Foundations in Ethical Research
GRAD 214

Session 4

K. Mark Ansel, PhD

Including material from Tori Sharma, PhD

Research Misconduct, Social Responsibility and the Importance of Research Security

- Introduction
  - A little history
  - Government regulation
  - Personal responsibility
- Research Misconduct
  - Federal definition and policies
  - Institutional policies
- Case Studies
  - Who is harmed by research misconduct?
  - Who is responsible to prevent and respond to research misconduct?

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Research Misconduct, Social Responsibility and the Importance of Research Security

- Why is it important?
  - Trust of the public: NIH budget of ~$47B/yr must compete with other important needs
  - The quality of scientific research is critical for the development of new therapies and diagnositics

Bad Publicity….

- Public disclosure of research misconduct cases at four major research centers in 1980
- Twelve serious cases of research misconduct between 1974-1981
- Reports that the National Institutes of Health (NIH), universities, and other research institutions were inadequately responding to those allegations.

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William Summerlin: 1974

- Reported that he could transplant tissue from genetically unrelated animals without rejection
- Invaluable for transplant medicine
- White mice with black patches
- A technician noticed that these "transplanted patches" were actually drawn on the skin of the mice with a felt-tipped marker and could be removed with alcohol.
- Summerlin admitted the fraud

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Dr. John R. Darsee, 1981

- Investigator in cardiology who published many research studies
  - Included faculty members as authors although they had minimal or no direct involvement
- Associates at Harvard caught him fabricating data….

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Continued…

- Investigation
  - Fabricated research publications beginning as a biology student at Notre Dame
  - Continuing through his medical residency and cardiology fellowship at Emory University
  - Ending at Harvard
- More than 10 primary journal articles and more than 45 abstracts were retracted as a result

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Continued…

- Highlighted the problem of using so-called "gift authors"
  - the presence of prestigious names may influence an editor
  - The co-authors did not know they were on the papers or had no direct involvement in the papers
- The case also revealed that the peer-review process could not be relied upon to find the fabrication

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Robert A. Slutsky, 1985

- Published one paper every 10 days for years (!)
- Included names of many co-authors to mislead editors and cover up for what later was learned to be a false data.
- Reviewer noted duplicated data in two articles
- Slutsky resigned
- Investigation found that, of the 145 publications that were reviewed
  - 77 were valid
  - 55 were questionable
  - 13 were fraudulent

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Congress Reacts: 1985 – Health Research Extension Act

- Secretary of HHS must issue a regulation requiring
  - Applicant/awardee institutions to establish (Section 493 Public Health Service (PHS) Act) an administrative process to review reports of scientific fraud
    - Report to the Secretary any investigation of alleged scientific fraud which appears substantial
  - The Director of the NIH, to establish a process for receiving and responding to reports from institutions

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Code of Federal Regulations

- "Responsibilities of Awardee and Applicant Institutions for Dealing With and Reporting Possible Misconduct in Science”
  - Published in the Federal Register on August 8, 1989
- Codified as 42 CFR Part 50, Subpart A

Three Areas of Misconduct Policies

- Establish **definitions** for misconduct in research
- Outline **procedures** for reporting and investigating misconduct
- Provide **protection** for whistleblowers and persons accused of misconduct

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Federal Definition of Research Misconduct

Fabrication, **falsification**, or **plagiarism** in proposing, performing, or reviewing research, or in reporting research results

Fabrication: making up results

Falsification: manipulation of research materials, equipment, or processes or changing or omitting results such that the result is not accurately represented

Plagiarism: the appropriation of another's ideas, processes, results, or words without giving credit

Must be a significant departure from accepted practices of the discipline

Must be committed intentionally, knowingly, or recklessly

(NOT: honest, unintentional error)

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The Federal Definition

- Is a minimum standard
- Does not imply that all other behaviors are acceptable
- Does not encompass
  - criminal behavior
  - personal disputes
  - violations of grant management policies
  - ***discrimination***
  - ***harassment***

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Descriptions of Responsible Research Practices

- Reports and policy statements
  - National Institute of Health (NIH)
  - **National Academy of Sciences, Engineering and Medicine**
  - American Association for the Advancement of Science
  - Association of American Medical Colleges
- Responsible publication practices published in journals
- Professional societies (professional codes)

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“Detrimental Research Practices”

Defined by the National Academies of Sciences, Engineering, and Medicine:

- Failing to retain data and maintain standards for doing so
- Authorship misrepresentation other than plagiarism
- Refusing to share data or methods
- Misleading statistical analysis that falls short of falsification.
- In addition to the behaviors of individual researchers, detrimental research practices also include actions taken by organizations, such as failure on the part of research institutions to maintain adequate policies, procedures, or capacity to foster research integrity and assess research misconduct allegations, and abusive or irresponsible publication practices by journal editors and peer review.

