Human & Animal Research

MIT Chemistry – NIH Responsible Conduct of Research

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Macrina, F. L. (2014) *Scientific Integrity – Text and Cases in Responsible Conduct of Research, 4th ed.* Washington, D.C.: American Society for Microbiology.

Humans in Experimentation - Overview

The most codified subject in scientific ethics

- History & regulation
- Definition & general concerns
- Institutional Review
- Special populations
- Embryonic & fetal tissue

OHRP

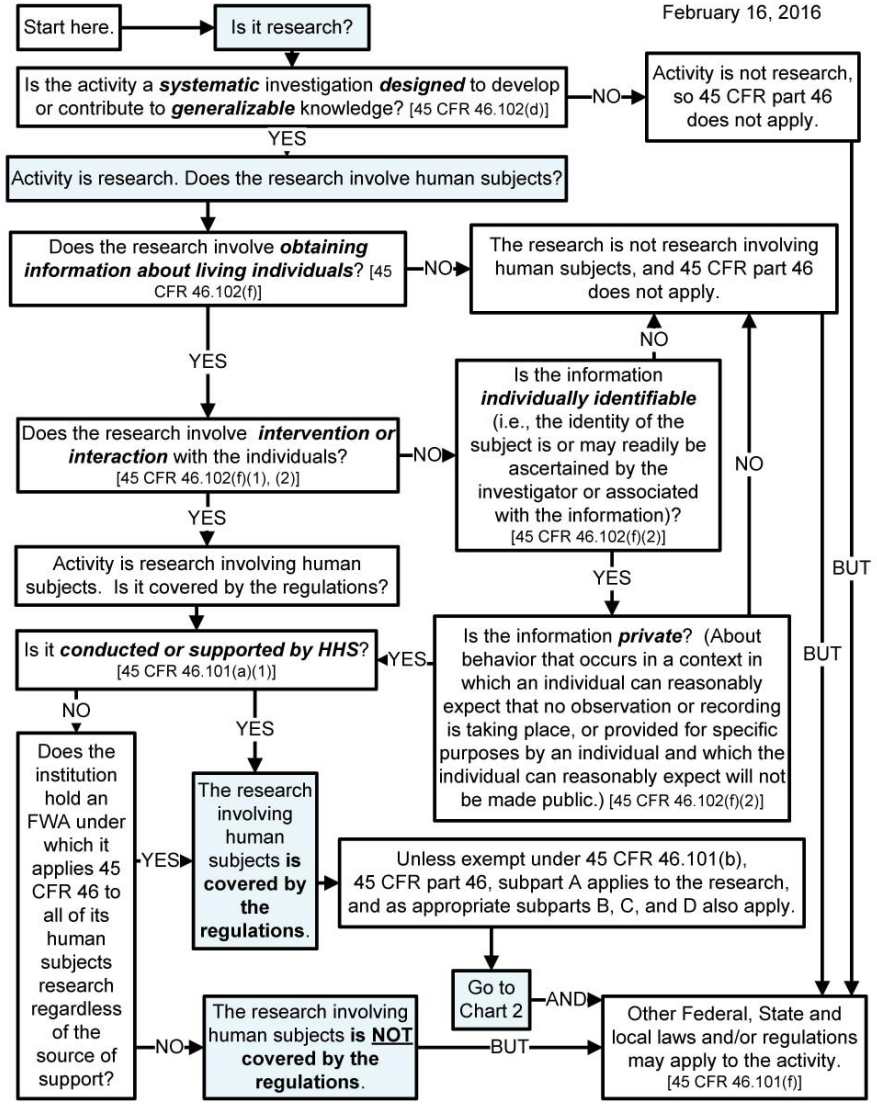
Office for Human Research Protections

History & Regulation

- First rules – Nuremberg Principles (WWII war criminal trials)
- Declaration of Helsinki (1964) – World Medical Association
  - International standard for biomedical research involving human subjects
- Belmont Report (1979) – National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
  - Respect for Persons (autonomy, consent)
  - Beneficence (“do no harm”)
  - Justice (benefits and burdens equally distributed)
- Office for Human Research Protections (OHRP) of the Department of Health and Human Services (HHS) – oversight of US federally funded human research

Definitions of Human Subjects Research

- Research: systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge
- Human subject: living individual about whom an investigator conducting research obtains
  1. Data through intervention or interaction with the individual, or
  2. Identifiable private information



