What motivates scientific misconduct?

- Career PRESSURE
- Laziness
- Ease of fabrication
Research misconduct does **not** include honest error, misinterpretation of results or differences of opinion.
HOWEVER............

Bias (toward one’s own theory/hypothesis) can sometimes lead to misconduct
Requirements for findings of research misconduct

- There must be a significant departure from accepted practices of the relevant research community.
  and
- The misconduct must be committed intentionally, knowingly, or recklessly.
  and
- The allegation must be proven by a preponderance of the evidence.
Examples of Falsification

- Substituting one subject’s record for that of another subject
- Inflating the number of samples (animals, subjects, etc) that were used
- Deleting data points
- Altering images to appear better
- Altering images and using them multiple times
Examples of Fabrication

- Creating data for experiments that were never done
- Making up subjects
- Splicing together different images to represent a single experiment
- Changing brightness and/or contrast of the image
- Any change that conceals information, even when it is considered not specific
- Showing only a very small part of the photograph so that additional information is not visible
My interest in Misconduct
Core binding factor beta, smooth muscle myosin heavy chain chimeric protein involved in acute myeloid leukemia forms unusual nuclear rod-like structures in transformed NIH 3T3 cells.


Patients with the M4EO subtype of acute myelogenous leukemia almost invariably are found to have a triplication 16q in their leukemic cells, which results in a gene fusion between the transcription factor called core binding factor beta (CBFbeta) on 16q and a smooth muscle myosin heavy chain (SMMHC) gene on 16p. Subcellular localizations of the wild type CBFbeta and the CBFbeta-SMMHC fusion protein were determined by immunofluorescence of NIH 3T3 cells that overexpress wild-type or fusion protein. Normal CBFbeta showed an unexpected perinuclear pattern consistent with primary localization in the Golgi complex. The CBFbeta-SMMHC fusion protein had a very different pattern. Nuclear staining included rod-like crystalline structures as long as 11 micron. The heterodimeric partner of CBFbeta, CBFalpha, formed part of this complex. Cytoplasmic staining included stress fibers that colocalized with actin, probably as a consequence of the myosin heavy chain component of the fusion protein. Selection of different regions of the CBFbeta portion of the fusion protein showed that binding to CBFalpha was not required for nuclear translocation. However, deletion of parts of the SMMHC domain of the fusion protein resulted in myosin-mediated filament formation resulting in proteins that did not form rod-like structures. These observations confirm previous indirect evidence that the CBFbeta-SMMHC fusion protein is capable of forming macromolecular nuclear aggregates and suggest possible models for the mechanisms of leukemic transformation.

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Related Articles
- The leukemic protein core binding factor beta (CBFbeta) smooth muscle myosin heavy chain (SMMHC) domain is involved in the oncogenic activity of the SMMHC fusion protein in vitro. [Blood 2005]
- The leukemic protein core binding factor beta (CBFbeta) smooth muscle myosin heavy chain (SMMHC) domain is required for the oncogenic activity of the SMMHC fusion protein. [Blood 2006]
- Coexpression of CBFbeta and SMMHC results in increased nuclear localization of CBFbeta. [Blood 2007]
- The CBFbeta-SMMHC fusion protein is localized to the nucleus and cytoplasm in human leukemia cells. [Blood 2008]
- The CBFbeta-SMMHC fusion protein is localized to the nucleus and cytoplasm in human leukemia cells. [Blood 2009]

Recent Activity
- Core binding factor beta-smooth muscle myosin heavy chain chimeric protein involved in acute myeloid leukemia.
Outcome

• Francis Collins / Amitav Hajra case

• Fabricated/falsified data in 5 papers

• Findings: NIH GUIDE, Vol. 26, Num. 23, July 18, 1997

• Collins role “Collins was praised for the forthright way he handled the case of misconduct, which had been discovered by a reviewer of a paper that Hajra had submitted to the journal *Oncogene.*” *(Cell, March 10, 2006)*
Misconduct Case: Gelsinger and Univ. of Pennsylvania

- Jesse Gelsinger was the first person publicly identified as having died in a clinical trial for gene therapy. He was 18 years old. Gelsinger suffered from ornithine transcarbamylase deficiency, an X-linked genetic disease of the liver, whose victims are unable to metabolize ammonia - a byproduct of protein breakdown. The disease is usually fatal at birth, but Gelsinger had not inherited the disease; in his case it was the result of a genetic mutation and as such was not as severe - some of his cells were normal which enabled him to survive on a restricted diet and special medications.