How is Research Misconduct Determined?

- The institution (e.g. UCSF) must conduct a Preliminary Inquiry in response to allegations of scientific misconduct.
- If sufficient reason, then this is followed by a full investigation.
- Full investigation must address each allegation;
- May impose penalties (retraction of papers, demotion, dismissal from position, etc.)
- Must report investigation and results to NIH Office of Research Integrity; ORI determines NIH penalties and makes this information publicly available

Misconduct Puts Careers at Risk

- Can result in being debarred from receiving Federal funds for a specified period of time
- Research institutions
  - may terminate a researcher's employment
  - may require supervision of future research activities
- Publicity
  - ORI Website
- Can result in a prison sentence (!)

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The New Common Federal Policy

- Provides guidelines for protecting
  - Whistleblower
  - Respondent (Accused)
- Research misconduct allegations must not be made public until they have been fully investigated and confirmed with exception of a threat to public health or safety (e.g. clinical trial)
- Research institutions and researchers must not in any way retaliate against whistleblowers who report research misconduct in good faith.
  - Even if accusations are not sustained
  - And as long as they are brought in good faith
  - Informants must be protected and given support since they play a vital role in professional self-regulation

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Federal Policy on Reporting and Investigation

- Researchers and research institutions bear the primary responsibility for reporting and investigating misconduct
- Consistent with the position, most researchers strongly support the idea that research is a profession and should regulate its own conduct
- BUT……

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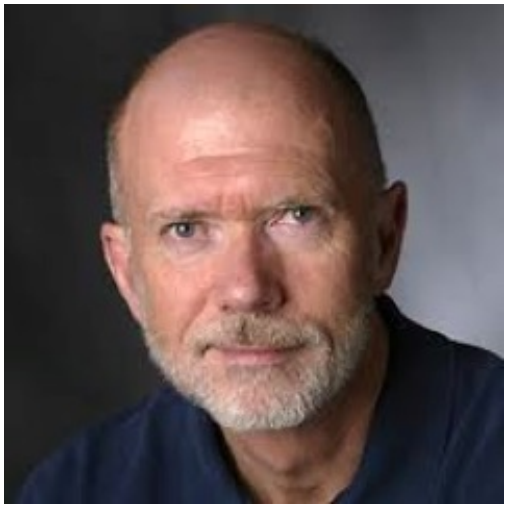
Research Misconduct Case 1: Cancer Therapy at Duke



Duke researchers:
Anil Potti, Oncology Fellow and
Joe Nevins, HHMI investigator; well known for work on E2F

Use RNA expression microarrays of lung and breast cancers to get signatures to guide chemotherapy; high profile papers in Nature Med (2006), Journal of Clinical Oncology (2007), PNAS, NEJM, etc., patent application in 2006. Founded company.

Research Misconduct Case 1: Cancer Therapy at Duke

Keith Baggerly,
Kevin Coombes,
Bioinformatists at
MD Anderson

- Researchers at MD Anderson take the original data set and cannot reproduce the main finding that gene signature predicts response
- They contact the Duke investigators describing problems in 2007; problems denied by Potti, Nevins.
- Potti and Duke start an NCI-funded clinical trial in 2009
- Baggerly and Coombes publish a paper in Annals of Applied Statistics (9/09) that they cannot reproduce Potti's findings using his data
- Clinical trial at Duke is put on hold; Duke initiates external review

Research Misconduct Case 1: Cancer Therapy at Duke

Keith Baggerly,
Kevin Coombes,
Bioinformatists at
MD Anderson

- External review committee, using annotated version of array data supplied by Potti, find that they can reproduce his findings (Dec 2009)

Research Misconduct Case 1: Cancer Therapy at Duke

Keith Baggerly,
Kevin Coombes,
Bioinformatists at
MD Anderson

- External review committee, using annotated version of array data supplied by Potti find that they can reproduce his findings (Dec 2009)
- While review is in process, Baggerly writes Duke officials and points out discrepancies between the annotated data and the original raw data set; Duke officials fail to report this irregularity to the review committee
- Duke restarts clinical trial Jan 2010

Research Misconduct Case 1: Cancer Therapy at Duke

- An anonymous source reports to the editor of The Cancer Letter, that Potti has significant inaccuracies on his CV, published in July 2010
- NCI director Harold Varmus stops clinical trial, asks Institute of Medicine to investigate; Duke re-investigates
- Evidently, someone (Potti?) manipulated the annotated data set to make the data fit the conclusion; the original data did not
- Nov 2010: Potti resigns, Duke terminates clinical trial permanently, JCO paper is retracted; later 9 other papers are retracted, Nevins retires.

