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**Statement for the Record**

**U.S. House Subcommittee on Health of the Committee on Energy and Commerce**

**February 8, 2022**

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On behalf of the Physicians Committee for Responsible Medicine, thank you for the opportunity to submit this statement for the record regarding the establishment of the Advanced Research Projects Agency for Health (ARPA-H). We request this statement be included in the record for the Subcommittee on Health's February 8, 2022 hearing entitled "ARPA-H: The Next Frontier of Biomedical Research."

The Physicians Committee is a 501(c)(3) nonprofit organization supported by over 175,000 members nationwide working for effective, efficient, and ethical medical research and product testing. We collaborate with federal and state agencies, the private sector, and academia to improve public health and medical practice.

As Congress provides the necessary framework for ARPA-H, the Physician Committee recommends the following objectives to ensure the new agency's ability to truly transform medical breakthroughs: (1) establish a strategic focus on human-specific approaches, (2) establish ARPA-H independently of the National Institutes of Health (NIH), and (3) commit to public transparency and accountability.

**1. Strategic focus and investment in human-specific approaches**

To achieve its goals of accelerating innovations and transforming health technologies and cures, ARPA-H must include a strategic focus on human-specific, nonanimal research. Human-specific research approaches, including tissue chips, organoids, and in silico models, use human cells, tissues, and data to better predict outcomes for patients. Not only do these approaches recapitulate human physiology, disease states, and clinical responses to drugs more closely than animals, they also permit key advantages over comparable animal-based systems, such as microenvironmental control, longitudinal monitoring, high throughput experimentation, and patient-specific modelling, all within a shorter time frame and with lower resource and ethical burdens.[1] Additionally, these innovative methods can account for complex and diverse human risk factors, helping to advance personalized medicine and reduce health disparities, a pillar of the ARPA-H concept.[2] Prioritizing funding for studies involving human subjects and investigating community and population health and health disparities will help address not only disparities in health outcomes, but also disparities in investigator award rates.[3]

[1] Ingber, Donald E. "Is It Time for Reviewer 3 to Request Human Organ Chip Experiments Instead of Animal Validation Studies?" Advanced Science 7, no. 22 (2020): 2002030. https://doi.org/10.1002/advs.202002030.
[2] The White House. "ARPA-H Concept Paper." Published online 2021. https://www.whitehouse.gov/wp-content/uploads/2021/06/ARPA-H-Concept-Paper.pdf.
[3] Hoppe TA, Litovitz A, Willis KA, et al. Topic choice contributes to the lower rate of NIH awards to African-American/black scientists. Sci Adv. 2019;5(10):eaaw7238. doi:10.1126/sciadv.aaw7238.

In addition to improving success in translating medical discoveries to interventions for patients, a strategic-focus on human-specific research at ARPA-H would aid animal research reduction and replacement efforts, lead to a higher return on investment of federal research dollars, and help the U.S. maintain global leadership in medical research. Medical research currently relies heavily on the biology of other animal species,[4] with as many as 100 million dogs, cats, monkeys, mice, rats, and other animals being used in U.S. laboratories each year.[5] However, analyses of many disease areas, including Alzheimer's disease,[6] cancer,[7] and sepsis,[8] demonstrate that information derived from animal experiments does not translate well to humans due to species differences in anatomy, physiology, lifespan, and disease characteristics. This lack of translation is costly[9]: around 95% of drugs fail in clinical trials after passing extensive animal testing.[10] Increasingly, scientists and various stakeholder groups including the NIH[11] acknowledge the shortcomings of animal experiments, concluding that there is a need to develop and promote methods that are more relevant for humans.[12]

The high-risk, high-reward nature of ARPA-H provides a crucial opportunity to shift U.S. medical research away from animals and ensure global leadership in human-specific research innovation and technology.[13] We therefore recommend that there be an explicit goal in authorizing legislation for ARPA-H to reduce research reliance on animals by including consideration of translatability to humans and reduction of animal use as explicit criteria for determining ARPA-H investments.

Experts and scholars in animal ethics and nonanimal methods can provide the ARPA-H director with global context and detailed input to advance progress in reducing medical research reliance on animals. Congress should ensure that partnerships with nonprofit organizations, including patient advocacy groups and animal protection groups, are pursued in the setting of strategic direction at ARPA-H.

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[4] Veening-Griffioen DH, Ferreira GS, Boon WPC, et al. Tradition, not science, is the basis of animal model selection in translational and applied research. ALTEX. 2021;38(1):49-62. doi:10.14573/altex.2003301.

