Class Syllabus: Rigor and Reproducibility (Fall 2024) (Mol Bio 235)

Purpose and Format:
Progress in science requires rigor in designing and performing experiments to achieve reproducibility of research findings. Scientific rigor promotes reliable findings through robust, unbiased and well-controlled experimental design, methodology, analysis and interpretation of results. Reliable findings become building blocks for future investigations. In this 8 hour course, we are examining these aspects of Rigor & Reproducibility in biomedical research using recent literature and case studies from NIH-funded videos. Course sessions comprise lectures and small group discussions in which topics raised in the lecture and case studies are discussed.

Learning Objectives:
Trainees will learn that reproducibility is a crucial aspect of biomedical research, and will learn and discuss approaches that can ensure rigorous experimental design and improve reproducibility.

Learning Outcomes:
• Understanding aspects of Rigor & Reproducibility such as bias, blinding and randomization, biological and technical replicates, exclusion criteria and transparency
• Evaluating scientific premise
• Learning about record keeping, authentication of reagents
• Application of statistical tests for data analysis

Class Sessions: **BSRB 154, Thursdays, 9-10 AM**

Course Web Site: https://bruinlearn.ucla.edu/courses/194093

Office Hours: By appointment

Grading:
- **For graduate students**: Grading is Pass/Fail. To earn a Pass, students must attend and participate in at least seven out of eight sessions.
- **For postdoctoral scholars:** In lieu of a grade, postdoctoral scholars will receive a certificate of completion if they attend and participate in at least seven out of eight sessions.

Where to find course reading materials:
- **PubMed**: http://www.ncbi.nlm.nih.gov/pubmed
- Routing through the UCLA library system offers increased accessibility to e-publications: http://www.ncbi.nlm.nih.gov/sites/entrez?tool=cdl&holding=uclalib&otool=cdlotool
- If you are using an off campus computer you will need to set up a proxy server - follow instructions on the UCLA IT Services site: https://www.it.ucla.edu/it-support-center/services/proxy-server.

Course Format:
Classes will include a combination of didactic presentations, examples and best practices from the literature, and small group discussions. Course materials will

include articles and video modules provided by the NIH and the NIGMS Clearinghouse for training in Rigor and Reproducibility.

Session 1 – October 3, 2024

Is Reproducibility a Problem in Biological Research?

There has been a growing awareness in recent years that too many biomedical research studies are not reproducible. Scientists need to rethink how they perform and teach research methodology to enhance rigor. Here, we will discuss evidence for a problem with reproducibility and strategies to improve research quality and rigor.

Reading:

- **Baker**. *Is There a Reproducibility Crisis?* Nature 533, 452-454 (2016).
- **Collins and Tabak**. *NIH Plans to Enhance Reproducibility*. Nature 505, 612-613 (2014).

Small group discussion:

In the group discussion, trainees will present challenges of "Rigor and Reproducibility" from their research. This could include critical procedures to ensure reproducibility in their own experiments/lab, or reasons for non-reproducibility of their experiments. Discussion points will include bias in analysis, blinding, randomization.

Session 2 – October 10, 2024

Bias, Blinding, Randomization

Blinding and randomization are experimental methods that reduce bias and minimize the likelihood of chance altering the outcome of an experiment by keeping the investigators unaware of assigned sample designations (e.g., wild-type vs. mutant, untreated vs. treated) until after completion of the experiment and, if possible, analysis of the results.

Reading:

- **Nuzzo.** *Fooling Ourselves*. Nature 526, 182-185 (2015).

Video Modules:

- **NIH:** *Blinding and Randomization* https://www.youtube.com/watch?v=NEcErxoOVm0
- **NIGMS Clearinghouse:** *Be Aware of Measurement Bias and Blind Yourself* *https://www.youtube.com/watch?v=Ac65JLrjLfs*
- **NIGMS Clearinghouse:** *Don't Be Wed to Your Hypothesis* https://www.youtube.com/watch?v=kndxCnD6a7c

Small group discussion:

The discussion will include the video modules, "Blinding and Randomization", "Be Aware of Measurement Bias and Blind Yourself" and "Don't Be Wed to Your Hypothesis." Trainees will discuss the suggested approaches to reduce bias, if bias affects their own experiments and if they blind or randomize samples in their own experiments. What are the differences between

two types of experimental approaches, hypothesis- driven or discovery-driven, and what are the advantages and pitfalls of each?