Research Misconduct Case 1: Cancer Therapy at Duke

Breakout instructions:

Each group chooses a moderator and a reporter

Moderator's job is to facilitate discussion; solicit comments from everyone in the group

Reporter: Be prepared to share one issue discussed and conclusion reached

Research Misconduct Case 1: Cancer Therapy at Duke

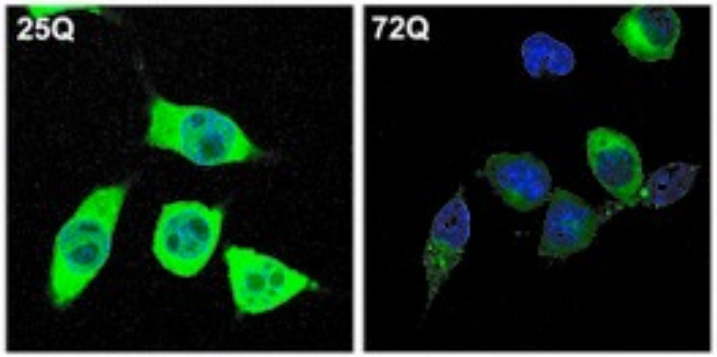
Lessons?

- Were consequences sufficient? Potti left science but continued to practice medicine; Nevins retired…
- Surprised at the fast pace to clinical trial/lack of oversight (this fraud took place over several years before it was discovered and resolved)
- Duke's conflict of interest may have played into the shoddy investigation
- Pressure on Potti might have influenced his actions
- Other co-authors were victims too

Research Misconduct Case 2:
That can’t happen here!

Research Misconduct Case 2: That can't happen here!

Fall 2012: UCSF faculty member Paul Muchowski is found to have falsified and fabricated data in NIH grant applications and resigns his position



Research Misconduct Case 2:
That can't happen here!

Specifically, ORI finds that the Respondent knowingly and intentionally:

- falsely reported research experiments when the results did not exist at the time the grant applications were submitted. Specifically:
  - in Figures 19-21 and related text of grant application R01 NS047237-06, the Respondent claimed he had successfully transduced human neuroblastoma SH-SYSY cells expressing α-synuclein (αSyn) with lentiviruses containing small hairpin RNAs (shRNAs) that targeted Cog6, Stx7, Vps52 or Vps33a. The Respondent reported lentiviral expressed Cog6 significantly exacerbated α-Syn toxicity in SH-SYSY cells, when only plasmid shRNAs were generated and utilized at the time the grant application was submitted.
  - in Figure 5 and the accompanying text of grant R01 NS054753-06A1, the Respondent described the insertion of toxic and inert mutant huntingtin (htt) fragments into maltose binding protein-Htt-Cerulean constructs with a nonpathogenic (25Q) or pathogenic (46Q) polyQ repeat, with and without Cerulean. The modified proteins were claimed to have been purified, when the constructs had not been made at the time the grant was submitted.

Research Misconduct Case 2:
That can't happen here!

- in Figures 5 and 6 and the accompanying text of grant R01 NS054753-06A1, the Respondent claimed to have cloned toxic and inert mutant htt fragments into lentiviral constructs and generated lentiviruses, when the constructs were not made.

- in Figure 6 and related text in grant R01 NS054753-06A1, the Respondent claimed to have tested immunoblots of lysates from primary neurons with an antibody against mutant htt, which demonstrated that levels of htt expression in transduced cells were roughly equivalent to levels in normal neurons, when the experiment was not conducted.

- falsified Figure 3 of grant application R01 NS054753-06 by labeling the Western blot images for the expression of mutant htt in lentiviral-transduced primary neurons as 'Cortex' (left panel) and 'Striatum' (right panel), when the results were actually from the microglial cell lines N9 and BV2, respectively.

Research Misconduct Case 2:
That can't happen here!

According to official statements, the misconduct was reported by a colleague.

The Investigator admitted these actions during the investigation and the investigating committee concluded these actions were not within the scientific norm; he then resigned his faculty position.

ORI reached a voluntary agreement with the Investigator that all NIH-supported research for the next two years would be done under a supervisory plan approved by ORI and that the investigator would not serve on any NIH review or advisory panels (so close to the least penalty).

