FASEB
Federation of American Societies for Experimental Biology

Representing Over 110,000 Researchers

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June 4, 2025

Jay Bhattacharya, MD, PhD
Director
National Institutes of Health
Bethesda, MD 20892

Transmitted electronically via email to NIHExecSec@nih.gov

Re: NIH Initiative to Reduce Animal Research

Dear Dr. Bhattacharya,

On behalf of the Federation of American Societies for Experimental Biology (FASEB), I write as its President to provide comment on the recently announced initiative to reduce the use of animals in research at the National Institutes of Health (NIH). As a coalition of 22 member societies representing over 110,000 biological and biomedical researchers, we at FASEB strongly support policies that promote the use of tailored methodologies to push innovation and progress in the biomedical sciences.

New alternative methods (NAMs) - *in vitro*, *in silico*, computational methodologies, and predictive artificial intelligence (AI) - present an opportunity to expand our scientific toolkit for biomedical innovation, and we applaud the creation of the Office of Research Innovation, Validation, and Application (ORIVA) to ensure the standardization and validation of these technologies. However, we caution against prematurely removing animal research from the scientific toolkit in lieu of approaches not yet ready to address important biomedical inquiries in full. Reviews into the current state of biomedical methodologies repeatedly highlight the continued need for animal studies alongside development of NAMs[1,2,3].

Given the significant impact that restricting animal research would have on the research community, **we request the opportunity for greater stakeholder engagement on the rollout of this initiative**. We believe the implementation of this initiative has the potential to hamper American biomedical and life sciences research but if done with care, holds great promise in moving many research fields forward. FASEB would like to see NIH integrate the considerations and recommendations detailed below into the rollout of this initiative.

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[1] Nonhuman Primate Models in Biomedical Research: State of the Science and Future Needs | The National Academies Press
[2] Human Organ-On-A-Chip: Technologies Offer Benefits Over Animal Testing but Challenges Limit Wider Adoption | U.S. GAO
[3] Catalyzing the Development and Use of Novel Alternative Methods | National Institutes of Health (NIH)

Sound science requires tailored approaches

One of the defining strengths of the American approach to biomedical research is a peer-reviewed funding process that elevates the opinions of subject matter experts to ensure scientific and ethical rigor. This process allows research to proceed based on the merit of proposals and the needs of individual research fields. FASEB is concerned that a singular mandate promoting NAMs at the expense of animal research would undermine this rigor and compromise scientific discovery.

Animal research continues to be the leading methodology in many fields due to its demonstrated translational potential and relevance to critical scientific inquiry. With animal models, investigators can replicate the full spectrum of whole-body physiological processes that are central to understanding human health and disease. This is particularly relevant in areas like oncology, where tumor progression, metastasis, and response to treatment depend not only on the characteristics of the tumor cells themselves, but also on the tumor microenvironment, immune response, and interactions with multiple host tissues and organs. Similarly, in the context of applied topics such as drug development, translational success depends on a comprehensive understanding of the complex, interacting processes across organ systems that govern drug metabolism and delivery. Animal models make it possible to study these systemic interactions, while controlling additional variables such as age, sex, and microbiome composition – factors that are difficult to fully capture in isolated *in vitro* systems but often relevant to clinical translation.

The limitations of alternative methodologies are particularly pronounced in the study of complex chronic illnesses, including autoimmune diseases (such as systemic lupus erythematosus and rheumatoid arthritis) and neurodegenerative disorders (such as Parkinson's disease and multiple sclerosis), which involve dynamic, multisystem interactions over time. Such conditions often manifest through subtle, systemic dysregulation across immune, nervous, and endocrine networks, and may involve a cascade of events that currently can best be understood by observing disease processes in a living system.

