Fostering Integrity in Research

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NASEM Committee
on Responsible Science

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Background

- Twenty five years ago the National Academies released the report ***Responsible Science***
- Much has happened in the **last two decades** with research being transformed, the result is that the **environment for the responsible conduct of research has changed**.
- This resulted in National Academies appointing a **new committee on responsible science in 2012.**

1992 National Academies report on "Responsible Science": Definitions

- **Research misconduct:** Fabrication, falsification, and plagiarism

- **Questionable research practices:** Actions that violate traditional values of the research enterprise and may be detrimental to the research process

- **Other misconduct:** Unacceptable behavior that is not unique to the research environment

The research environment has changed significantly in the last two decades:

- **Increased collaboration, team research**
- **Globalization**
- **Technological changes**
- **Funding, competitive pressures**

Statement of Task

- What is the **state of current knowledge**?
- What are the **impacts of changing trends** in the dynamics of the research enterprise?
- What are the **advantages/disadvantages of current educational efforts**?
- What are the **appropriate roles of the various stakeholders** in promoting responsible research?
- What should the **definition of research misconduct** be?
- Should existing practices be expressed as principles to guide RCR? Committee encouraged to **prepare model guidelines.**

General Recommendations

- The current federal definition of research misconduct as **"fabrication, falsification, and plagiarism"** is endorsed.
- The category **"other misconduct"** also retained.
- Items in the "questionable research practices" category really are **"detrimental research practices (DRPs)"** and there needs to be an expanded focus on this.
- There is a need to understand the **social and behavioral aspects** that results in research misconduct and DRPs.
- There is a lack of **data, data, data!**

Detrimental Research Practices (DRPs)

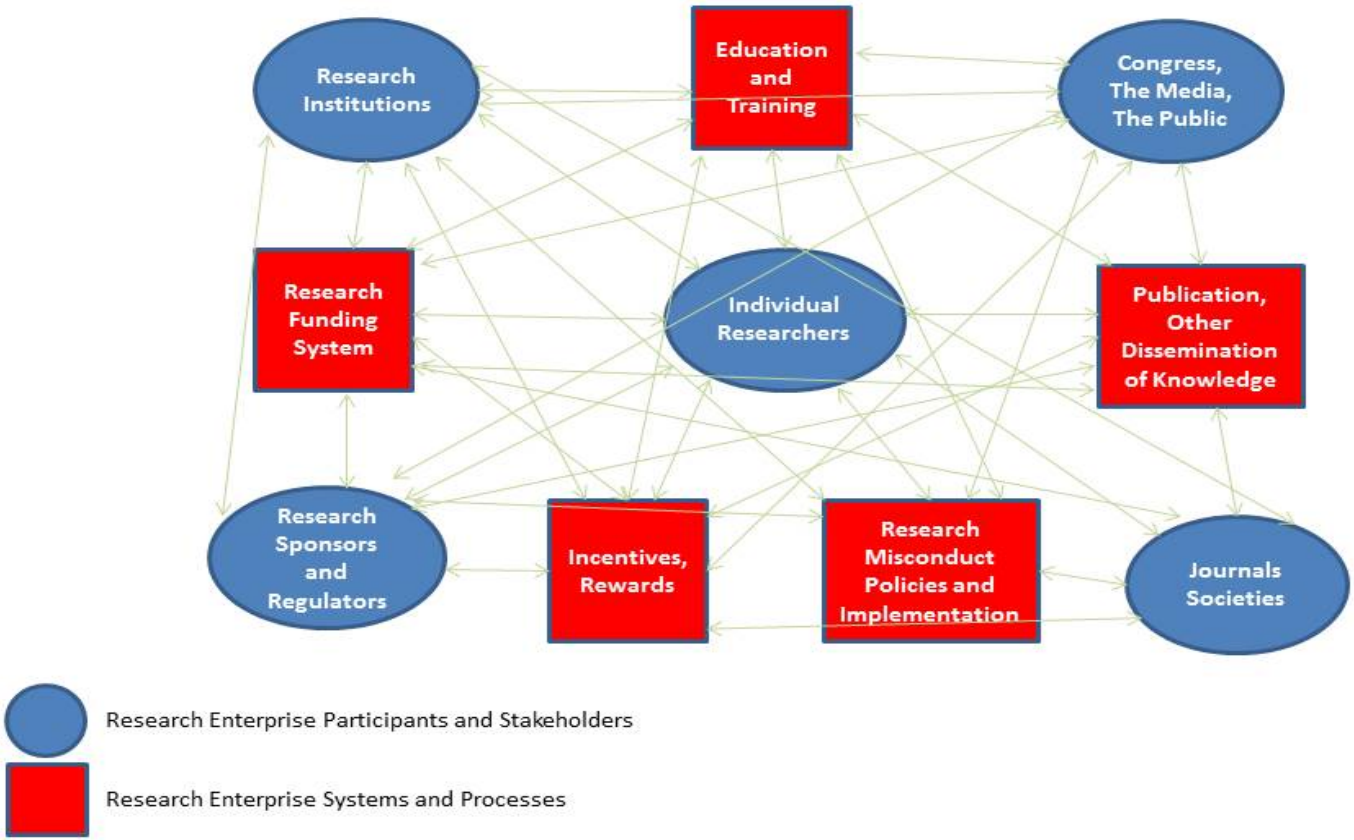
- **Authorship misrepresentation** (falsifies the credit/responsibility)
- Not retaining or making **data, code, or other information available**
- **Misleading statistical analysis**
- **Neglectful or exploitative supervision** in research
- **Inadequate institutional policies**
- **Irresponsible publication practices** by journal editors and peer reviewers