Federal law (45 CFR 46.103)
https://www.hhs.gov/ohrp/regulations-and-policy/decision-charts/index.html#c1

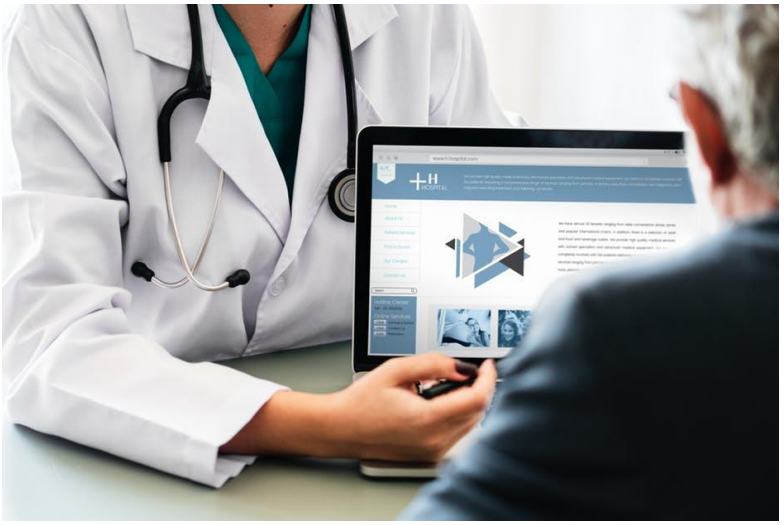
Informed Consent

- Consent forms must:
  - Describe detailed risks & benefits
  - Describe compensation for participation
  - Explain participant's rights
  - Assure participants that no rights will be forfeited by refusal to participate
  - Provide contact information for investigator & institutional review board

- Ongoing process – not a one-time signing of a form

Informed Consent

- “Competent to consent”
  - Able to understand consequences and make decisions
- Voluntary (free from coercion)
  - Coercion can come from many sources – family, researcher, physician, institution, health care system
- Informed
  - Must have adequate information to make a valid decision (requirements, risks)
  - Comprehension required



Institutional Review Boards (IRB)

- Institutions receiving federal support are required to have an IRB to oversee human subjects research
- Requirements for IRB:
  - At least 5 members
  - At least one member in nonscientific profession
  - At least one member not affiliated with the institution (also nonscientific)
- Approval requires simple majority vote
- Proposals must be reviewed at least yearly

Institutional Review Boards

- Criteria for review:
  - Risks to subjects must be minimized consistent with aims of research
  - Technically valid
  - Risks must be reasonable in relation to anticipated benefits
  - For comparisons – there must be a valid null hypothesis that both treatments are equivalent
  - Adequate provision for monitoring data & protection of privacy
  - Equitable selection of subjects
  - Informed consent
- Prohibited from considering long-range effects on public policy that may result from research

Exempt Research

- Minimal-risk: no greater in magnitude or severity than risks normally encountered by average healthy individuals
  - Educational instructional strategies
  - Educational tests, surveys, interviews, observations of behavior (if deidentified)
  - Secondary data or specimens that are previously collected (retrospective, if deidentified)
  - Public agency evaluation of programs
  - Taste or food quality research (if ingredients remain below allowable levels)

Special Populations

- Incompetent patients
  - Not necessarily excluded, consent from legally responsible person, special care to avoid coercion
- Prisoners
  - Only studies that either have the intent to improve the health or well-being of subject, or are directly related to prisons or prisoners
  - Prisoner or prisoner representative must be a member of IRB
- Children
  - Parents or guardians must give consent
  - Assent from child is required if IRB deems they are capable
  - Greater restrictions on risk/benefit analysis

Fetal Tissue & Embryonic Stem Cells

- Regulated by NIH Guidelines for Human Stem Cell Research (2009)
- Cell lines approved and monitored
- Guidelines to ensure proper consent and minimal coercion regarding harvesting cells/tissues

HIPAA

- Health Insurance Portability and Accountability Act (1996)
- Regulates privacy and security of health care information
- Authorization needed for subject permission to use Protected Health Information (any information gathered by healthcare provider that could directly or indirectly identify patient)

- Doing research without individual authorization allowed when:
  - Using deidentified data sets
  - Using a limited data set
  - Obtaining a waiver from IRB