At least one of the grant applications with fabricated or falsified data ended up being funded

Research Misconduct Case 2:
That can't happen here!

The Investigator wrote a response letter published on "Retraction Watch":

The ORI found that I "falsely reported research experiments when the results did not exist at the time the grant applications were submitted." In these instances, I stated that the experiments had, in fact, been performed prior to their completion. Based on previous experience with such experiments, I believed that I could perform these experiments by the time that my grant would be reviewed. These experiments were successfully completed or found to be non-essential for the research program, but only after the grants were reviewed.

I hasten to add that my research findings have never been in question. There will be no retractions based on these findings. In fact, the grant that was at issue was not withdrawn and I am still receiving funding from that grant.

I unquestionably committed serious errors in judgment. I regret these completely. I had no intention of misleading the research community about our research studies in any way. My mistakes in judgment contained in the grant applications had no material effect on the outcome of that research.

Lessons?

Research Misconduct Case 2:
That can't happen here!

Lessons?

- Grant funding continued! Was this the right thing to do?
- Pressure created by competitive funding environment
- Does the need for "preliminary data" create an opportunity/incentive to cheat?
- Whistleblowers can be negatively impacted by revealing misconduct. (Continuing grant funding for their work is arguably justified despite the misconduct, though this means someone else's work was not funded)

The hard part of defining ethical research

- There is no one best way to undertake research
- No method applies to all scientific investigations
- Accepted practices can and do vary from discipline to discipline and even from laboratory to laboratory

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Ethics in Research are Governed by

- Professional codes
- Government regulations
- Institutional policies
- *Personal convictions*

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Important Shared Values

- HONESTY
- TRUST
- FAIRNESS
- OPENNESS
- ACCOUNTABILITY
- STEWARDSHIP
- IMPARTIALITY/INDEPENDENCE
- ACCURACY/RELIABILITY
- EFFICIENCY
- OBJECTIVITY

Macrina, Francis L.. 2014. Scientific Integrity, Fourth Edition

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Useful Links at UCSF

- Office of Ethics and Compliance
- Code of Conduct and Integrity of Research

Code of Conduct and Integrity of Research
Quality research requires adherence to the highest standards of integrity in proposing, conducting, and reporting research.

What to do if you witness or suspect research misconduct
Report suspected research misconduct such as fabrication, falsification, or plagiarism to researchintegrity@ucsf.edu

Individuals should not undertake investigations of suspected research misconduct on their own. The Office of Ethics and Compliance is responsible for evaluating and investigating all allegations of misconduct related to research at UCSF.

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Reporting Misconduct

- All individuals associated with the campus should report observed or suspected research misconduct to researchintegrity@ucsf.edu

Whistleblowing

If you perceive a situation or activity that you think constitutes research misconduct, as a scientist and professional you have a responsibility to report it. While that is part of the underlying bargain of accountability that professionals make with society, whistleblowers usually act on the basis of personal hurt or outrage. However, an allegation of research misconduct must be handled as a very serious matter.

Reporting Misconduct

- All individuals associated with the campus should report observed or suspected research misconduct to researchintegrity@ucsf.edu
- The University has well developed procedures for investigations
- Procedures are in place to protect the anonymity of whistleblowers to the extent possible to prohibit retribution.
- Typically, investigations of this type hinge on examination of the research records (notebooks, etc.), so anonymity can be preserved.
- Don’t investigate yourself, and it is best not to talk about your suspicions with others.

Misconduct Inquiries Policy

- Proceedings of an inquiry are confidential to protect to the maximum extent possible
  - Members of the inquiry panel
  - Individual(s) filing the allegation
  - Person accused
  - Witnesses
- All individuals are asked to refrain from discussing the matter with anyone, including
  - Faculty members
  - Students
  - Family members
  - Media

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How Common is Research Fraud?

- 0.01% of researchers according to federal misconduct findings
  (Generally 20-30 substantiated findings of research misconduct per year)
- Average number of allegations to ORI
  - 1994 to 2000, 45 per year
  - 2001 to 2010, 85 per year
  - 2020 (only), 204
  - 2021 (only), 230
  - 2022 (only), 269
  - Increasing reporting or increasing fraud?
- According to surveys (Daniele Fanelli)
  - 2% admitted to fabrication or falsification at least once
  - 14% observed the behavior in colleagues
  - 33% admitted to questionable research practices