The Reproducibility Challenge

- The **reproducibility of research results is a major issue,** and failure to be able to reproduce results has several causes
- **A certain level of irreproducibility is normal**,
- **Research misconduct and DRPs can be causes**,
- **Tolerance of DRPs** can cause irreproducibility and can prevent/delay uncovering misconduct,
- Several **initiatives are underway** to address the challenge

Therefore, we need to **expand the focus** beyond individual researchers **to the entire system** in order to foster integrity

Figure 1-1: The Research Enterprise as a Complex Adaptive System



Incidence and Consequences

- Report reviews the available **evidence that is largely anecdotal.**
- It is thus **impossible to say what the incidence truly is** of research misconduct and DRPs.
- Whatever the level, there are the direct financial costs, opportunities lost, the costs to careers, public health costs, and **damage to the credibility of research.**
- **These are all significant!**

Findings/Recommendations - I

Recognize the complex interactions among the many components of the research system and implement improved approaches

Rec 1: **All participants need to improve** and update policies/practices

Rec 2: **Research institutions/organizations are central**: these need to uphold the highest standards of integrity, going beyond simply compliance

Rec 3: Steps to protect good-faith **whistleblowers**

Rec 4: Establish **Research Integrity Advisory Board**

Findings/Recommendations - II

Increase openness and accountability to foster integrity AND improve quality

Rec 5: Framework for **authorship standards**

Rec 6: Research sponsors and journals should ensure that **info sufficient to reproduce results** is provided at the time of publication

Rec 7: Sponsors should **support long-term storage and access** to data/code

Rec 8: Researchers should **disclose all statistical tests** and negative results

Findings/Recommendations - III

Invest in new knowledge to develop better evidence-based approaches

Rec 9: Research sponsors should **invest in research to quantify and develop responses** to conditions associated with misconduct and DRPs; should use this knowledge to monitor and modify policies and regulations

Rec 10: Research sponsors and research institutions should develop, assess, and implement **more effective approaches to RCR education**

Findings/Recommendations - IV

Working to ensure research integrity at the global level is essential to strengthening science both in the United States and internationally

Rec 11: Researchers, research institutions, and research sponsors that participate in and support **international collaborations should leverage these partnerships** to foster research integrity through mutual learning and sharing of best practices,

Three Recent Cases That Are Teaching Opportunities

- **The Hwang Woo-Suk Case**
- **The Riken-STAP Case**
- **The Anil Potti Case**

The Hwang Case

- **In 2004 a *Science* article** on the research of Hwang Woo-suk claimed to have **"generated embryonic stem cells from an adult human cell,"** a process called therapeutic cloning

- A follow-up *Science* article published in 2005 claimed that the lab had **"created human embryonic stem cells genetically matched to specific patients"**

- These results turned out to be **based on fabricated experiments**

The Hwang Case (Continued)

- In 2005, following the announcement of a clinical trial, a former researcher in Hwang's lab revealed to the Korean Television Network that **Hwang had told him "there are no cloned embryonic stem cells"**

- A Seoul National University investigation determined that **both *Science* articles were fraudulent and based on falsified data**

- Hwang was sentenced to a **two-year suspended prison sentence,** and he **continues his research with private funding**

The Hwang Case and Gerald Schatten

- A University of Pittsburgh stem cell researcher **Gerald Schatten had provided editorial input** into the Hwang articles and drafted the second one, on which he **was a senior author**

- Because of some ethical issues, **Schatten asked that his name be removed** from the 2005 publication