[5]Carbone L. Estimating mouse and rat use in American laboratories by extrapolation from Animal Welfare Act-regulated species. Sci Rep. 2021;11(1):493. doi:10.1038/s41598-020-79961-0; USDA APHIS | Research Facility Annual Summary & Archive Reports. Accessed April 24, 2021. https://www.aphis.usda.gov/aphis/ourfocus/animalwelfare/sa_obtain_research_facility_annual_report/ct_research_facility_annual_summary_reports.

[6] Pippin JJ, Cavanaugh SE, Pistollato F. Animal Research for Alzheimer Disease: Failures of Science and Ethics. In: Herrmann K, Jayne K, eds. Animal Experimentation. Vol 22. Working Towards a Paradigm Change. Brill; 2019:480-516. Accessed February 4, 2022. https://www.jstor.org/stable/10.1163/j.ctvjhzq0f.27.

[7] Mak IW, Evaniew N, Ghert M. Lost in translation: animal models and clinical trials in cancer treatment. Am J Transl Res. 2014;6(2):114-118. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3902221/.

[8] Seok J, Warren HS, Cuenca AG, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci. 2013;110(9):3507-3512. doi:10.1073/pnas.1222878110.

[9] Animal testing and its alternatives – the most important omics is economics. ALTEX - Altern Anim Exp. 2018;35(3):275-305. doi:10.14573/altex.1807041.

[10] National Center for Advancing Translational Sciences. "About New Therapeutic Uses." Published March 18, 2015. https://ncats.nih.gov/ntu/about; Thomas DW. Clinical Development Success Rates 2006-2015. Published online 2016. https://www.bio.org/sites/default/files/legacy/bioorg/docs/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf.

[11] National Center for Advancing Translational Sciences. "About Tissue Chip." Published March 16, 2015. Accessed February 4, 2022. https://ncats.nih.gov/tissuechip/about.

[12] U.S. Government Accountability Office. Animal Use in Research: Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives. 2019;(GAO-19-629). Accessed August 20, 2020. https://www.gao.gov/products/GAO-19-629

[13] "On a 30-Year Mission to Replace Animal Tests with Alternative Methods." EU Science Hub - European Commission. Accessed February 4, 2022. https://ec.europa.eu/jrc/en/news/30-year-mission-replace-animal-tests-alternative-methods.

Authorizing language for ARPA-H should also establish that Program Managers, as selectors of projects to be supported by ARPA-H, take into consideration the following criteria, which are absent in currently proposed ARPA-H authorizing language: (a) the relevance of the project to human biology and disease, (b) the project's minimization or elimination of animals, (c) the project's inclusion of women and minorities as subjects, and (d) the diversity of perspectives and research modality expertise on the research team. Together, these criteria will help to advance translation, reduce reliance on animals, promote innovation, and foster workforce diversity.

**2. Independence from the NIH**

For ARPA-H to be truly transformational, it is crucial that it remains independent from the structure and culture of the NIH by being housed separately within the Department of Health and Human Services (HHS). Scientist attitudes toward animal experiments and the human-specific approaches capable of replacing them are key cultural components driving research trends and model choice.[14] NIH culture, through strategic planning documents and processes, grant review procedures, and ethics policies, upholds the idea that animal experiments are a gold standard; this view would hinder the ability of ARPA-H to accelerate innovations and transform health technologies.

A recent NIH Advisory Committee to the Director working group on Enhancing Rigor, Transparency, and Translatability in Animal Research stated that "tackling the cultural incentives to keeping the status quo" will be required to improve the translatability of model systems.[15] While we agree with this sentiment, the working group and the NIH both fail to understand that the biggest problem with the status quo is not that animal research lacks certain characteristics like rigor, reproducibility, and validity; it is the continued NIH reliance on animal use and its unwillingness to move away from this paradigm that stalls progress. ARPA-H must shift away from a culture of continually prioritizing animal-based methods and toward a culture that supports the development of more ethical and more translatable nonanimal methods through innovation and risk-taking. To ensure this independent culture, ARPA-H should be housed independently of the NIH.

Furthermore, housing ARPA-H at HHS would allow more seamless coordination between and collaboration with agencies other than the NIH that also play a crucial role in the prevention and treatment of disease, such as the Centers for Disease Control and the Food and Drug Administration. Transforming medical breakthroughs at ARPA-H will require a diversity of perspectives, tools, and collaborations, as well as a flexibility that are best fostered at an independent agency built from the ground up, rather than through existing structures.

