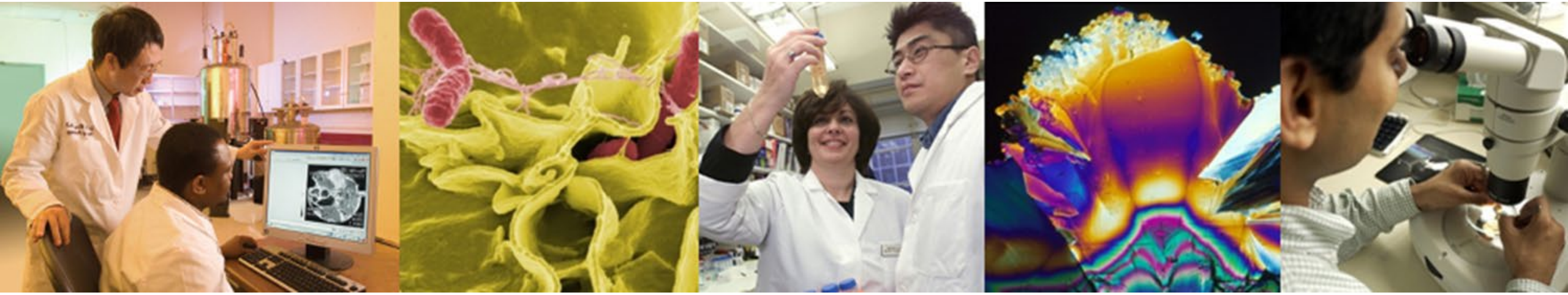
ACD Working Group on Enhancing Reproducibility and Rigor in Animal Research Interim Report

119th Meeting of the Advisory Committee to the Director (ACD)

December 12, 2019



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Bren Professor of Molecular Biology
California Institute of Technology

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Principal Deputy Director, NIH
Department of Health and Human Services

Agenda

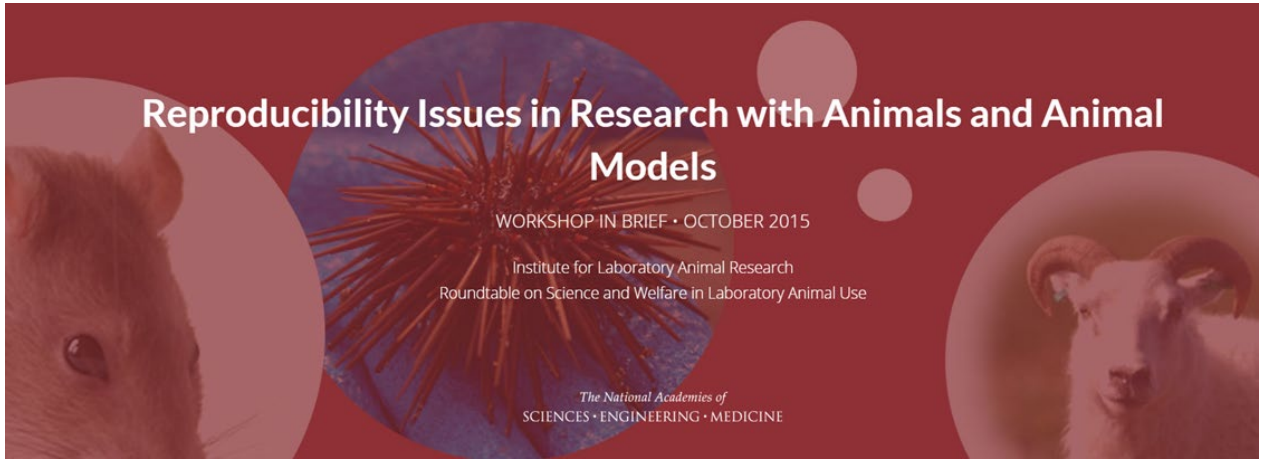
- **The charge**
- Interim Progress
- Next Steps

Background

Animal experiments often serve as the foundation for human clinical trials. Thus, there is a cost when reproducibility and translatability fail.