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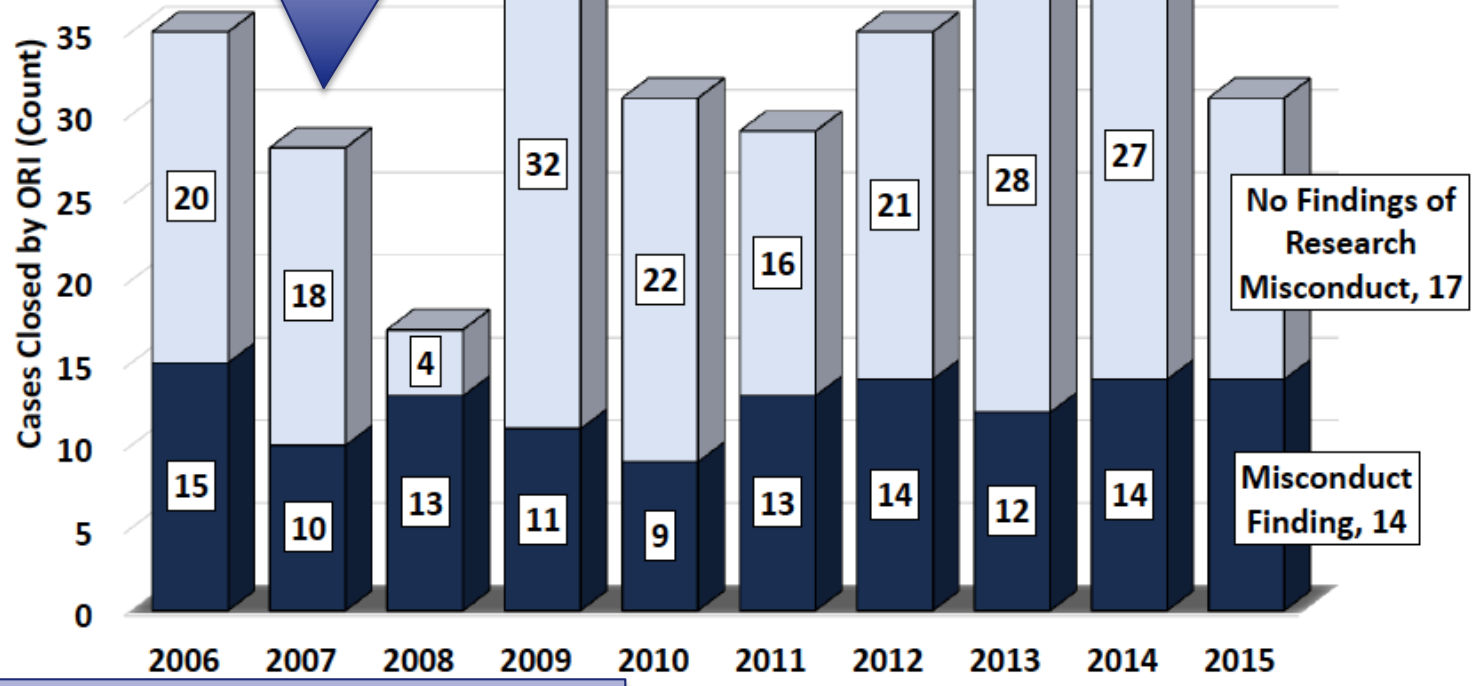
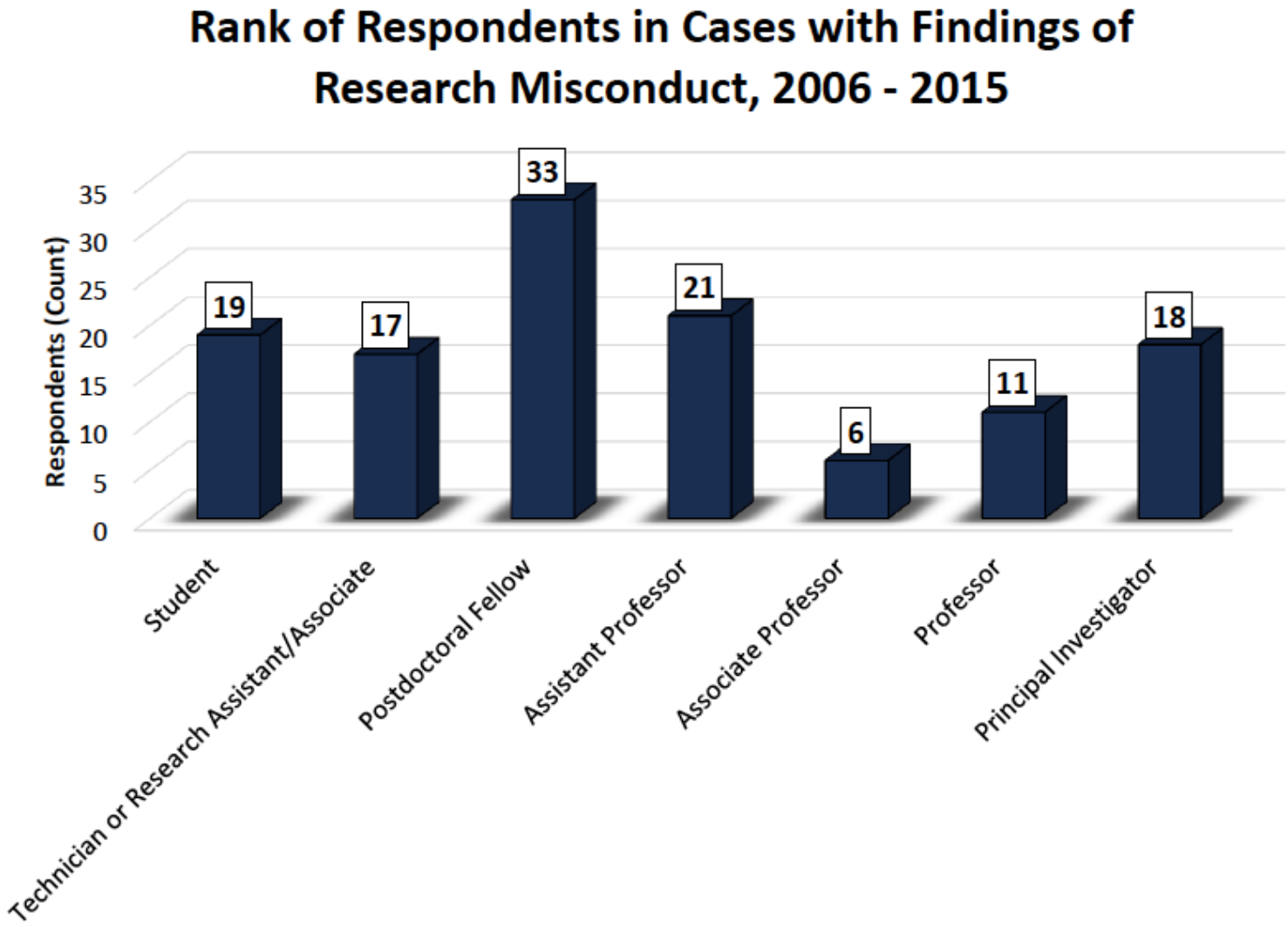
Research Misconduct Case Outcomes by Year, 2006 - 2015