- Gelsinger joined a clinical trial run by the University of Pennsylvania that aimed to correct the mutation. On Monday, September 13 1999, Gelsinger was injected with adenoviruses carrying a corrected gene in the hope that it would manufacture the needed enzyme. He died four days later, apparently having suffered a massive immune response triggered by the use of the viral vector used to transport the gene into his cells. This led to multiple organ failure and brain death. Gelsinger died on Friday, September 17th at 2:30 PM.
MISCONDUCT CASE: GELSINGER VS U PENN

- This case includes breaches of protocol
- Inadequate informed consent
- Problems with reporting adverse events
- Conflict of interest
FDA investigation of Gelsinger Case

Earlier patient signs not reported, FDA says

- The FDA approved the trial with certain restrictions. One of them called for the trial to be stopped if patients suffered serious side effects, all of which were to be reported to the FDA.

- On Wednesday, at the start of a three-day meeting investigating what happened in the therapy trial, the FDA accused the researchers of failing to flag reports to the agency of two earlier patients whose tests indicated liver damage that should have stopped the trial.

- The FDA also said the researchers did not inform them that Gelsinger’s ammonia level was so high that he should have been excluded from the trial on the day they gave him the experimental drug.

- The University of Pennsylvania researchers acknowledged they could have called the FDA about the high levels in the two other patients, but said they acted within the agreed-upon protocol.
Not all allegations of “misconduct” in clinical research meet the definition for “Research Misconduct”

The distinction between research misconduct and other problems (such as protocol violations or fiscal malfeasance) is important because

• institutions have different mechanisms for handling the different situations (e.g. inquiry/investigation research misconduct process vs IRB oversight and corrective actions for protocol violations)

• reporting requirements (to oversight agencies such as ORI, OHRP, FDA, sponsors, etc) are different
IRB, OHRP, FDA issues that are **not** research misconduct (in the absence of falsification/fabrication):

- Failure to report adverse event(s) to the IRB/spONSOR
- Protocol deviations (entering ineligible participant or using off-protocol drug)
- Forging physician’s signature on orders
- Failing to obtain or properly document informed consent
- Breaching human subject confidentiality
Research Misconduct: Case Study 1

- Informed Consent documents for a research study contained multiple places for a participant to sign. Audit of study revealed that on some of the signed informed consents, signatures on one part of the form did not match signatures on another part of form (i.e., some signatures appeared to be forged). Was this research misconduct?
- No. Why not?
Research Misconduct: Case Study 1

- Even though this was a noncompliance with federal regulations regarding obtaining informed consent, it was determined not to be “material failure” to comply with federal regulations, nor did it constitute falsification of data or plagiarism.
- The matter was reported to the appropriate federal agency as serious noncompliance but not as research misconduct.
Research Misconduct: Case Study II

- Postdoc’s data could not be replicated by his/her faculty advisor (Dr. Shull) or lab workers.
- Research Misconduct allegation filed by Dr. Shull. Determination: the postdoc falsified and fabricated DNA sequences in unpublished data about a tumor suppressor gene. Was this Research Misconduct?
- Yes. Why?
Research Misconduct: Case Study II

- **Respondent:** Lois Bartsch (University of Nebraska Medical Center)
- **Conclusion of university and ORI:** falsification of data
- **Respondent entered into voluntary exclusion agreement with ORI:**
  1. Debarment for two years
  2. Exclusion from serving in advisory capacity to PHS for three years.
Research Misconduct: Case Study II
– notable quotes from investigation

• “Dr. Shull and I will never be on speaking terms or have a good relationship” (stated by another former Postdoc)
• “There was a general problem of integrity of the work coming out of that lab. Dr. Shull didn’t really audit any of the data. He just wanted answers that matched his hypothesis” (stated by yet another former Postdoc)
Research Misconduct Case Study III: Ward Churchill, Univ. of Colorado