- There was, however**, a 2005 *Nature* paper that reported the achievement of the first cloned dog, Snuppy.** Schatten was a co-author on the Snuppy paper, and this result was never discredited

The Hwang Case and Schatten (cont)

- Schatten also had received **$40,000 in honoraria and $200,000 in research support**
- A University of Pittsburgh investigation found that Schatten had not fabricated data and thus was **not guilty of research misconduct but guilty of "research misbehavior"**
- Schatten admitted that his **major contribution** to the Snuppy paper was to **suggest using a professional photographer**

The RIKEN-STAP Case

- STAP stands for **"Stimulus – Triggered Acquisition of Pluripotency"**
- The **lead author** on an article in *Nature* was **Haruko Obokata, a Ph.D. student**
- Obokata **collaborated with Charles Vacanti,** in whose Boston lab the idea originated
- Other researchers were **not able to replicate the study**

日本語要約

Stimulus-triggered fate conversion of somatic cells into pluripotency

Haruko Obokata, Teruhiko Wakayama, Yoshiki Sasai, Koji Kojima, Martin P. Vacanti, Hitoshi Niwa, Masayuki Yamato & Charles A. Vacanti

Nature **505**, 641–647 (30 January 2014) doi:10.1038/nature12968
Received 10 March 2013 Accepted 20 December 2013 Published online 29 January 2014
Retraction (July, 2014)

Abstract

Here we report a unique cellular reprogramming phenomenon, called stimulus-triggered acquisition of pluripotency (STAP), which requires neither nuclear transfer nor the introduction of transcription factors. In STAP, strong external stimuli such as a transient low-pH stressor reprogrammed mammalian somatic cells, resulting in the generation of pluripotent cells. Through real-time imaging of STAP cells derived from purified lymphocytes, as well as gene rearrangement analysis, we found that committed somatic cells give rise to STAP cells by reprogramming rather than selection. STAP cells showed a substantial decrease in DNA methylation in the regulatory regions of pluripotency marker genes. Blastocyst injection showed that STAP cells efficiently contribute to chimaeric embryos and to offspring via germline transmission. We also demonstrate the derivation of robustly expandable pluripotent cell lines from STAP cells. Thus, our findings indicate that epigenetic fate determination of mammalian cells can be markedly converted in a context-dependent manner by strong environmental cues.

Subject terms: Reprogramming

The RIKEN-STAP Case (Continued)

- An internal RIKEN investigation found **"duplicated and manipulated images, constituting falsified data"**
- The 2014 journal article was retracted. **Obokata was found guilty of research misconduct and did not receive her Ph.D.**
- **Adviser Yoshiki Sasai committed suicide,** and Vacanti resigned as department chair

The Anil Potti Case

- In 2006 papers began appearing in major journals asserting that the **gene activity in a patient's tumor cells could be used to determine which chemotherapy drugs** would be most effective

- The **lead author was Anil Potti,** who worked in the laboratory of Joseph Nevins at Duke University

- In 2007, based on these results, **Duke launched clinical trials,** and an additional trial was started at the Moffitt Cancer Center

The Anil Potti Case (Continued)

- **Duke applied for patents,** and **several companies were launched** to commercialize the research
- At the same time, **Keith Baggerly and Kevin Coombes at M.D. Anderson began working to replicate** the Duke results
- They found **many significant problems,** including incorrect results which in some cases would lead patients to be treated with the least effective chemotherapy

The Anil Potti Case (Continued)

- In addition to the work of Baggerly and Coombes, **an NCI researcher was unsuccessful in replicating Potti's work**
- There also were **detailed concerns raised** in the spring of 2008 by **Bradford Perez, a third year medical student** performing research with Potti
- **Perez asked that his name be removed** from the four papers to which he had contributed and left the Nevins/Potti lab
- **In 2010 Duke suspended the clinical trials and terminated Potti's employment**

The Anil Potti Case (Continued)

- A 2012 IOM report stated that **Duke "did not institute extra oversight or launch formal investigations during the first 3 years** after the original publication triggered controversy and after concerns about the… prematurely initiation of clinical trials"

- In 2015 the HHS Office of Research Integrity (ORI) concluded that **Potti had "engaged in research misconduct"** and as a result, **Potti agreed not to conduct PHS-supported research unless supervised for 5 years**

- **Many patients in the suspended clinical trials brought legal actions** against Duke, which were settled out of court

Common Elements in all These Cases

- Articles were **published in top journals,** then retracted
- Investigators were **researchers at top institutions**
- There were **"whistleblowers"** in two of the three cases
- There were **tragic personal outcomes**

Human Subject Research

- **Policies and procedures governing human subject research are separate** from those for research misconduct
- Human subject protocols are under the responsibility of an **Institutional Review Board (IRB)**
- **Non-compliance** with an IRB-approved protocol may be viewed as **a form of research misconduct**
- This type of research misconduct in some cases can have **serious consequences**

Best Practices for Research Integrity

- Chapter 9 in the report provides an overview of **best practices** for individual researchers, research institutions, research sponsors, journals, and scientific societies
- Best practices speak to **relationships between components of the system**
- **Concise checklists** are provided for each constituent group.