In 2007, ORI closed 28 cases, 10 resulted in sustained findings of research misconduct and/or PHS actions against the respondents.

Total of 330 cases reported by ORI. 125 with findings of misconduct. Universities reported 645 internal investigations over this same period.



3 received minor penalties (3-4 yr "certification" or "supervisory" periods), but 7 received debarment (1 for life, 2 for 5 yr; 4 for 3 yr).


Rank of Respondents in Cases with Findings of Research Misconduct, 2006 - 2015
Respondents (Count)
0
5
10
15
20
25
30
35
19
17
33
21
6
11
18
Student
Technician or Research Assistant/Associate
Postdoctoral Fellow
Assistant Professor
Associate Professor
Professor
Principal Investigator

What are the motivations?

- Career pressure
- Belief that one already knows the right answer
- Notion that data may not be reproducible anyway
- The “work structure” of modern science

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Research Misconduct

Pressure to lie

Personal Responsibility and Problems with Rules

- Rules generally set minimum standards for behavior
- Should strive for a higher standard of conduct
- Responsible research requires more than simply following rules
- Rules will not resolve some of the personal conflicts and moral dilemmas
- Rules also cannot replace the critical reasoning skills
- Researchers will face ethical dilemmas in research

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So Many Regulations, What Should I Do? The Simple Test…

- Imagine what you are preparing to do will be posted immediately on the web (FB, google news, etc)
- If you are comfortable having colleagues, friends, and family know what you did, chances are you acted responsibly

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Office of the Ombuds

Use of services provided by the Office of the Ombuds is voluntary and confidential.

- All conversations with the Office of the Ombuds are confidential and off the record.
- The Office does not create or maintain records for the University.
- Any notes taken during the course of a case are routinely destroyed on a quarterly basis once the Office determines the case is closed.

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End for today

Questions?

