ILAR Workshop on Reproducibility Issues in Research with Animals and Animal Models.

An Ounce of Prevention worth a Billion of Cure: Proactive Planning in the Preclinical Research Arena

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Talking points

- Responsible conduct of research
  - Misconduct vs. Questionable Research Practices
- Physiologic conditions affecting reproducibility in preclinical science.
- Environmental situations that affect reproducibility
- Potential Solutions.
What is the Responsible Conduct of Research (RCR)

RCR is Displaying Integrity and Professionalism in the Planning of Research, The Accurate Collection of Data and The Analysis of Experimental Results. RCR Also Embodies Reporting Research Results Honestly and Without Deception or Deceit.

Although we are living in a culture that is increasingly more dishonest, more deceitful, less civil and more corrupt, researchers are held to a higher standard. Researchers and the research enterprise is under increasing scrutiny and expectation to conduct science collegially, professionally and to the highest ethical standards.
Misconduct and Questionable Research Practices.
PHS/NIH and by the NSF.

• Research Misconduct
  – The US federal government (45 CFR 689) has defined research misconduct as
    • Fabrication
    • Falsification
    • Plagiarism
  1. Very rigorous definitions.
  2. Intentional
  3. Preponderance of evidence.
Incident of Misconduct

• **Self report**
  • 2.0% (95%CI: 0.9–4.5) of scientists admitted to FFP

• **Colleagues**
  • 14-12% (95% CI: 9.9–19.7) FF

• Misconduct was reported more frequently by biomedical researchers.

• The data seems to indicate that true misconduct is rare, but others suggest that it is likely under-reported.
How Many Scientists Fabricate and Falsify Research? A Systematic Review and Meta-Analysis of Survey Data
Daniele Fanelli PLOS: May 29, 2009

Incident of Questionable Behavior

- Colleagues
  - Up to 72% for other questionable research practices
- Self report
  - Up to 33.7% admitted other questionable research practices.

Reported more frequently by biomedical researchers than others.
Questionable Research Practices in the planning of research, collecting research data and the reporting of Research.

- Inadequate research records
- Incomplete data reporting.
- Inappropriate sample size. Underpowered study design.
- Adding additional animals to a study where the data fails to show a significant effect, merging the data.
- Using inappropriate statistical methods inappropriately.
- Discarding outliers.
- Incentive to publish results quickly
Why is so much of the data suspect?

• Poor peer review
  – CITI Program satisfaction survey RCR course
  – ~70% of faculty responders indicated that peer review is done by students and post docs.
    – Student responses and faculty responses were similar.

• Poor or incomplete training in research ethics.

• Poor or incomplete training in research study design.

• Internationally, research study design is usually learned from the research advisor.
Reasons for lack of reproducibility

- Poor quality control of reagents, cells lines or animal strains.
- The use of model systems that may be reproducible and reliable in the lab, but are not predictable for human conditions.
- Bias in the experimental design imposed by lack of randomization strategies.
- Bias imposed by the researcher knowing which groups were getting the test agent. No blinding.
- No or inappropriate control groups.
Reasons for lack of reproducibility

Lab environment

• Intense competition among laboratories and intra lab personnel promotes:
  – Risky behavior. Taking Shortcuts. The “quick and dirty” end point increasing the chance of error and inappropriate conclusions.
  – Questionable research practices and perhaps misconduct
  – Poor control of experimental conditions from experiment to experiment.

• Busy, inattentive supervisors.

• Sloppy Science
Reasons for lack of reproducibility

Questionable Publication Practices

• Failure to report basic elements of experimental design. For example:
  – **Animal characteristics** e.g., Strain, age, gender, body weight, source, acclimation period.
  – **Husbandry issues.** cage change frequency, bedding type, enrichment, temp, light dark cycles (circadian and circannual rhythms), activity cycles.
  – **Treatment basics.** Treatment AM or PM, Reagent quality control. Machine calibrations.
  – **Study design.** Blinding, randomization, replications, sample-size calculation and gender differences.
Reasons for lack of reproducibility

Questionable Publication Practices

• Failure to report basic elements of experimental design. For example:
  – The 'secret sauce' to make their experiments work — withhold details from publication or describe them only vaguely to retain a competitive edge.

• Dishonest and deceptive authorship practices.

• Sloppy science

Unprofessional irresponsible science
What can be done to enhance reproducibility

• Engage national animal research associations to promote reproducibility of science.
  – PRIMR, AALAS, AAALAC Int., SCAW, NABR, ILAR
  – Promote accreditation of the lab animal programs.

• Encourage IACUCs to be more rigorous in their protocol review.
  – Hypothesis testing, model appropriateness, model failure.
  – Ask what will be done to assure data quality and reproducibility.

• Promote the inclusions of statisticians (consultants) in the research team.
What can be done to enhance reproducibility

• National organizations can promote
  – Open, transparent and collaborative research
  – Promote the use of web based e-notebooks.
    • Open data, promote critical analysis, collaboration.
    • Retain the IP

[https://www.slas.org/default/assets/File/2012_JALA_Readers_Choice_Award.pdf](https://www.slas.org/default/assets/File/2012_JALA_Readers_Choice_Award.pdf)
What can be done to enhance reproducibility

• National organizations can Promote
  – Multicenter efficacy trials of agents in pipeline for clinical trial.

• National Center for Advancing Translational Sciences (NCATS) CTSA.
  • Huge grants designed to transform recipient institutions (CTSI) into centers that encourage, enable and expedite the translation of basic preclinical science to clinical application.
  • Mostly the clinical side of translational research (GCP, biostatistics, clinical research study design).
What can be done to enhance reproducibility

Engage the Education Providers
  – ALAS, CITI Program at the U of Miami, SQA

• Topics
  – Lab animal welfare, and the RCR
  – Responsible publication practices
  – Research study design with animals.
    • Quantitative study design
    • Factors known to affect responses.
  – Biostatistics.
  – Good Laboratory Practice; GLP labs.
Conclusions
The key to promoting reproducible science is for all members of the research team to have a clear understanding that:

1. Promoting data integrity and reproducibility of science is a shared responsibility in our community.

2. Sloppiness in planning, execution and reporting of animal research is unprofessional and unacceptable.

3. Larger Labs, more students and post docs, playing a greater role. More responsibility falls on the PI to insure staff are technically proficient and that the planning, execution and reporting of research is to the highest standards.

4. Peer review of manuscripts and grant applications should not be relegated students and post docs w/o permission.
Further:

4. Greater emphasis should be given to training students and young investigators in research study design.

5. National organizations that promote animal welfare and animal research should take an active role in promoting the reproducibility of science.

6. If we do not get the house in order, the issues will become politicized and additional regulatory burden will be imposed to insure that the Public’s Trust in research and the publically funded research enterprise is preserved.