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August 16, 2023

Office of Science Policy
National Institutes of Health
Bethesda, MD

Re: Request for Information on Catalyzing the Development and Use of Novel Alternative Methods to Advance Biomedical Research, NOT-OD-23-140

Submitted electronically

The Association of American Medical Colleges (AAMC) appreciates this opportunity to comment to the NIH Director's Advisory Committee's (ACD) Working Group on Novel Alternative Methods (NAM), We commend the NIH for convening the range of expertise reflected in the NAM Working Group and for moving energetically and methodically on an important topic that encompasses so many different fields and research frontiers.

The AAMC is a nonprofit association dedicated to improving the health of people everywhere through medical education, health care, medical research, and community collaborations. Its members are all 157 U.S. medical schools accredited by the Liaison Committee on Medical Education; 13 accredited Canadian medical schools; approximately 400 teaching hospitals and health systems, including Department of Veterans Affairs medical centers; and more than 70 academic societies. Through these institutions and organizations, the AAMC leads and serves America's medical schools and teaching hospitals and the millions of individuals across academic medicine, including more than 193,000 full-time faculty members, 96,000 medical students, 153,000 resident physicians, and 60,000 graduate students and postdoctoral researchers in the biomedical sciences. Following a 2022 merger, the Alliance of Academic Health Centers and the Alliance of Academic Health Centers International broadened the AAMC's U.S. membership and expanded its reach to international academic health centers.

The AAMC recognizes the extraordinary contribution that high-quality, ethical research in animal models has made to our understanding of biological systems and advancement of treatments that improve both human and animal life. We also value the continued development of pathways to discovery that maximize available resources. To that end, our central comment concerns the framing of this exercise. While the term "*alternative*" was chosen advisedly in consideration that some segments of the public are interested in seeing valid research approaches serve as alternatives to the use of animal models, or also possibly as alternatives to some human subjects research, the AAMC believes a more accurate description from the researchers' perspective would be "*complementary*" methods.

The request seeks information on the three specific areas: the use of novel alternative methods to study human biology, circuits, systems, and disease states; approaches for catalyzing the development and validation of novel alternative method technologies; and strategies for maximizing

the research value of novel alternative method technologies. We provide here our recommendations for the direction and dissemination of findings from the ACD Working Group in advance of a highly anticipated public workshop scheduled for August 21. The technical and methodological information that would be most helpful to the working group is that generated from the experience and judgement of the scientists working closely with novel methods and models. Therefore, the AAMC has strongly encouraged the research community and leaders at our member institutions to respond to NIH directly in response to this request. These institutions, as we have noted previously, perform more than half of the extramural research sponsored by NIH, and we hope that the agency receives a vigorous response in time for the NIH's expert panel convening.

In the pursuit of basic discovery, using multiple approaches tends synergistically to strengthen findings and help to eliminate errant conclusions. For example, the medical community has never considered *in vivo* and *in vitro* methods to be mutually exclusive, at least not categorically. As the NAM Working Group has noted, new categories have been added, such as *in silico* methods (computer-based modeling) and *in chemico*. We cannot say what other approaches may exist in future, but the AAMC expects that differing approaches will continue to fortify the process of discovery, not necessarily replace each other.

The NAM Working Group is focused on ways that the NIH can best promote future development of complementary approaches and set standards for using such approaches as research models or benchmarks. The AAMC recommends that the Working Group also consider the potential for further development of animal resources themselves. For one reason, the accelerating capacity for genomic sequencing and other platforms makes it possible to include more species as potential research models, including species that may be easier to breed, maintain, or study; consider for example, the rapid growth in adoption of zebrafish as model for studies in developmental biology. Second, the advent of more powerful gene-editing tools like CRISPR-CAS9 have profound potential for engineering more powerful and specific animal models, comparable to the (gene) knock-out mouse technology developed decades ago. Animal models that incorporate human tissue, such as humanized mice, or are made susceptible to human diseases are already widely deployed. The research potential for novel non-animal models, like organs-on-chips and organoids, should be compared not only for their power against current animal models, but to future models as well.

The AAMC believes it is highly unlikely that new approaches will replicate, let alone replace, benefits from studies with whole organisms, particularly in preclinical research, because tools like organ chips or chemical assays are not designed to detect entirely unanticipated effects, such as how a compound intended as a heart medication might inadvertently impair neurological development.[1]

The AAMC proposes that the working group's recommendations should include a plan for creating public communications resources to help explain the actual potential of different complementary approaches. At a minimum, the NIH and research community should clarify that we do not envision that new research models will make obsolescent whole organism studies. The AAMC is gratified that the NAM Working Group also raised this topic at the recent discussion the Director's Advisory

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[1] The recent National Academies report on Non-Human Primates, for example, clarified the irreplaceable importance of such models to continued pharmaceutical R&D. National Academies of Sciences, Engineering, and Medicine. 2023. Nonhuman primate models in biomedical research: State of the science and future needs. Washington, DC: The National Academies Press. https://doi.org/10.17226/26857.

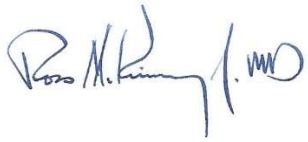
Committee. A communications resource should also help clarify the inherent limitations of any research model. A toolbox with a variety of tools is inherently more useful. Experience from human clinical trials shows that experimental drug candidates typically have disparate effects within the treatment arm; in that sense, even human individuals are only a limited "model" for other humans, providing there are adequate statistical controls.

To best catalyze the development and validation of Novel Alternative Models, the AAMC notes that two approaches that will benefit the working group are already reflected in major NIH initiatives: the new policies to promote data sharing; and efforts around improving the rigor and reproducibility in research. The NAM Working Group should determine best ways to integrate NAM development with these initiatives, and particularly to integrate the findings from the recent working group on rigor and reproducibility in animal research. The AAMC also stresses the need for efforts to recognize and provide credit to data generators.[2]

It is vitally important that efforts to support the development of NAM do not inadvertently close off avenues of exploration, and not risk discarding good models while they remain necessary or useful. Ultimately, new policy should defer to the research teams themselves to determine the most fruitful approach. Their decisions may be based on multiple factors, including consistency with prior standards, familiarity with prior models and techniques, the availability of particular, reliable models at hand, as well as the technical virtuosity of a new approach. With the funding support of the federal government, the nation relies on our scientists to consider and explore diverse paths while leveraging previous research results. The continued development of parallel or complementary, rather than truly alternative methods can accelerate our understanding of disease mechanisms and human health. The AAMC reiterates the importance of developing a public communications plan and resources for justifying to the public the need for multiple approaches.

We are grateful for the opportunity to provide comments, and for continuing engagement with the research community. Please feel free to contact me or my colleague, Stephen Heinig, Director of Science Policy (sheinig@aamc.org) with questions about these comments.

Sincerely,



Ross McKinney, MD
Chief Scientific Officer

cc: David J. Skorton, MD, AAMC President and Chief Executive Officer

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[2] Pierce HH, Dev A, Statham E, Bierer BE. Credit data generators for data reuse. Nature. 2019 Jun;570(7759):30-32. doi: 10.1038/d41586-019-01715-4. PMID: 31164773.