Sessions 3 & 4 – October 17 & 24, 2024

Statistical Concepts and Methods and their Roles in Reproducibility – Mary Sehl

Following a brief refresher of statistical concepts such as hypothesis testing, p-values, effect sizes, confidence intervals, and power, we will discuss how some common statistical practices may have inadvertently contributed to the reproducibility crisis. We will then discuss sound statistical methods that have helped identify reproducibility problems, as well as how statistical methods can improve rigor and reproducibility.

Reading:

- **11/3 Ioannidis.** *Why most published research findings are false*. PLoS Medicine 2, 696-701 (2005).
- **11/10 Gosselin.** *Statistical analysis must improve to address the reproducibility crisis: The ACcess to Transparent Statistics (ACTS) Call to Action.* BioEssays 42,1900189 (2020).

Discussion Questions: (1) Should p-values be abolished? If yes, what, if anything, should take their place? (2) How could/should the ACTS proposal be implemented in practice? Beyond the ideas put forth in Gosselin, do you have any suggestions on how statistical practices could help improve rigor and reproducibility?

Session 5 – October 31, 2024

Sample Size / Outliers and Authentication

Sample size is the optimal number of samples that should be used to reach sufficient statistical power. Outliers and exclusion criteria are standards set out before a study to determine whether a sample should be included or excluded. Characterization of “normal” for a specific experiment is an important component to identifying outliers and determining exclusion criteria. Biological and/or chemical resources such as cell lines, antibodies, and specialty chemicals need to be authenticated, and the basic methods to authenticate the most common biological and chemical resources.

Reading:

- **Lorsch et al**. *Fixing Problems with Cell Lines*. Science 346, 1452-1453 (2014).
- **Lithgow et al**. *A Long Journey to Reproducible Results*. Nature 548, 387-388 (2017).
- **Bandrowski**. *How a Typo in a Catalog Number Led to the Correction of a Scientific Paper — and What We Can Learn from It*. Retraction Watch (2018).

Video Modules:

- **NIH:** *Sample Size, Outliers and Exclusion Criteria* www.youtube.com/watch?v=Pc0h-GOcBLE
- **NIGMS Clearinghouse:** *Replicates in an Experiment: Account For Variability with Replicates* https://www.youtube.com/watch?v=TubzzXYN6X8

Small group discussion:
The discussion will center the case study “Sample Size, Outliers, and Exclusion Criteria” and ”Replicates in an Experiment: Account For Variability with Replicates.” Questions for discussion include the following. Do you have a standard approach to determining the appropriate sample size? Are you authenticating reagents in your lab, and if so, how?

Session 6 – November 7, 2024

Biological and Technical Replicates

Biological replicates are parallel measurements of biologically distinct samples that capture random biological variation. Technical replicates are repeated measurements of the same sample that represent independent measures of the random noise associated with protocols or equipment.

Video Modules:

- **NIH:** *Biological and Technical Replicates* www.youtube.com/watch?v=wSWunBYzl8c
- **NIGMS Clearinghouse:** *Replication in Research: How To Think About Replication* https://www.youtube.com/watch?v=w0Q9uci2QDQ

Small Group Discussion:

Based on the NIH case studies “Biological and Technical Replicates” and “Replication in Research: How to think about replication”, trainees will discuss whether it is common to report data from a single experiment to generate an “exciting” finding. Is it appropriate to leave out information about the type of replicates? How would you have portrayed the data? Should grant applications/papers delineate the use of biological vs. technical replicates in the figure legends? Is there a standard for the number of repeats of an experiment in your field of research, does it depend on the type of experiment?

Session 7 – November 14, 2024

Record Keeping and Lab Notebooks

Record keeping is a critical component for ensuring that experiments are reproducible. I also promotes being thoughtful about the experimental process and can improve observation by clarifying what you are expecting from the experiment.

Reading:

- **Baker**. *Quality Time*. Nature 529, 456-458 (2016).