Many alternative methods are not yet equipped to capture the temporal aspects of disease – namely, onset, latency, and progression. Understanding these stages is critical for determining windows of therapeutic opportunity, anticipating long-term disease trajectories, and tailoring care plans to individual patients. For instance, early inflammatory events that occur before the clinical onset of type 1 diabetes[4] or Alzheimer's disease[5] can offer valuable clues for prevention, but these signals are often context-dependent and require a longitudinal, systemic view that NAMs currently cannot provide. The absence of integrative contexts in many NAMs limits their current

[4] Innate inflammation in Type 1 diabetes | PMC
[5] Inflammation as a central mechanism in Alzheimer's disease | PMC

utility for translational research and for developing interventions that are safe and effective in humans.

Combinatorial NAMs, such as integrating AI with cell-based platforms or linking *in vitro* systems to mimic organ-organ communication, are often proposed as a means to overcome the limitations of individual model types. While these hybrid approaches offer exciting potential, especially for improving mechanistic insights and predictive capabilities, they remain constrained by technological and translational challenges. For example, while AI can make predictions about systemic contexts, it is reliant on the information provided through training datasets – information often only available from animal research and currently missing for many active areas of research. FASEB urges NIH to consider complete replacement of animal research only for systems in which validated NAMs can perform as well or better than the accepted animal models and promote the use of multimodal systems that include both animal models and NAMs where this is not possible.

NAM validation must precede mandated use

FASEB fully supports the 3Rs framework (Replace, Reduce, Refine) for the ethical use of animals in research. Towards these goals, we applaud this initiative's support for the development of NAM technologies that provide an avenue for safe replacement and reduction in the use of animals. However, the replacement of research animals should not be pursued at the expense of the greater purpose of biomedical research: to improve our understanding of human health and translate that knowledge into interventions that help people lead healthier lives.

Validation of NAMs is the critical first step to ensuring safe and effective research is done in the absence of animal research. Timelines for mandating NAMs over animal models need to reflect this priority. FASEB recognizes that model validation – and scientific confidence more broadly – is a complex, time-consuming, and expensive process that requires standardized metrics, meaningful endpoints, benchmarking studies, as well as consultation with regulatory and public stakeholders. However, without consistent validation guidelines and confirmatory data from human and animal studies alike, the development of NAMs will continue to outpace scientific standards and applications, resulting in inefficient use of research time and federal dollars.

Validation must go beyond proof of concept to include consistent demonstration of reproducibility, biological relevance, and translational utility across a range of experimental and disease contexts. Importantly, the successful validation of a NAM in a specific context should not be automatically interpreted as justification for its universal application. Requiring the use of individual NAMs in research should be based on a clear understanding of the method's limitations in addition to its performance. Comparable standards must be applied when evaluating NAMs alongside established animal models. FASEB emphasizes the need for a case-by-case assessment to ensure that any mandated replacement of animal models maintains the scientific rigor, safety, and reliability required to advance human health.

Requesting opportunities for additional stakeholder feedback

FASEB appreciates NIH's longstanding commitment to engaging the scientific community in shaping research policies. Given the potential scope and implications of this initiative, particularly its influence on research infrastructure, funding mechanisms, and workforce training, stakeholder engagement should be central to the planning and implementation process. Critical elements such as transition timelines, criteria for determining where NAMs are appropriate, and strategies to support the continued use of animal models where necessary should be developed transparently and in close collaboration with a broad range of stakeholders.

The diversity of research fields affected means that a one-size-fits-all approach could inadvertently hinder innovation. A successful rollout will require flexible, field-specific implementation that is informed by the practical realities and evolving needs of the research community. We encourage NIH to proactively include the voices of investigators, especially those working at the intersection of NAM development and animal model refinement, to guide the roll out of this initiative.

Conclusion

As scientists committed to advancing biomedical research through both humane animal studies and rigorously validated non-animal models, FASEB would appreciate the opportunity to provide feedback on a detailed plan for enacting the announced initiatives. Stakeholder feedback is central to sound policymaking. We look forward to future engagement opportunities on this topic.

Sincerely,

Beth Garvy, PhD
FASEB President