Best Practices: Researchers

- **Research integrity**: Maintain high standards, **raise questions/problems promptly and professionally**, and strive to be a generous and collegial colleague

- **Data handling: Develop data management/sharing at the outset of the project**; understand/follow data collection, management, and sharing standards

- **Authorship**: Ensure/follow disciplinary standards; **acknowledge the roles/contributions of authors** and team members

- M**entoring and Supervision**: **Model and instruct best practices**; regularly check work of subordinates

Best Practices: Research Institutions

- **Institutional management**: Demonstrate that fostering research integrity is **a central priority**; provide training to faculty on effective mentoring

- **Climate assessment**: **Perform regular assessments of the institutional climate** for research integrity

- **Research misconduct investigations**: Have policies and capabilities for performing **fair, thorough, and timely investigations**; guard against **institutional conflicts**; incorporate external perspectives; **protect whistle blowers**

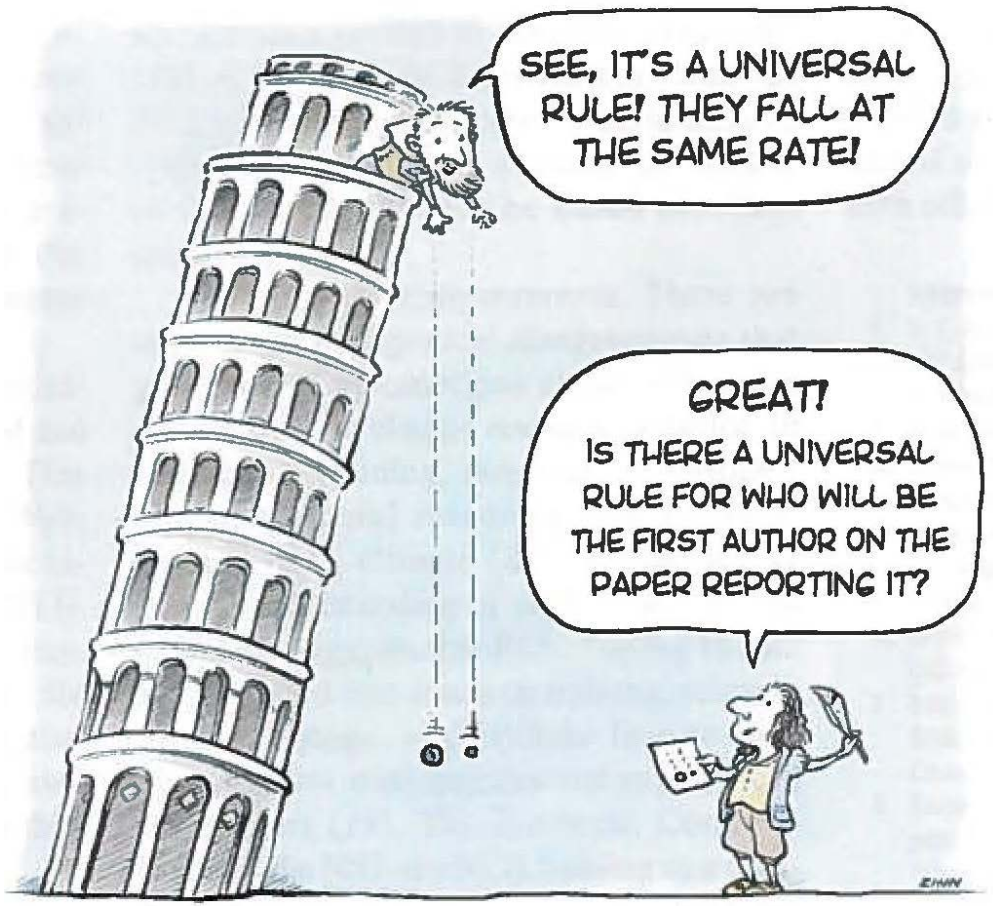
- **RCR training and education**: Engage faculty, **make federal requirements a "floor" not a "ceiling"**