Video Modules:

- **NIGMS:** *Research Tips: Lab Notebook* https://youtu.be/G4mRm6iyLnI
- **NIGMS Clearinghouse:** *Experimental Design Case Study: A Useful Approach to Record Keeping https://www.youtube.com/watch?v=rSFYWayYtDg*

Small group discussion:

The discussion will also use two case studies, “Research Tips: Lab Notebook” and

"Experimental Design Case Study: A Useful Approach to Record Keeping" and showcase an accompanying lab notebook template. The presented approaches to notebook keeping and favorite alternative ways will be discussed.

Session 8 – November 21, 2024

Transparency
In order to reproduce another's findings adequately, the experimental methods, rationale, and other pertinent information must be accessible and understandable. What are strategies to enhance the transparency of research?

Evaluating the Scientific Premise
Evaluating the strengths and weaknesses of prior research from the literature. Factors that make prior research reliable include findings that are obtained by several laboratories independently, findings supported by independent approaches (Western blot and microscopy, knockout/siRNA and rescue, same effect in different cell lines/mouse/fly/yeast).

Rigorous Experimental Design
We will cover approaches to improve reproducibility and to ensure unbiased experimental design (with appropriate controls), methodology, analysis, interpretation and transparent reporting of methods and results.

Video Module:
- **NIH:** *Lack of Transparency* https://www.youtube.com/watch?v=U4A-ZSTUEUo

Reading:
Sudhof. *Truth in Science Publishing: A Personal Perspective*. Plos Biology 14(8):e1002547 (2016).

Small group discussion:
The group discussion will use a case study from Module 1, "Lack of Transparency", of the NIH Rigor and Reproducibility Training Modules as a starting point. Key questions include why the results in the case study were not reproducible, what helped the researchers to identify the reason for this, and how trainees might deal in similar situations.

Student Resources

UCLA policies that support tolerance: All students are asked to treat one another with kindness and respect. Harassment and discrimination based on: **race, ethnicity, ancestry, color; sex, gender, gender identity, gender expression, sexual orientation; national origin, citizenship status; religion; disability, pregnancy, medical condition, genetic predisposition; domestic partnership/marital status; age; or veteran status** may violate UCLA regulations and lead to serious consequences. Information on how to obtain redress or counseling if you are subjected to such harassment or discrimination can be found at https://equity.ucla.edu/report-an-incident/.

UCLA is bound by Title IX, a federal law that applies to any education program receiving federal assistance. Title IX prohibits gender discrimination, including sexual harassment, domestic and dating

violence, sexual assault, and stalking. Students who have experienced sexual harassment or sexual violence can receive confidential support and advocacy at the CARE Advocacy Office for Sexual and Gender-Based Violence, 1st Floor Wooden Center West, CAREadvocate@caps.ucla.edu, (310) 206-2465. You can also report sexual violence or sexual harassment directly to the University's Title IX Coordinator, 2241 Murphy Hall, titleix@conet.ucla.edu, (310) 206-3417.

Student Resources:

It is normal for students to feel stress about assignments, exams and life in general and there are many resources on campus for students in need of various types of counseling. These include:

For Graduate Students:

- **UCLA Behavioral Wellness Center For Graduate Students**
  A student mental wellness center open to GPB graduate students, medical students, and medical residents. https://medschool.ucla.edu/bwc
- **The Bruin Resource Center** With the mission of supporting students' development, well-being, and academic success, and fostering an inclusive and socially just campus community. https://www.brc.ucla.edu/
- **Support for Undocumented Students:** UCLA provides many resources to support undocumented students and links to many of them can be found on the following web site: https://equity.ucla.edu/know/immigration/.
- **Graduate and Postdoctoral Case Manager:** A case manager can help with any issues affecting academic progress, mentoring issues, or challenges with lab or training. Case managers connect students with resources and suggest options. casemanagers@grad.ucla.edu

For Postdoctoral Scholars:

- **UCLA Staff and Faculty Counseling Center** UCLA provides counseling, assessment and referral services to faculty and staff and their immediate family members as well as management consultations and coaching to department managers.
  https://www.chr.ucla.edu/employee-counseling/counseling-consultation
- **Graduate and Postdoctoral Case Manager:** A case manager can help with any issues affecting academic progress, mentoring issues, or challenges with lab or training. Case managers connect postdocs with resources and suggest options.
  casemanagers@grad.ucla.edu