Case Study

Donald Weinstein, an associate professor of physiology at University Medical Center (UMC), is a member of UMC's IRB. He suffers from a type of dermatitis that is uncomfortable, but his condition is not obvious to his colleagues. He has been told by his physician that he probably has a syndrome known as "chronic dermal condition" (CDC), the cause of which is unknown and for which there is no effective treatment. To confirm this unusual disease, a skin biopsy must be done. Dr. Weinstein has not yet had a biopsy. In his latest package of assignments for IRB review, Dr. Weinstein receives a protocol that proposes to study CDC, and a skin biopsy will be performed on all who sign up to be considered for enrollment. The study has two components: an evaluation of factors that may be related to the causation of CDC and the monitoring of the response of CDC to a combination of experimental drugs that has shown promise in other clinical trials. Dr. Weinstein is impressed with the study and submits a favorable review. Further, he decides to pursue enrolling in the study. He reasons that at least he can get a definitive answer about his CDC diagnosis by submitting to a skin biopsy. At most, if he has CDC, he may benefit from the experimental therapy. He comes to you, chair of UMC's IRB, to let you know his intentions. What will you tell him?

Animal Research

- Question of “rights” and moral judgments
- Third principle of Nuremberg Code – “The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment”
- Two most influential philosophies in animal rights:
  - Singer (utilitarianism) – “sentience - the ability to feel pleasure or pain - is the key characteristic required for admittance into the moral universe.”
    - Animal experiments should not be conducted unless they would be allowed for humans
  - Regan (deontology) – “inherent value”
- Scientific regulation & research influenced heavily by public opinion and influence of animal rights groups

Legislation & Regulation

- National Academy of Sciences – *Guide for the Care and Use of Laboratory Animals*
- Animal Welfare Act (1966)
- Public Health Service Policy (1986)
- Institutional Animal Care and Use Committee (IACUC)
  - 3-5 people
  - One member must be a DVM
  - One member nonaffiliated with institution
  - Evaluate animal care and use program and facilities every 6 months
- NIH requires approved animal research protocol for funding

Animal Research Protocols & Review

- Should include:
  - Rationale for experiments & selection of species
  - Alternatives considered and why they were rejected
  - Justification for number of animals in study
  - Detailed experimental procedures
  - Description of anesthetics, analgesics, or sedatives to be used
  - Criteria & process for removal from study
  - Evidence that work is novel (not already done)

IACUC Protocol Review

- “Must ensure that protocols are designed to avoid or minimize discomfort, distress, and pain to animals consistent with sound research design”
- IACUC will often suggest alterations to protocols to improve it and make it acceptable
- Training is required for anyone involved in care and/or research of animals (this includes PIs)

Three Principles for Humane Use of Animals

- **Replacement** – “attempt to substitute insentient materials or, if this is not possible, a lower species that might be less susceptible to pain and distress”
- **Reduction** – “attempt to use the minimum number of animal lives necessary to answer the research question”
  - But also a large enough group to make the work statistically significant and valid
- **Refinement** – “attempt to reduce the incidence or severity of pain and distress experienced by laboratory animals”

Case Study

- Your colleague, Dr. Jay Mahata, is an NIH-supported investigator who has an established collaboration with a field biologist, Dr. Ellen Yu, in another state. Dr. Yu does not receive any grant support for her research. Dr. Mahata sometimes receives blood and other tissue samples for analysis from the wild rodents that Dr. Yu traps for her research. Dr. Mahata has asked you to read his latest IACUC protocol before its formal submission. You know about his collaboration with Dr. Yu but note that it is not mentioned in the protocol. When you ask Dr. Mahata about this, he says that he "does not have to report this activity to the IACUC because there are not any animal welfare concerns involved." He points out to you that he does not euthanize the rodents or collect the blood and tissues. He maintains that the relevant animal welfare concerns are between Dr. Yu and her institution. Last, he suggests that because the NIH does not support her work, it does not have to conform to the same guidelines to which is own work is subject. What is your analysis of this situation? What is your recommendation for going forward?

Collaboration in Science

Alex Taguchi

Outline

- Recent trends, regulations, benefits, and challenges of collaboration
- We will explore two broad categories of collaboration:
  - Within the same university
  - Between two different universities
- Discussion questions and case studies

What is Collaboration?