Background

- Work is being done by many outside organizations
  - The National Academies of Sciences, Engineering, and Medicine
  - National Centre for the Replacement, Refinement, and Reduction of Animals in Research
  - Scientific Societies e.g. American Physiological Society, Society for Neuroscience



Background

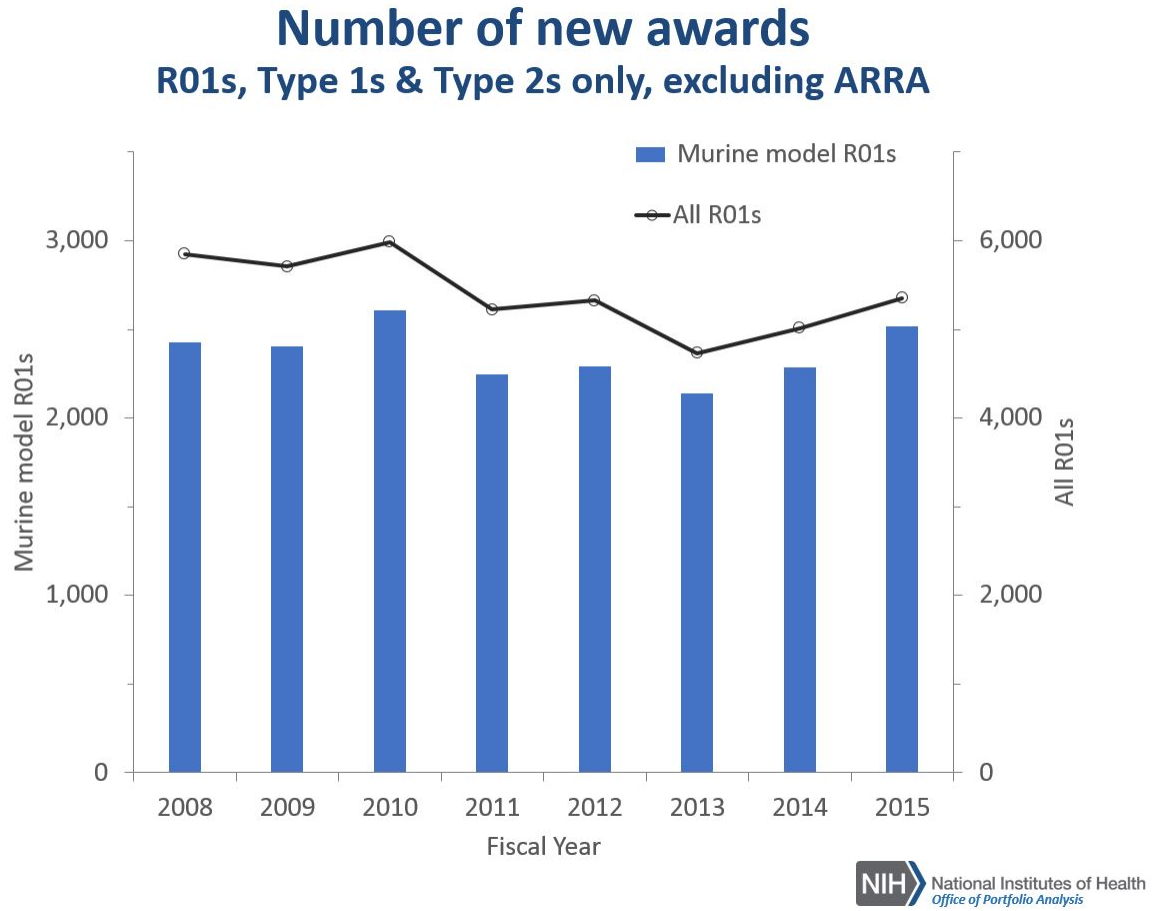
- NIH has taken steps in recent years, including establishment of an ACD working group in response to the 21st Century Cures Act, to improve research rigor and reproducibility.
- The next step in examining rigor and reproducibility is to focus on animal research.