• Wrote essay in 2002 about Sept. 11th terrorist attacks, referring to the WTC workers as “little Eichmanns,” a reference to Nazi Adolf Eichmann.
• Following an public outcry, CU chancellor filed a research misconduct allegation against Churchill.
• Formal finding: “serious research misconduct,” including falsification, fabrication, and plagiarism.
  ◦ Misrepresentation of others’ works to create independent support for claims
  ◦ Cited to other works as independent verification for claims when works were ghost-written by Churchill.
• Disposition: CU fired Churchill in 2007
• Churchill filed wrongful-termination lawsuit
Research Misconduct: Case Study IV

- Co-investigator working on a project alleged that principal investigator created a hostile working environment and did not comply with reporting requirements of the grant. Was this Research Misconduct?

- No. Why not?
Research Misconduct: Case Study IV

- The hostile working environment determined to be an employment issue.
- The failure to comply with reporting requirements was determined not to be a “material failure” to comply with federal regulations, nor did it constitute falsification of data or plagiarism.
Research Misconduct: Case Study V

- Following a 5 years long research misconduct investigation, respondent admitted to falsifying data in 17 grant applications to the NIH and fabricating data in 10 publications over a period of 10 years. Was this Research Misconduct?
- Yes
Research Misconduct: Case Study V

- Dr. Poehlman banned forever from receiving public research money
- Retraction or correction of 10 scientific papers
- Ordered to serve 1 year and 1 day in federal prison for falsifying data in a grant application.
- Agreed to repay $180,000.00 to settle civil complaint by University of Vermont for cost of investigation plus $16,000 to the complainant for attorney’s fees.
Individual and Institutional Responses to Misconduct

- The PHS is responsible for ensuring the integrity of research it supports and monitoring compliance with the federal regulations. Allegations of misconduct generally involve scientists, and scientific expertise may be needed to resolve questions that arise at different stages of review. At the same time, institutions have the administrative and scientific personnel resources to assess allegations. Thus, primary responsibility for responding to allegations of scientific misconduct rests with institutions, while the ORI generally performs a review and oversight function and provides technical assistance, workshops and policy guidance to institutions to enable them to conduct their own investigations.

- The HHS scientific misconduct regulation provides protection for respondents (the accused) and complainants in scientific misconduct cases. Institutions are required to protect the confidentiality of the individuals involved. Respondents are informed about the allegation. During an inquiry, a respondent is usually interviewed, confronts and presents evidence, and suggests witnesses. The draft inquiry report is presented to the respondent for comment. If an investigation follows, the respondent is interviewed, sometimes more than once, confronts and presents additional evidence, and suggests additional witnesses. The investigation report is also presented to the respondent for comment. In addition to protecting the confidentiality of the complainants, institutions are required to undertake diligent efforts to protect the position and reputation of these individuals who make allegations of scientific misconduct in good faith.
Additional Lessons Learned from Research Misconduct Cases

• Any person involved in research may be responsible for misconduct, regardless of rank or duties on the project
• The majority of respondents have held technical positions and not doctoral degree holders
• Common excuse for research misconduct: excessive work loads and/or time pressure.
• Scientific “divorces” are often bitter and irrational; however, the accusations usually do not constitute research misconduct.
Impact of Findings of Misconduct for Individuals and Institutions

- Physical/monetary/psychological harm to employees, research subjects, students or trainees
- Degradation of the University’s reputation, loss of public trust
- Additional regulatory oversight resulting in greater scrutiny, expanded programmatic requirements and greater institutional investments
- Suspension/disqualification of individual researchers
- Fines, penalties, punitive/compensatory damages, debarment and legal defense costs
Tulane’s Research Misconduct Policies:

1. Tulane Research Misconduct Policy (primary policy), Applicable to all allegations of research misconduct except when research is funded by National Science Foundation (“NSF”) or Public Health Service (“PHS”): http://tulane.edu/provost/upload/Faculty-Handbook-updated-Apr13-2009.pdf


- “OIG” is the investigative arm of NSF
- “ORI” is the investigative arm of PHS
Tulane Research Misconduct Policy  
(secondary policy)

- Located in Faculty Handbook, Sec. III(H)(3)
- Defines Research Misconduct as:
  1. **Falsification of data**: ranging from fabrication to deceptive, selective reporting, including the purposeful omission of conflicting data with the intent to falsify results;
  2. **Plagiarism**: representation of another's work as one's own; or
  3. **Violation of Federal Regulations**: material failure to comply with federal requirements that uniquely relate to the conduct of research.
- If the activity is not falsification of data, plagiarism, or violation of federal regulations, the activity is not research misconduct.
Tulane Research Misconduct Policy – the process

• Investigation of a research misconduct allegation is a serious and lengthy process.