“The term ‘collaboration’ in academic research is usually thought to mean an equal partnership between two academic faculty members who are pursuing mutually interesting and beneficial research. Today, however, many collaborations involve researchers of differing stature, funding status, and types of organizations.”

https://ori.hhs.gov/education/products/rcradmin/topics/colscience/tutorial_1.shtml

NIH and NSF are Supporters of Interdisciplinary Collaboration

- NIH:
  - Adopted a co-principal investigator model for grant applications
  - CTSA (Clinical Translational Science Awards): Provides funding to bring together basic, translational, and clinical researchers
  - Physical Science and Oncology Centers and the Integrative Cancer Biology Program: Each center is run by a physical sciences investigator and a cancer research investigator
- NSF:
  - Training grants and fellowships geared towards interdisciplinary research

Challenges of Collaborative Research

- Departmental organization at the university level
  - Collaborations may be seen by some as undermining the integrity of traditional department infrastructure
- Peer review: Study sections may not have the membership diversity to properly judge an entire application
  - NIH has moved towards a more interdisciplinary model
  - Sometimes additional reviewers are invited to provide needed expertise
- Publication: Discipline-specific journals do not always embrace interdisciplinary approaches in papers
  - Journal prospects can affect collaboration decisions
  - Can lead to collaborative conflict in which journal to submit to
  - Underweighting of an author's contributions by collaboration
  - Noting the role of each author in the collaboration in the paper is an increasingly common practice

Collaborator Accountability

- All researchers involved in a collaboration must be fully aware of and honor all formal policies, regulations, or laws attached to the subject matter of research
  - Working with human subjects, animals, controlled substances, hazardous substances, or select infectious agents
- Collaborations are subject to grant management regulations mandated by the funding agency
  - Any rebudgeting requires approval of all collaborators and the funding agency
- Partners in collaboration should be aware of the necessary steps when outcomes – planned or otherwise – have implications in intellectual property (IP)
  - Mutual agreement before public disclosure
- All collaborators must be aware that failure of anyone associated with the project to comply with regulations may carry consequences to all scientists involved in the study

Collaborative Agreements and Institutional Commitment

- Collaboration may start out informally
- However, once it is recognized that it is a collaboration, it is important that an agreement be made in writing
  - An agreement need not be extremely formal; a series of email exchanges can be sufficient
- Contents of collaborative agreement
  - Goals and objectives of the research
  - Roles and responsibilities in the research
  - Clearly outlining how and when the group will communicate
  - How information will be shared and stored
  - Discussion of how conflicts will be managed (tricky)
  - Discussion of IP when relevant (tricky)
- May be especially important for early-career scientists
  - What are the benefits and possible downsides of collaboration for early-career scientist?

Collaborative Grant Applications

- The highest degree of formality in academics is required when investigators who planning a collaboration seek grant support
- The application will contain a letter from the collaborator describing his or her role in the research
- The collaborator's biographical sketch will also be included in the application
- Budget requests for collaborator salary, supplies, and travel are also possible

Model of Team Development (Bruce Tuckman 1960's)

1. Forming: Bringing a group together to focus on a scientific problem not easily addressed by a single person
2. Storming: Recognizing and accepting conflict and involving all parties to come to an agreement
3. Norming: Group settles into a comfortable rhythm
4. Performing: Group becomes highly productive

- Keys to success:
  - Setting expectations, creating conditions for open and honest discussion, schedule regular meetings, avoid using jargon
  - What do you think are the keys to successful collaboration?

Power

- If a person has information other collaborators do not, the person has a high ranking academic, political or industrial position, or the person is of large physical size and stature, then that person is in a position of power
- Individuals with more power in the team have a responsibility to proactively create environments where the participants feel safe
- Failure of those in power to create a professional environment for other collaborators leads to psychological damage to those of less power and lower overall productivity

Diversity

- Having people from different identity groups bring their various skills, insights, backgrounds and experiences together, adding value
- Inclusion of people with different personalities, race, culture, and gender should always be encouraged
- Diversity vs Inclusion:
  - Diversity – noun: Composition of the workforce
  - Inclusion – verb: Actions and behaviors

Authorship and Ownership

- Authorship criteria should be laid out at the beginning of the collaboration
- Discussion of authorship should begin with the leaders of the collaborative parties, and subsequently all members
- Authorship criteria/order should be discussed early and regularly, and revised as appropriate
- Collaborators must establish ground rules for sharing of data that emerges from joint research projects
  - For NIH funded projects, the data are owned by the grantee institution
  - However, ownership of joint materials across different universities must be worked out by the collaborators
  - If a student visits a collaborator's lab and writes code on their computers, who is the primary owner of the data?