Background

- Rigor and reproducibility in animal research is influenced by:
  - Selection of poorly validated models of human disease
  - Study design and misapplication of statistical analyses
  - Overlooked variables, such as animal care and husbandry
  - The stages of the scientific research pipeline
  - Transparent reporting of experimental design and methods
  - The ways we communicate animal research, including vocabulary

Model Organism Research at the NIH

- NIH supports research using many model systems to answer questions of basic and disease biology.
- NIH analyses found support for model organism research remains relatively stable since 2008.
- About 40% of our R01 grants use murine models.
- A greater proportion of new awards involve use of murine models each year



Charge to the Working Group (October, 2019)

- **Identify gaps and opportunities** to improve the rigor, reproducibility, translational validity, and transparency of animal models studies
- Evaluate **how animal models of human disease are currently developed, validated, and accepted into routine use**, and how this process could be improved
- Assess the current state of science for **validating alternative models** to animal research

Charge to the Working Group (October, 2019)

- Consider the benefits and burdens of **registering animal studies** that aim to lead to first in human trials
- Model the **financial implications of potential changes in the average costs** of grants using animal models, the number of studies funded, or the need to develop consortia to achieve appropriate statistical power
- Consider how rigor in animal research is incorporated into **training**

ACD Enhancing Reproducibility and Rigor in Animal Research Working Group Members

EXTERNAL MEMBERS

- **Barbara Wold, PhD (Co-Chair)**
  California Institute of Technology
- **Nancy Ator, PhD**
  Johns Hopkins School of Medicine
- **Lais Berro, PhD**
  University of Mississippi Medical Center
- **Eliza Bliss-Moreau, PhD**
  University of California, Davis
- **Romer A. Gonzalez Villalobos, MD, PhD, FAHA**
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- **Claire Hankenson, DVM, MS, DACLAM**
  Michigan State University
- **Veronique Kiermer, PhD**
  PLOS
- **Keisa Williams Mathis, PhD**
  University of North Texas Health Science Center
- **Sarah Nusser, PhD**
  Iowa State University
- **Regina Nuzzo, PhD**
  American Statistical Association
- **Eric Prager, PhD**
  Journal of Neuroscience Research
- **F. Daniel Ramirez, MD, MSc**
  CHU Bordeaux, IHU Liryc
- **Karen Svenson, PhD**
  Jackson Laboratory

ACD Enhancing Reproducibility and Rigor in Animal Research Working Group Members

USG MEMBERS

- **Lawrence A. Tabak, DDS, PhD (Co-Chair)**
  Principal Deputy Director, NIH
- **Brian Berridge, DVM, PhD, DACVP**
  National Institute of Environmental Health Science, NIH
- **Paul Brown, PhD**
  Center for Drug Evaluation and Research, FDA
- **Janine Clayton, MD**
  Office of Research on Women's Health, NIH
- **Joshua A. Gordon, MD, PhD**
  National Institute of Mental Health, NIH
- **Michael Lauer, MD**
  Office of Extramural Research, NIH
- **Robyn Lee-Stubbs, MS, CPIA, PStat®**
  United States Army Medical Research Institute of Chemical Defense
- **Glenn Merlino, PhD**
  Scientific Director for Basic Research, National Cancer Institute, NIH
- **Shai Silberberg, PhD**
  National Institute of Neurological Disorders and Stroke, NIH
- **Carrie Wolinetz, PhD**
  Office of Science Policy, NIH

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- **Interim Progress**
- Next Steps

Discussions Topics

The working group has identified several areas for initial discussion:

