Science Advancement & Outreach
A DIVISION OF PETA

1536 16th St. N.W., Washington, DC 20036

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

Submitted online on August 9, 2024

Title: Preclinical Systematic Review Collaboratory (PSRC)

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 the "reproducibility crisis" and failures in the translation of research findings to the clinical setting. Depending on the metrics used, basic, translational, 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 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.

There are several ways in which experiments using animals may contribute to the low reproducibility and translatability of biomedical and behavioral research. These factors include fundamental biological differences between species, poor methodological quality, preclinical vs. clinical design differences, poor reporting, and publication bias.

Systematic reviews are one way by which animal models or specific experiments on animals could be rigorously and objectively assessed to determine which combination of factors is contributing to their low rates of reproducibility and translational success. However, there has been no concerted effort on the part of NIH to conduct or commission preclinical systematic reviews, even in disease areas that are recognized as the most problematic and where animal models for the study of those diseases have been long criticized as contributing to failure, but are still being heavily funded by the agency.

Addressing the crises of reproducibility and translatability requires funding agencies to step back and assess—with great care and accuracy—the sources of these problems. Systematic reviews provide an evidence-based 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.
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.
Ritskes-Hoitinga M, Pound P. The role of systematic reviews in identifying the limitations of preclinical animal research, 2000–2022. JLL Bulletin: Commentaries on the history of treatment evaluation. 2002.
van de Wall B, van Hattem A, Timmermans J, Ritskes-Hoitinga M, Bleich A, Leenaars C. Comparing translational success rates across medical research fields – A combined analysis of literature and clinical trial data. ALTEX. 2023;40(4):584-594.

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

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.
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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.

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Request for Information:
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Title: Transition to Human-Relevant Research Task Force

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

The Common Fund should establish an NIH-wide task force dedicated to planning the phase-out of animal use in biomedical research and pivoting toward human-relevant research. It has become increasingly evident that many of the existing animal models of human behavior, physiology and disease are inadequate. Species differences in anatomy, physiology, gene expression, and disease resistance or susceptibility have created an intractable "translation gap" between data emerging from animal-based research and meaningful clinical applications. Current animal models rely on artificially induced symptoms and/or reductive versions of complex human behaviors, traits, and pathologies. Confounds introduced by the laboratory environment and the homogeneity of most animals in laboratories further reduce the likelihood that data from these experiments will translate to humans.

The continued failure of animal-based models contributes to the increased cost of drug development and the erosion of the public's trust in science. Despite the well-established limitations of numerous animal models, increasing ethical concerns surrounding the use of animals in experimentation, and requests from Congress to replace animals in biomedical research wherever feasible, the NIH continues to utilize public monies to fund projects that rely on ineffective animal-based methods.

Though NIH claims that both "NIH and NIH-funded scientists are continually working to reduce animal use," there is currently no coordinated effort, office, strategic plan, or task force within or across NIH institutes to phase out the use of live animals in NIH-funded research. Additionally, there are currently no systematic mechanisms in place to allow the NIH to consistently assess the utility of the various animal models being funded. There are also no NIH-wide tools in place to educate NIH-funded investigators or Scientific Review Groups on the limitations of animal models or the utility of New Approach Methodologies (NAMs). Without dedicated resources aimed at eliminating the use of animal experiments wherever possible, many invasive and ineffective animal experiments will continue, harming animals unnecessarily, delaying treatments and cures for patients, and wasting taxpayer resources.

By establishing a task force dedicated to creating a roadmap for the phase-out of animal use and its replacement with human-relevant research methods, the Common Fund can facilitate the validation of uptake of NAMs, increase the translatability of NIH-funded research, and reduce the use of animals in invasive and lethal procedures.

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

A Common Fund sponsored task force charged with planning the phase-out of ineffective animal models is necessary to ensure that human-relevant research is being used wherever possible and that investigators have the resources necessary to transition away from costly and ineffective models. This task force would be responsible for developing an NIH-wide Strategic Plan to phase out the use of animals in biomedical research. The task force could convene working groups and/or advisory committees comprised of diverse stakeholders to determine areas where animal-based methodologies have clearly failed and should no longer be funded, identify all areas where existing non-animal methods are superior, and pinpoint gaps in the availability of animal alternatives. Stakeholders can also establish areas where human-relevant research should be prioritized based not only on scientific necessity but on ethical concerns surrounding the use of animals (for example, eliminating procedures that involve unrelieved pain, multiple major life surgeries, or lengthy captivity for animals with extended life spans). A concrete actionable plan with well-defined and measurable goals should be included in this task force's deliverables.