Conflict in Collaboration

- Disagreement about the science
  - Healthy conflict is encouraged, and forms the basis for robust questioning, rethinking, and reformulating
  - Journal clubs are specifically designed to promote debates amongst students
- Personal conflict
  - First decide if the conflict is important enough to try to resolve
  - Confront the person in private
  - Involve a third party if severe enough
  - Avoid actions that may harm the trust between you and others

Collaboration with Industry

- Collaborative arrangements with industry are becoming increasingly popular at universities
- Respect that consequences include restrictions on public disclosure and publication of research
- May be inconsistent with pre- and postdoctoral training philosophies and must be carefully weighed in that context
  - How might industrial collaboration affect a students pHD career?
- More strict written collaborative agreements are necessary in regards to sharing research materials, IP, and what may be disclosed in publications or at conferences
- Frequently, industrial research laboratories require the completion of a material transfer agreement (MTA) before sharing research materials. These agreements are also increasingly used by academic or government laboratories, especially if there is some inherent IP in the research materials

Collaboration with International Partners

- Awareness that international collaborations involves dealing with differences in ethical and cultural standards, especially in clinical research (laws and regulations concerning treatment of human subjects and animals, biomaterial safety…)

- Learning about a country's customs, expectations, and signs of respect in advance to the collaboration

Science Paper on Collaboration

- Teamwork in science increasingly spans beyond university boundaries
- Elite universities play a dominant role in this
- Examining 4.2 million papers published over three decades multi-university collaborations
  - Are the fastest growing type of authorship structure
  - Produce the highest-impact papers when they include a top-tier university
- Despite the rising frequency of research that crosses university boundaries, the study suggests a concentration of the production of scientific knowledge in fewer rather than more centers of high-impact science.

Jones, B., Wuchty, S., Uzzi, B. Multi-University Research Teams: Shifting Impact, Geography, and Stratification in Science, *Science* (2008)

“Death of Distance”

F. Cairncross, The Death of Distance (Harvard Univ. Press, Cambridge, MA, 1997)

- Technology is inevitably removing the barriers of distance to collaboration
- High-speed forms of transportation (driving, train, flying by plane)
- Online access to journal articles and publications
- Informal electronic communication (E-mail, phone, texting, social media, video conferencing)

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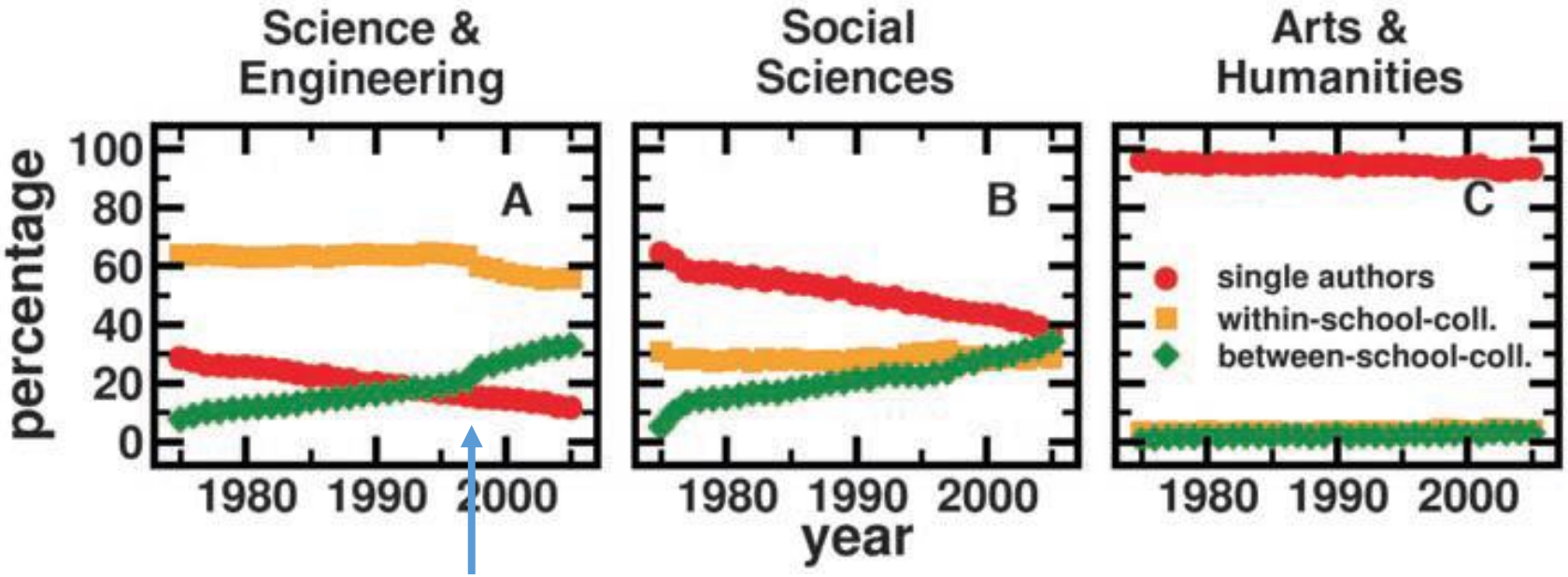
Multi-University Collaboration (1975-2005)