How much damage?
Andrew Jeremy Wakefield

- Published that there was a link between the administration of the MMR vaccine and autism and bowel disease
- Other researchers were unable to reproduce the findings
- Reporter Brian Deer identified undisclosed financial conflicts of interest on Wakefield's part
- The British General Medical Council (GMC) conducted an inquiry into allegations of misconduct against Wakefield and two former colleagues
  - 4 counts of dishonesty
  - 12 counts involving the abuse of developmentally challenged children

Andrew Jeremy Wakefield

- The Lancet fully retracted the 1998 publication noting that elements of the manuscript had been falsified
- The editor-in-chief said the paper was "utterly false" and that the journal had been "deceived"
- Wakefield was struck off the UK medical register and was barred from practicing medicine
- He had planned to launch a venture on the back of an MMR vaccination scare that would profit from new medical tests and "litigation driven testing"

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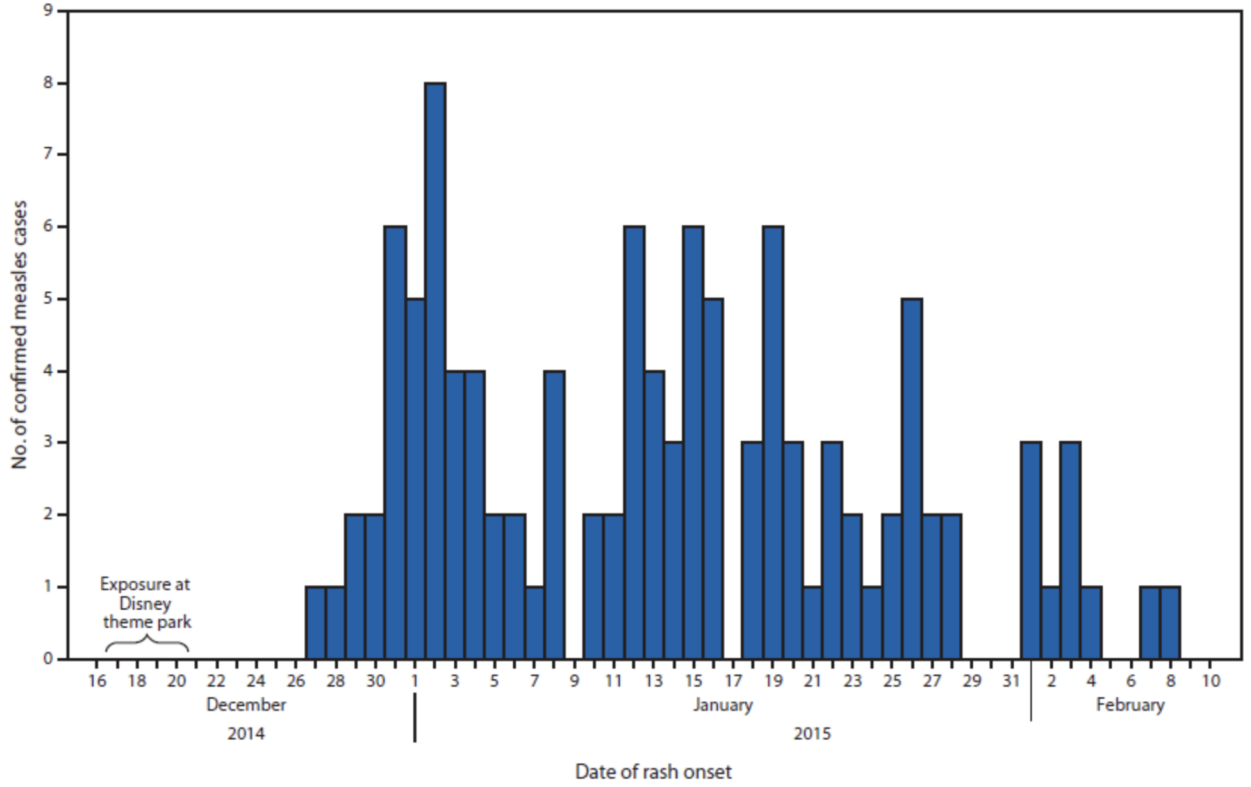
Disneyland Measles Outbreak 2014-2015

FIGURE. Number of confirmed measles cases (N = 110),* by date of rash onset — California, December 2014–February 2015



* Reported to the California Department of Public Health as of February 11, 2015.

More recently from the CDC:

Measles cases in 2019

- From January 1 to December 31, 2019, 1,274* individual cases of measles were confirmed in 31 states.
- This is the greatest number of cases reported in the U.S. since 1992.
- The majority of cases were among people who were not vaccinated against measles.

