Science Advancement & Outreach
A DIVISION OF PETA

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Request for Information: NIH Common Fund is Soliciting Ideas for NIH-wide Challenges and Opportunities

Response from People for the Ethical Treatment of Animals, August 2023

A critical challenge or exciting emerging opportunity in biomedical/behavioral research

The past two decades have brought to light many obstacles in scientific research, including both the "reproducibility crisis" and failures in the translation of research findings to the clinical setting. Depending on the metrics used, basic and preclinical research fail to lead to human benefit between 90 and 95 percent of the time, representing an enormous inefficiency of resources and a failure to meet the needs of patients and their families in a timely manner. In some areas of disease research, such as neurodegenerative diseases, sepsis, and stroke, the failure of new drugs to provide a significant clinical benefit to patients is at or near 100 percent.

Societal concern over the use of non-human animals in biomedical research has also grown consistently over the years, with the public's acceptance of this practice predicated on the expectation of resulting societal benefit. Most scientists and non-scientists alike would disagree with the use of animals—particularly for harmful and/or invasive experiments—if the research were not expected to generate results that are useful to advance human health. Most taxpayers would not agree to have their hard-earned wages earmarked for this purpose.

There are several ways in which experiments using animals may contribute to the low reproducibility and translatability of biomedical and behavioral research. These factors have been reviewed elsewhere (see Hooijmans and Ritskes-Hoitinga 2013) and include 1) fundamental biological differences between species, 2) poor methodological quality, 3) preclinical vs. clinical design differences, 4) poor reporting, and 5) publication bias.

There are ways by which animal models or particular types of animal experiments could be rigorously and objectively assessed to determine which combination of the above factors is contributing to their low rates of reproducibility and translational success. However, there has been no concerted effort on the part of U.S. funding agencies to conduct or commission these types of analyses, even in disease areas that are recognized as the most problematic and even when these agencies are allocating billions in taxpayer funding to these disease models.

Addressing this crisis requires funding agencies to step back and assess—with great care and accuracy—the sources of inefficiencies. Systematic reviews provide a method for doing this.

Supporting Resources:

Contopoulos-Ioannidis DG, Ntzani E, Ioannidis JP. Translation of highly promising basic science research into clinical applications. *Am J Med*. 2003;114(6):477-484.

de Vries RB, Wever KE, Avey MT, Stephens ML, Sena ES, Leenaars M. The usefulness of systematic reviews of animal experiments for the design of preclinical and clinical studies. *ILAR J*. 2014;55(3):427-437.

Hooijmans CR, Ritskes-Hoitinga M. Progress in using systematic reviews of animal studies to improve translational research. *PLoS Med*. 2013;10(7):e1001482.

Freedman LP, Cockburn IM, Simcoe TS. The economics of reproducibility in preclinical research. *PLoS Biol*. 2015;13(6):e1002165.

Howells DW, Sena ES, Macleod MR. Bringing rigour to translational medicine. *Nat Rev Neurol*. 2014;10(1):37-43.

Pound P, Ebrahim S, Sandercock P, Bracken MB, Roberts I; Reviewing Animal Trials Systematically (RATS) Group. Where is the evidence that animal research benefits humans? *BMJ*. 2004;328(7438):514-517.

Resources, tools, or knowledge that are needed to address the important challenge or opportunity

According to the Cochrane Library, systematic reviews (SRs) “identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a specific research question. Researchers conducting SRs use explicit, systematic methods that are selected with a view aimed at minimizing bias, to produce more reliable findings to inform decision making.” A new Preclinical Systematic Review Collaboratory (PSRC), supported by the NIH Common Fund, would provide the NIH and other federal funding agencies with clear evidence on which they could reliably base future policy and funding decisions and improve the agency’s return on investment.

The PSRC could support the execution of SRs at two levels. First, the PSRC could convene or commission an unbiased team to conduct SRs to assess the effectiveness of the preclinical and translational research models being used by NIH intramural and extramural researchers. These SRs would assess whether the methods are fit-for-purpose by including information on past translation of the research model and the return-on-investment received by the public for the results of experiments using such models. They could also assess the costs of the model, including the harms experienced by animals, where applicable. These SRs could measure the quality of the

research in terms of design and reporting. Second, the PSRC could develop best practices and training modules to aid researchers in designing and performing their own SRs and provide funding for them to do so, as SR training is beneficial for study quality and knowledge transfer.