Boom in internet and modern digital communications technologies

Jones, B., Wuchty, S., Uzzi, B. Multi-University Research Teams: Shifting Impact, Geography, and Stratification in Science, *Science* (2008)

Multi-University Collaboration (1975-2005)

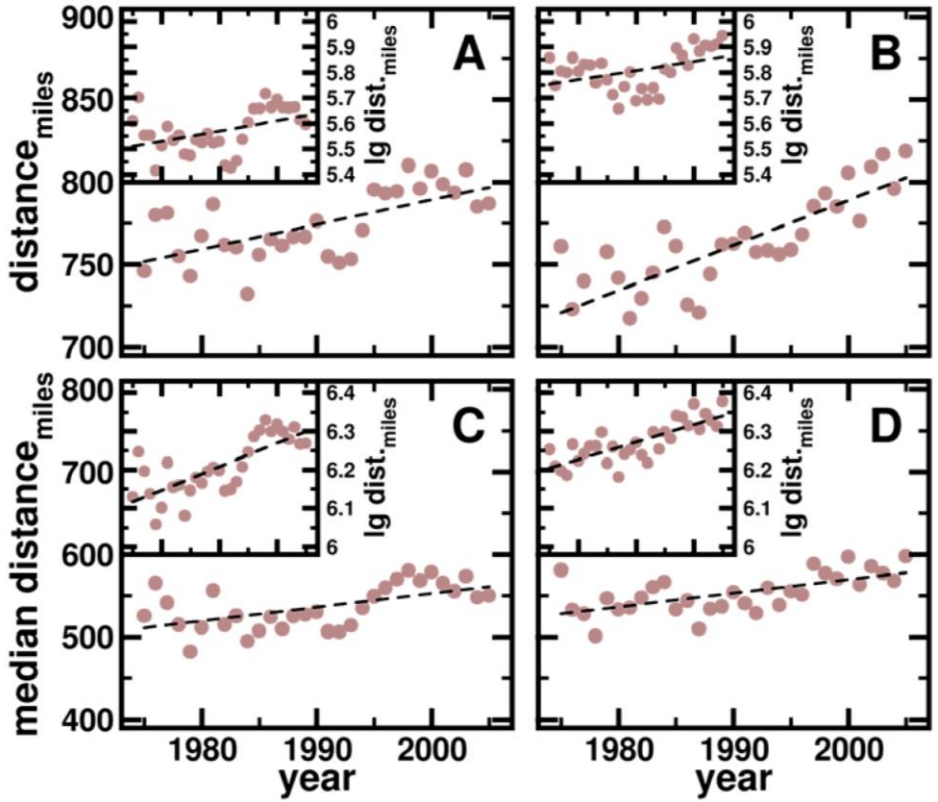
- Despite the sudden removal of barriers to collaboration that ensued in the 1990's, the rate at which multi-university collaborations increased over the following years didn't accelerate much

- This suggests multi-university collaborations were largely driven by factors that predated recent communication technologies
  - Supports that collaborations are the result of a real scientific need, as opposed to out of convenience
  - To what degree are scientific collaborations founded in real need, as opposed to out of convenience?