Initiatives such as the one suggested here already exist elsewhere. For example, in the Netherlands, the Transition Programme for Innovation without the use of animals (TPI) was established to bring together stakeholders and offer a platform for identifying and developing activities to increase the pace of the transition toward animal-free innovation. In the U.K., the general election-winning Labour Party has pledged to phase out testing on animals and partner with scientists, industry, and civil society to reach this goal.

PETA scientists have already created a roadmap which could complement the task force's work: the Research Modernization Deal (RMD). The RMD, available at https://www.peta.org/wp-content/uploads/2023/01/peta-research-modernization-deal.pdf, suggests common-sense steps for achieving this goal:

1. End animal use in research areas in which animals have been demonstrated to be poor "models" of humans and their use has impeded scientific and medical progress.
2. Conduct systematic reviews of the efficacy of animal use to identify additional areas in which non-animal methods are available or the use of animals has failed to protect human or environmental health and can, therefore, be ended.
3. Redirect funds from animal studies to the use and development of reliable, non-animal methods.
4. Implement a cost-benefit analysis system for research involving animals that includes an ethical perspective and consideration of lifelong harm inflicted on animals, such as is used in the U.K.
5. Work with other world leaders to harmonize and promote international acceptance of non-animal testing methods for regulatory toxicity testing requirements.
6. Educate and train researchers and regulators in the benefits of and how to use non-animal testing approaches.

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

The failure to translate animal-derived data into meaningful treatments and cures for humans is a well-known problem within the scientific community. Regulators, taxpayers, patients, and funding oversight committees are frustrated by the lack of meaningful progress in developing new treatments for prevalent diseases such as cancer, strokes, neuropsychiatric conditions, and neurodevelopment and neurodegenerative disorders. As evidence of the limitations of animal-based experimentation mounts, and the lack of effective treatments for numerous human diseases continues, the NIH will be under continued pressure to deliver tangibles to taxpayers and patients.

Additionally, as evidence for the complexity, sentience, and consciousness of nonhuman animals continues to emerge, the scientific community, legislators, and the public are becoming increasingly uncomfortable with their use. A concerted effort towards replacing animals in experimentation would alleviate the myriad ethical concerns associated with this harmful practice. It would also reduce the danger of zoonotic disease transmission, lessen the risk of compassion-fatigue in laboratory staff, and eliminate any purported animal resource shortages or risk of devastating populations of species used in animal experimentation.

Motivated by both the ethical concerns surrounding animal-based experimentation and testing as well as the limited translatability of animal-based data, advances in complex, 3-D cellular models, such as microphysiological systems, organoids, spheroids, and 3-D bioprinted structures derived from human cell lines and based in human biology have expanded in the past decade. Many of these models simulate human physiology and disease more accurately than traditional *in vivo* models using animals. These ongoing innovations in complex, human-derived models have the potential to solve both the translational and ethical problems associated with animal-based research.

A dedicated roadmap for eliminating the use of animals in NIH-funded research will accelerate U.S. research towards more accurate, relevant, efficient, and ethical results—and, therefore, more acceptable to government oversight committees, patient advocacy groups, and the public.

Other Comments

Establishing an initiative dedicated toward phasing out animal experimentation would meet the goals of Common Fund supported programs as follows:

- **Transformative:** This proposal will improve the translatability of preclinical and basic science research by accelerating away from animal use and toward human-derived cellular models; increase the accessibility of NAMs to all researchers as well as their visibility; eliminate the waste of public resources on ineffective animal models; increase the translational value of basic research; and minimize the harm to nonhuman animals.

- **Catalytic:** An initiative of this sort would ensure the NIH make good on its promises to reduce or replace the use of ineffective animal models and better support more effective and accurate human-based research and increase both the NIH's accountability to, and reputation with, the public that funds its missions.

- **Synergistic:** All NIH ICs and Centers and the research they fund would benefit from the increased use and availability of human-relevant research. Additionally, much of the progress being made in advancing non-animal tools by the National Center for Advancing Translational Sciences (NCATS) and other institutes remains siloed and requires a dedicated team to disseminate new information

- **Cross-cutting:** The systematic phase-out of animal experiments will advance science, expedite new treatments and cures for humans, and ultimately eliminate the ethical considerations associated with experimenting on nonhuman animals.

- **Unique:** The NIH Common Fund is the agency's only funding source that could successfully establish and manage this initiative. This would also be NIH's only multi-institute resource dedicated to the tactical phase-out of animal-based experimentation.

Most importantly, this task force would move the NIH closer to its mission, "to enhance health, lengthen life, and reduce illness and disability."