Best Practices: Journals

- **Practice transparency**: **Publish retractions/corrections and reasons for them in a timely fashion**; provide link to data and code; require full description of methods

- **Ensure openness on information**: Data, code and records of any image altercations; author funding and conflicts of interest

- **Author contributions**: Describe **the roles and contribution of each co-author**


SEE, IT'S A UNIVERSAL RULE! THEY FALL AT THE SAME RATE!
GREAT!
IS THERE A UNIVERSAL RULE FOR WHO WILL BE THE FIRST AUTHOR ON THE PAPER REPORTING IT?
EHN

Framework for Authorship Standards

- **Authorship should be based on significant intellectual contributions,**

- **Contributions can occur in many ways**: design, conduct, data analysis and drafting for intellectual content,

- Standards should **disclose the contribution of each author to the research in a manuscript.**

- All authors should **approve final manuscript**,

Framework for Authorship Standards (continued)

- **Standards should identify** author(s) responsible for entire work,
- **Standards should specify that gift/honorary, and ghost authorship are unacceptable**,
- **Those who have contributed** but have not made significant intellectual contributions **should be acknowledged** but not be co-authors**.**
- **Disciplinary standards** should be developed by leading societies and/or journals

Transparency in authors' contributions and responsibilities to promote integrity in scientific publication

Marcia K. McNutt, Monica Bradford, Jeffrey M. Drazen, Brooks Hanson, Bob Howard, Kathleen Hall Jamieson, Veronique Kiermer, Emilie Marcus, Barbara Kline Pope, Randy Schekman, Sowmya Swaminathan, Peter J. Stang,and Inder M. Verma

PNAS February 27, 2018

Institutional Investigations

- Institutions face significant challenges in ensuring that **research misconduct allegations are effectively addressed and investigated.**

- One source of difficulty is the **infrequency at most institutions of cases** that advance from the inquiry stage to the investigation stage.

- This means that **institutional officials may lack hands-on experience** with the necessary tasks including forming investigative committees.

Institutional Investigations (continued)

- **Investigative reports vary greatly in quality** and there thus is a need to **improve the consistency** of institutional reports to ensure the highest quality possible

- Institutions also can have **a conflict of interest** due to concerns that the alleged research misconduct could affect the **institutional reputation, clinical trials** that have been established, **and/or startup companies** that have been launched

Institutional Investigations (continued)

- There thus is a **need for standards** to ensure that basic questions that any report should have are in fact addressed
- Reports could be enhanced by either having an **external person on the investigation committee or through peer review**
- **Institutional reports** on alleged research misconduct investigations can be **peer reviewed** just as we do manuscripts submitted for publication
- Improving the consistency and quality of investigative reports will be **an evolving process**

Research Integrity Advisory Board

- The Committee believes that a **more focused effort should be devoted to encouraging integrity** rather than just reacting to research misconduct

- Research integrity across disciplines/sectors is **not the core mission of any current US organization**

- The **establishment of a Research Integrity Advisory Board (RIAB) could serve this purpose of fostering a continuing focus,** one that is broader and involves detrimental research practices

- RIAB could **facilitate the exchange of information** on a variety of challenges including **serving as a forum** for the discussion of issues where no community consensus exists

Role of RIAB in Institutional Investigations

- I**ncrease the capacity of institutions to foster integrity,** serve as a forum to share knowledge and expertise, and be a focal point of efforts to improve standards and develop consensus

- **Collect and analyze data** on allegations of research misconduct, and develop model practices and policies

- **Consult on specific cases** in particular where there is a lack of experience and/or a clear institutional conflict of interest

- **Provide assistance in organizing an external review,** even participation in investigative committees and reports

Two Other Recent NASEM Reports

- One is "Optimizing the Nation's Investment in Academic Research: A New Regulatory Framework for the 22nd Century."
- Published in 2016, the "regulatory report" **recommends the establishment of a Research Policy Board.**
- The other is a report on "The Next Generation of Biomedical and Behavioral Science Researchers."
- Published in 2018, this report calls for a **new independent, not-for-profit body, a Biomedical Research Enterprise Council.**

Netherlands Code of Conduct for Research Integrity

2018

Some Final Thoughts

- It is the responsibility of the research community to conduct itself in a manner so as to **ensure having the trust of the public**
- This means going **beyond simple compliance** with current federal standards/policies
- It includes developing **more effective ways to educate** trainees, as well as faculty and PIs, in the responsible conduct of research
- As research moves forward, **is it time to establish a Research Policy Board to address on a continuing basis the challenges involved in the fostering of research integrity?**