NIH already supports the concept that SRs should be used to guide funding decisions. NIH is a member of the Ensuring Value in Research Funders' Forum (EViR). EViR states as its second guiding principle, "Research should only be funded if set in the context of one or more existing systematic reviews of what is already known or an otherwise robust demonstration of a research gap." It explains, "This is important because new research not set in the context of what is already known leads to unnecessary duplication, studies that cannot change decision making (e.g. will not change the meta analysis), or inappropriate design (e.g. inappropriate outcome measures, incorrect prevalence assumptions, failure to learn from past previous studies)." To apply this principle, EViR says that funders must "[r]outinely assess whether an adequate review has been done and whether the results of that review support the case for further clinical or preclinical research."

When established, the PSRC will create valuable new data on model efficacy that will be accessible to all NIH institutes as well as the larger research community. PSRC deliverables will guide funding decisions to improve efficiency and the translatability of NIH-supported research findings into prevention and therapies, helping NIH to realize its goals of protecting and improving health, ensuring a high return on the public's investment in research, and promoting the highest level of scientific integrity.

Supporting Resources:

https://www.cochrane.org/our-evidence/what-are-systematic-reviews

https://www.syrcle.network/

http://www.dcn.ed.ac.uk/camarades/default.htm

https://evir.org/our-principles/applying-the-principles/#principle2

https://www.elsevier.com/connect/authors-update/why-systematic-reviews-matter

Menon, et al. 2021: https://doi.org/10.1371/journal.pone.0260619

Ritskes-Hoitinga and Pound, 2022: https://doi.org/10.1177/01410768221093551

Russell, et al. 2022: http://dx.doi.org/10.1136/bmjos-2021-100219

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Scientific advancements or other factors that make addressing the important challenge or opportunity particularly timely

The quality and quantity of in vitro, in silico, and human imaging tools for conducting non-animal, human biology-based research have increased dramatically in recent years. Studies consistently show that these methodologies are better at modeling human diseases and human responses to drugs than experiments on animals are. For example, a human liver-on-a-chip "was able to correctly identify 87% the tested drugs that caused drug-induced liver injury in patients despite passing animal testing evaluations. These drugs that initially passed animal testing evaluations ultimately caused nearly 250 deaths and 10 liver transplants" (Ewart, et al. 2022).

With technology now available to replace many uses of animals in biomedical and behavioral research, it is paramount that this transition begins in the most evidence-based way, first replacing experiments on animals that have particularly low translational value (as would be determined by the work of the proposed Common Fund Preclinical Systematic Review Collaboratory (PSRC)).

Additionally, the PSRC would be a way by which NIH can respond to the increase in requests from Congress and the public for the agency to better examine its support of and use of animal-based research.

Supporting Resources:

Barrile R, van der Meer AD, Park H, et al. Organ-on-chip recapitulates thrombosis induced by an anti-CD154 monoclonal antibody: Translation potential of advanced microengineered systems. *Clin Pharmacol Ther*. 2018;104(6):1240-1248.

Dirven H, Vist GE, Bandhakavi S, et al. Performance of preclinical models in predicting drug-induced liver injury in humans: A systematic review. *Sci Rep*. 2021;11(1):6403.

Ewart L, Apostolou A, Briggs SA, et al. Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology. *Commun Med (Lond)*. 2022;2(1):154.

Luechtefeld T, Marsh D, Rowlands C, Hartung T. Machine Learning of Toxicological Big Data Enables Read-Across Structure Activity Relationships (RASAR) Outperforming Animal Test Reproducibility. *Toxicol Sci*. 2018;165(1):198-212.

Mace N, et al. Letter to Lawrence Tabak. Sent February 10, 2022. Accessed August 8, 2022. https://www.peta.org/wp-content/uploads/2022/02/Mace-Lieu-NIH-Letter.pdf

Nehls TE, Davis D. Letter to Lawrence Tabak. Sent April 3, 2023. Accessed August 8, 2022. https://www.peta.org/wp-content/uploads/2023/04/2023-04-03-congressional-letter-to-nih-re-caucaseco.pdf.

Roybal-Allard L. Letter to Francis Collins. Sent September 4, 2019. Accessed August 8, 2023. https://www.peta.org/wp-content/uploads/2019/09/Count-and-Reduce-Letter-9.4.19.pdf.