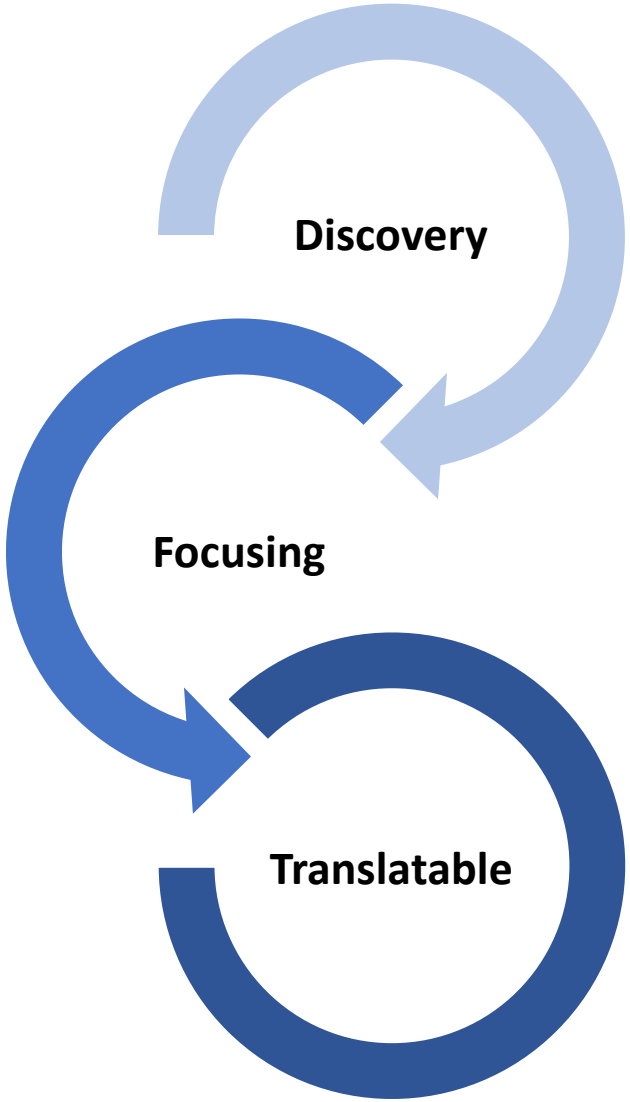
- Adopting a common vocabulary
- Factors in the selection of animal models
- Robustness of study design, including statistical analysis
- Factors that influence reproducibility in animal research

Discussions Topics

The working group has identified several areas for initial discussion:

- The needs along different stages of the scientific research pipeline
- Impacts and limitations of preregistration
- Reporting guidelines and checklists
- Measuring the effect of our interventions
- Tackling the cultural incentives to keeping the status quo

Framing: Scientific Research Pipeline



- There's a cost to failure of rigor and reproducibility that gets higher and higher the further you get up the translational chain.
- Conversely, there is a cost to insisting upon high levels of rigor and reproducibility at low ends of the chain.

Developing Themes

- **Selection** of animals of relevance to human disease for modeling
- Strengthening experimental **design and analysis**
- Impact of animal **care and husbandry** on experimental outcomes
- Enhancing **transparency**
- Training and continuing **education**, including vocabulary
- **Measuring the effect** of our interventions
- Tackling the **cultural incentives** to keeping the status quo

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Timeline

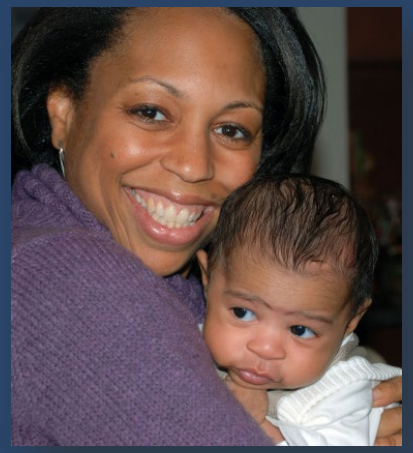
“Essentially all models are wrong, but some are useful.”

- George Box

We want to make sure that when animal research is conducted with the goal of answering a question related to human biology or disease, that the animals used as a model are appropriate, and that the experiments are designed in a way that leads to rigorous, reproduceable, translatable results.

Timeline

- October/November 2019: Kickoff meetings
- **December 2019: Interim report to ACD**
- January 2020- April 2020: In-person and teleconference meetings
- 2020: Final recommendations to ACD

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Turning Discovery Into Health

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