Measles cases in 2022

- From January 1 to December 31, 2022, a total of 121 measles cases were reported by 6 jurisdictions.

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HEALTH

OCT 9 2015, 5:05 PM ET

Measles Vaccine Gaps Put U.S. At Risk, Reports Show

by MAGGIE FOX

This Electron Micrograph Reveals Both A Paramyxovirus Measles Virus, And Virions Of The Polyomavirus, Simian Virus Sv40 Smaller Circles. The Envelope Of The Measles Virus Has Broken, Exposing The Nucleocapsid Filaments. Interest In Sv40 Has Increased In The Last Several Years Because The Virus Was Found In Certain Forms Of Cancer In Humans, For Instance Mesotheliomas Rare Tumors Located

LETTER

doi:10.1038/nature21369

Early brain development in infants at high risk for autism spectrum disorder

Heather Cody Hazlett[1,2], Hongbin Gu[1], Brent C. Munsell[3], Sun Hyung Kim[1], Martin Styner[1], Jason J. Wolff[4], Jed T. Elison[5], Meghan R. Swanson[2], Hongtu Zhu[6], Kelly N. Botteron[7], D. Louis Collins[11], John N. Constantino[7], Stephen R. Dager[8,9], Annette M. Estes[9,10], Alan C. Evans[11], Vladimir S. Fonov[11], Guido Gerig[12], Penelope Kostopoulos[11], Robert C. McKinstry[13], Juhi Pandey[14], Sarah Paterson[15], John R. Pruett Jr[7], Robert T. Schultz[14], Dennis W. Shaw[8,9], Lonnie Zwaigenbaum[16], Joseph Piven[1,2] & the IBIS Network*

Brain enlargement has been observed in children with autism spectrum disorder (ASD), but the timing of this phenomenon, and the relationship between ASD and the appearance of behavioural symptoms, are unknown. Retrospective head circumference and longitudinal brain volume studies of two-year olds followed up at four years of age have provided evidence that increased brain volume may emerge early in development[1,2]. Studies of infants at high familial risk of autism can provide insight into the early development of autism and have shown that characteristic social deficits in ASD emerge during the latter part of the first and in the second year of life[3,4]. These observations suggest that prospective brain-imaging studies of infants at high familial risk of ASD might identify early postnatal changes in brain volume that occur before an ASD diagnosis. In this prospective neuroimaging study of 106 infants at high familial risk of ASD and 42 low-risk infants, we show that hyperexpansion of the cortical surface area between 6 and 12 months of age precedes brain volume overgrowth observed between 12 and 24 months in 15 high-risk infants who were diagnosed with autism at 24 months. Brain volume overgrowth was linked to the emergence and severity of autistic social deficits. A deep-learning algorithm that primarily uses surface area information from magnetic resonance imaging of the brain of 6–12-month-old individuals predicted the diagnosis of autism in individual high-risk children at 24 months (with a positive predictive value of 81% and a sensitivity of 88%). These findings demonstrate that early brain changes occur during the period in

(see Methods for diagnostic and exclusion criteria). The three groups were comparable in (mean) race/ethnicity (85% white), family income, maternal age at birth (33 years old), infant birth weight (8 lb), and gestational age at birth (39 weeks). The HR-ASD group had more males than the other two groups (83% of the HR-ASD group was male compared to 59% and 57% of the LR and HR-neg groups, respectively) and mothers in the LR group had a higher education level (Extended Data Table 1).

Infants were evaluated at 6, 12 and 24 months of age, which included detailed behavioural assessments and high-resolution magnetic resonance imaging (MRI) of the brain, to prospectively investigate brain and behavioural trajectories during infancy. The analyses described below were conducted on a subset of 106 high-risk ($n = 15$ HR-ASD; $n = 91$ HR-neg) and 42 low-risk infants for whom all three MRI scans were successfully obtained. On the basis of our previous findings at 2–4 years of age[2], we hypothesized that brain overgrowth in ASD begins before 24 months of age; that overgrowth is associated with hyperexpansion of the cortical surface area; and that these early brain changes are temporally linked to the emergence of the defining behaviours of ASD. We also investigated whether differences in the development of brain characteristics might suggest early biomarkers (that is, occurring before the onset of the defining behaviours of ASD) for the detection of ASD.

We first examined group differences in the trajectories of brain growth rate (Fig. 1). The growth rate of the total brain volume (TBV) did not differ between groups from 6 to 12 months of age. However, pairwise comparisons at 24 months showed large effect sizes for HR-ASD

Autism develops much earlier than the MMR vaccine is given

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