Jones, B., Wuchty, S., Uzzi, B. Multi-University Research Teams: Shifting Impact, Geography, and Stratification in Science, *Science* (2008)

...or conversely, were academics simply slow to adopt these technologies?

Although the incidence of between-school collaboration has grown rapidly, the average distance between collaborators has risen only slightly



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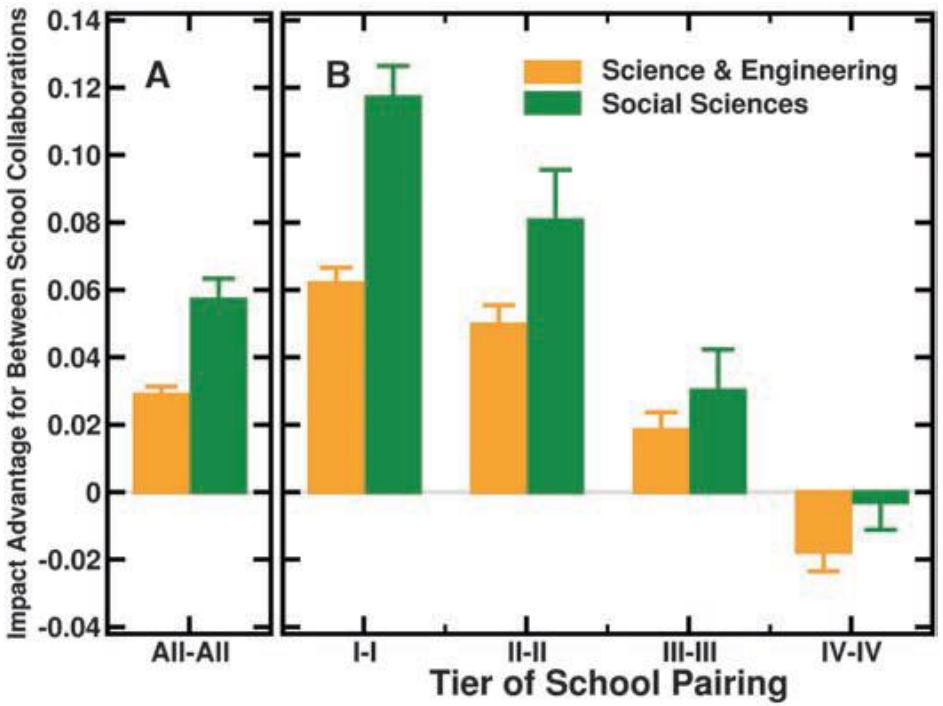
Citation Advantage of Multi-University Collaborations



Why don't lower-tier schools benefit from multi-university collaborations as much as higher tier schools?

What are the consequences on how research teams decide on collaborators?

The citation impact of between- versus within-school collaborations is compared. Impact is measured as the probability that a paper receives above-average citations.

Jones, B., Wuchty, S., Uzzi, B. Multi-University Research Teams: Shifting Impact, Geography, and Stratification in Science, *Science* (2008)

“Strongest-Partner” Instead of “Weakest-Partner” Model

Science and Engineering

School Tiers	Within-School Collaboration Baseline	Between-School Collaboration Marginal Advantage Over Within-School Baseline		
Panel A: All Schools				
All	32.7%	↑ 2.89%		
Panel B: Schools separated by Tier				
		All Tiers	Top Tier	Non-Top Tier
Tier I	37.2%	↑ 1.82%	↑ 4.66%	↓ 2.26%
Tier II	32.7%	↑ 3.48%	↑ 7.15%	↓ 1.58%
Tier III	29.5%	↑ 3.66%	↑ 6.43%	↓ 1.72%
Tier IV	23.5%	↑ 4.54%	↑ 7.23%	↑ 1.05%*