**3. Transparency and accountability**

The U.S. commitment to the 3Rs principles of refinement, reduction, and replacement of animals in research is laid out in the Guide for the Care and Use of Laboratory Animals, the use of which is required by the Public Health Service Policy.[16] Integral to this commitment are the accurate counting of animals used in experiments and the accurate reporting of federal funding dedicated to projects involving animals. It has been NIH's policy since 1985 to collect an "average daily inventory" of vertebrate animals housed in research facilities that wish to receive agency

[14] Veening-Griffioen, Désirée H., Guilherme S. Ferreira, Wouter P. C. Boon, Christine C. Gispen-de Wied, Huub Schellekens, Ellen H. M. Moors, and Peter J. K. Van Meer. "Tradition, Not Science, Is the Basis of Animal Model Selection in Translational and Applied Research." ALTEX 38, no. 1 (2021): 49–62. https://doi.org/10.14573/altex.2003301.
[15] ACD Working Group on Enhancing Rigor, Transparency, and Translatability in Animal Research. NIH Advisory Committee to the Director. Accessed December 6, 2021. https://www.acd.od.nih.gov/working-groups/eprar.html.
[16] U.S. Government Accountability Office. "Animal Use in Research: Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives," no. GAO-19-629 (September 24, 2019). https://www.gao.gov/products/GAO-19-629.

funding.[17] Domestic facilities are required to file such documentation every four years as part of an Animal Welfare Assurance. However, copies of these documents are available to the public only through Freedom of Information Act requests, making large-scale tracking and accountability efforts impossible.

Congress should therefore improve the accuracy and transparency of such information at ARPA-H by requiring that animal information is collected annually and requiring each ARPA-H-funded facility to report the total number of animals per species bred and used by the facility in the previous year, organized by pain and distress category. Congress should also require ARPA-H to create a publicly accessible website for dissemination of this information, including the completed forms.

In addition, Congress should require ARPA-H to implement a system that tracks which agency-funded projects involve the use of animals and that makes this information publicly accessible. The NIH currently collects such information with every grant application using the Research & Related Other Project Information form, which asks applicants to answer "Yes" or "No" to the question "Are Vertebrate Animals Used?"[18] Congress should require ARPA-H to have a similar form and ensure that the answer to that question for each funded project is searchable via a tool comparable to the NIH's Research Portfolio Online Reporting Tools website, as many other categories of information are.[19]

The public holds a necessary and valuable stakeholder perspective and public comments enable accountability. Therefore, Congress should require the ARPA-H director to seek advice from members of the public via public comments during the development of strategic plans and the evaluation of programs and practices. In addition, Congress should require ARPA-H Advisory Committee meetings to be open to the public and allow for public comments. Every NIH Advisory Council and other HHS Advisory Councils (e.g., Advisory Council on Alzheimer's Research, Care, and Services) hold publicly available meetings to promote transparency and accountability.

Finally, non-federal perspectives will be necessary and valuable to the development of strategic priorities at ARPA-H and in the carrying out of its goals. Every NIH Advisory Council and other HHS Advisory Councils (e.g., Advisory Council on Alzheimer's Research, Care, and Services) have positions for non-federal members. Congress should therefore require that ARPA-H advisory committee membership includes non-federal representatives, including positions for non-federal subject matter experts in areas of clinical and community research, human-specific methods, and animal protection.

In conclusion, improving the effectiveness and efficiency of medical research, and therefore the health of our entire nation, requires that research funding, policies, and practices keep pace with scientific and technological advances. Human-specific approaches have the potential to transform our understanding of disease risks and mechanisms and to enhance the development of safer and more effective interventions. The Physicians Committee appreciates the Subcommittee's efforts to advance human-specific methods at ARPA-H to accelerate innovations and transform health breakthroughs. Please do not hesitate to reach out with any questions.

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[17] National Institutes of Health. "PHS Policy on Humane Care and Use of Laboratory Animals | OLAW." Accessed February 7, 2022. https://olaw.nih.gov/policies-laws/phs-policy.htm.
[18] National Institutes of Health. "G.220 - R&R Other Project Information Form." Accessed August 20, 2020. https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/general/g.220-r&r-other-project-information-form.htm.
[19] National Institutes of Health. "RePORTER." Accessed February 4, 2022. https://reporter.nih.gov/.