• Attempt an informal resolution, by speaking with supervisor or responsible academic officer (e.g., Chair, Dean, etc.).
Tulane Research Misconduct Policy – the process

- Complainant files written allegation with respondent’s Dean or chief administrator of the division in which the respondent resides:
  - **Complainant**: person making the accusation of research misconduct
  - **Respondent**: person accused of research misconduct

- Complaint can also be filed with Research Compliance Officer, (“RCO”) who will report allegation to Dean.
  - RCO has duty to consult confidentially with persons uncertain about whether to submit a research misconduct allegation
Tulane Research Misconduct Policy
– the process (continued)

- Complainant can request to remain anonymous.
- University must protect complainant who has made an allegation in good faith, even if the allegation is not sustained.
- Respondent (person accused of misconduct) has due process rights, and the identification of respondent must be kept confidential throughout process.
Tulane Research Misconduct Policy – the process (continued)

4 Stages of the process:

1. Inquiry
2. Investigation
3. Formal Finding
4. Appropriate Disposition.
Tulane Research Misconduct Policy - Inquiry

• Dean makes the initial determination as to whether the allegation falls under the definition of research misconduct.

• If yes, then Dean begins an “Inquiry.” Dean may conduct the Inquiry or appoint an ad hoc Inquiry Committee.

• Respondent must be informed of the allegation at the outset of Inquiry and of the right to seek advice of counsel.
Tulane Research Misconduct Policy - Inquiry

• Inquiry committee gathers and reviews all factual information to determine if reasonable cause for an Investigation exists and reports to the Dean.
• Dean makes the final determination as to whether or not a reasonable cause for Investigation exists.
• If “no,” complainant can renew complaint.
• If “yes” or complaint renewed, next step is Investigation.
Tulane Research Misconduct Policy - Investigation

- Investigation is conducted by the Grievance Committee of the respondent's school.
- Respondent is notified of Investigation and has a right to a hearing before the Grievance Committee.
- If NSF/PHS funded research, must notify NSF/PHS of investigation
Tulane Research Misconduct Policy – Formal Finding

• Grievance Committee drafts a report with findings.
• Respondent can comment on report
• Committee must consider comments in making a determination of research misconduct and recommended disciplinary action, if any.
• Provost can accept or reject recommendations of Committee and notifies complainant and respondent.
Tulane Research Misconduct Policy – Disposition

- Examples of disciplinary actions include:
  - Letter of reprimand;
  - Removal from the particular project;
  - Special monitoring of future work
  - Suspension or expulsion (students)
  - Termination of employment (staff)
  - Dismissal of faculty member
Tulane Research Misconduct Policy – Disposition

- Respondent can appeal recommendations of Committee and Provost’s decision to the Senate Committee on Faculty Tenure, Freedom, and Responsibility (“FTFR”).
- FTFR submits recommendation to Provost, who makes final determination regarding nature and severity of disciplinary action.
Tulane Research Misconduct Policy – Disposition

• University notifies sponsoring agencies if there is a finding of research misconduct.
  ◦ Sponsoring agencies may accept the university’s findings or conduct a further investigation and impose additional measures

• Provost may choose to notify:
  ◦ Co-authors, co-investigators, collaborators
  ◦ Professional societies and licensing boards
  ◦ Editors of journals
Federal Research Misconduct Policy –
disciplinary actions by sponsors

- Letter of reprimand
- Restrict expenditures under award
- Suspension or termination of award
- Require correction of research record
- Prohibition of individual as federal agency reviewer, advisor, or consultant
- Prohibition of individual and/or institution from receiving federal funds (debarment)
Tulane Research Misconduct Policy – Disposition

- For NSF/PHS sponsored research, Tulane shall make all reasonable and practical efforts to protect or restore the reputation of a respondent when no finding of research misconduct is made.
Questions?

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