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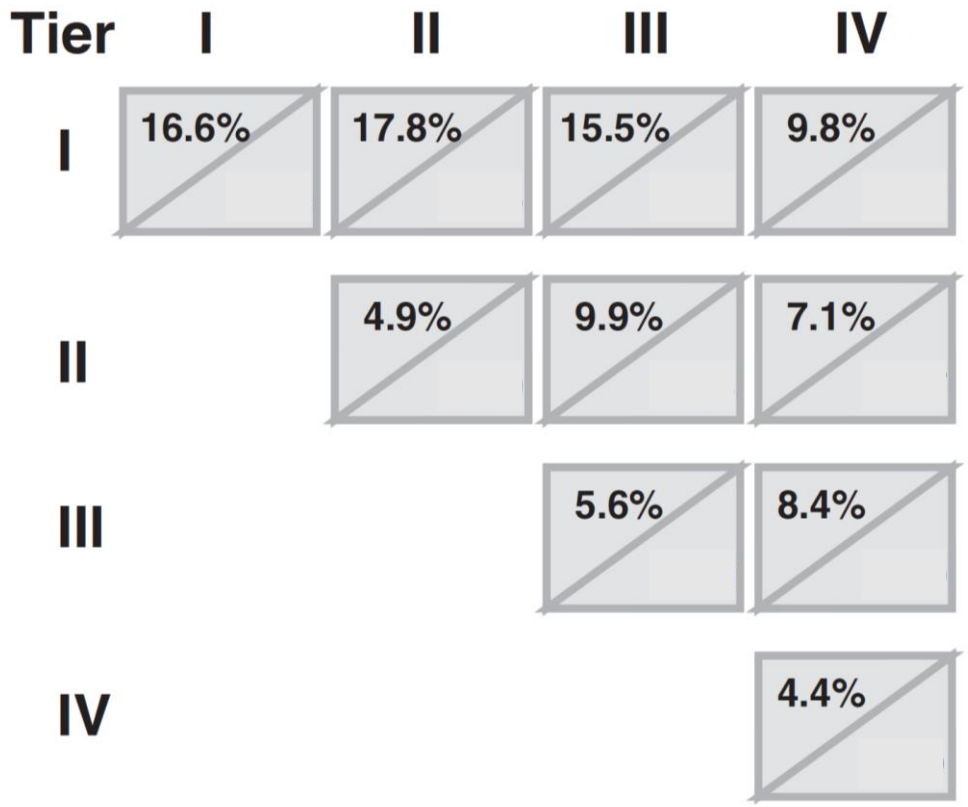
Schools Seek Collaborations with Higher-tier Schools



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Summary

- Tier I–tier I collaborations rose with time as compared with the expected rate, whereas tier I–tier IV collaborations fell
- Multi-university partnerships:
  - Are the fastest growing type of authorship structure
  - Produce the highest-impact papers when they include a top-tier university
- Geographic distance is of decreasing importance, social distance is of increasing importance in research collaborations
- Multi-university collaboration tends to embed the production of outstanding scientific knowledge in fewer rather than more centers of high-impact science.

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Discussion Questions

- Consider the faculty mentor-postdoctoral trainee relationship. Do you consider it to be a scientific collaboration as described in this presentation? How is it different than collaborations between two faculty scientists?
- Suppose you have been invited to collaborate on a research project with someone you have never met. How will you proceed to reach a decision on whether or not to accept the invitation?
- If one author fakes data, should all collaborators be held accountable?
- Should assistant professors collaborate with more experienced scientists outside their discipline?

Case Study #1

Dr. Riviera gives a new gene expression system to Dr. Singh. A description of the plasmid and host strain has not been published. Riviera describes the usefulness of the plasmid over dinner, and lists out its features on a napkin. Singh welcomes having the strain sent to her, and uses it to successfully gain important results she now intends to publish. Neither Riviera nor Singh mentioned anything about a collaboration at dinner. Singh believes a simple thanking in the Acknowledgements is sufficient, but Dr. Riviera demands position on the paper as a co-author.

Case Study #2

Dr. Anna Kryniak is a physician-scientist who is preparing a clinical trial to test an experimental drug developed at Meecham Pharmaceuticals. She does not believe she has enough patients to enroll at her own institution. She is recommended to collaborate with two other investigators to fill this need. A collaborative grant is approved and funded. She later finds out one of the co-PIs is on the speaker's bureau for Meecham Pharmaceuticals. Alarmed, Dr. Kryniak calls the PI for an explanation as to why they didn't inform her of this and the danger of a conflict of interests. The PI is adamant that he only accepts requests to speak on topics unrelated to the experimental drug. Anna considers withdrawing from the collaboration. Should Anna have done something differently to prevent this dilemma? Assuming that she does have a problem now, what are her options for pursuing a solution?