Science Advancement & Outreach
A DIVISION OF PETA

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Request for Information: National Institute on Aging Strategic Directions for Research (NOT-AG-24-028)

Submitted online on September 13, 2024

We are writing on behalf of Science Advancement and Outreach, a division of People for the Ethical Treatment of Animals—PETA entities have more than 9 million members and supporters globally—regarding the National Institute on Aging's (NIA's) Strategic Directions for Research, 2026-2030.

The NIA's Strategic Directions for Research, 2020-2025 included many worthwhile goals and objectives, including the emphasis on elucidating personal, interpersonal and societal contributions to human aging. However, the institute's approach to basic and translational research was over reliant on traditional but ineffective animal-based models. This is despite well-documented issues (such as failures in translation, validity, and reproducibility), requests from Congress to reduce and replace animal use, and declining support for the use of animals in biomedical research.

We urge the NIA to modernize its plans for 2026-2030, evolving its portfolio to participate in new agency initiatives (such as the Common Fund's Complement-ARIE program), take full advantage of advancements and opportunities in human-relevant research, and adhere to agency directives to "conduct or support research into…methods of biomedical research and experimentation that do not require the use of animals [and]…methods of such research and experimentation that reduce the number of animals used in such research."[1]

Our key recommendation for NIA is to conduct and fund basic, translational, and preclinical research using only human biology-based systems and not those that use other species. Below, we expand on specific recommendations for basic, translational, and preclinical research supported and conducted by the NIA.

We also take this opportunity to share our Research Modernization Deal, a plan of action with detailed recommendations for advancing biomedical research in the U.S., applicable across various research domains, including neurodegenerative diseases, cancer, cardiovascular disease, and diabetes. This plan can be accessed at https://www.peta.org/wp-content/uploads/2023/01/peta-research-modernization-deal.pdf.

[1] 42 U.S.C. § 283e(a)(1)(A)-(C)

We are happy to meet and discuss with the NIA any questions related to this response or the topics covered in the Research Modernization Deal.

What emerging research needs and future opportunities that reflect the next five years should be included in the Strategic Directions for Research, 2026-2030 document?

For the NIA to achieve its goal of extending the healthy, active years of life, it needs to uphold the most translatable research possible. Therefore, in its mission to "Support and conduct genetic, biological, clinical, behavioral, social, and economic research on aging; Foster the development of research and clinician scientists in aging; [and] Provide research resources,"[2] NIA should prioritize innovative, non-animal, human relevant research.

In its Strategic Directions for Research, 2026-2030, the NIA should include the following to improve translatability and better achieve its goals. More detailed recommendations are given below.

- A clear statement that NIA will prioritize basic biological and translational research based in human biology
- A plan to provide training and other critical tools that the NIA's intramural and extramural researchers and staff will need to compete in the human-focused future of aging research
- A plan to improve transparency and track progress of the resources NIA allocates toward intramural and extramural research on animals, compared to non-animal methods, to be released publicly each year
- A plan to conduct or commission systematic reviews for the research models that the NIA uses and funds in each disease area
- A plan to develop, maintain, and share research resources by investing in new, non-animal research infrastructure, or convert existing animal use infrastructure into non-animal facilities
- A plan to assess whether methodological biases, such as animal methods bias, are affecting the fair consideration of proposals using non-animal research methods
- A plan to ensure that review groups include members that have experience using non-animal methods and to allow for adequate evaluation of their suitability for the specific research question or context of use

A clear statement that NIA will prioritize basic biological and translational research based in human biology; A plan to provide training and other critical tools that the NIA's intramural and extramural researchers and staff will need to compete in the human-focused future of aging research

As we will describe in the next section, key aspects of human aging do not occur in other species or occur in mechanistically different ways. This is most clearly reflected in the considerably

[2] National Institute on Aging. Mission. nia.nih.gov. Updated August 4, 2022. Accessed September 6, 2024. https://www.nia.nih.gov/about/mission

shorter life spans of species commonly used in experimentation and lower rates or nonexistence of age-related diseases, such as Alzheimer's disease. For these reasons, elaborated below, the NIA must shift the focus of its aging research to human biology-based systems, such as technologies for human cell culture—including patient-specific cell lines and samples, bioprinting, *in silico* methodologies such as digital twins, advanced computing (AI/ML), human imaging, and other research methods that employ human samples and data.

Promisingly, the NIA has already taken some strides in this direction. We support the NIA's participation in the recent funding announcement for Tissue Chips in Space 2.0 and were encouraged to see that, in July, the institute hosted a workshop on 3D *in vitro* tissue systems for aging research. Similarly, the NIA should continue its support for human imaging studies that contribute to the understanding of the human aging process. Some examples of these are the recent study by Yang, et al., who used deep learning to study how the human brain ages, linking patterns to clinical, lifestyle, and genetic factors,[3] and one by Mosconi, et al., where Positron Emission Tomography (PET) was used to correlate hormone receptor density and neuroendocrine aging in women.[4]

These are good first steps. However, the NIA is currently funding 1,576 projects that involve the use of animals, accounting for $1,089,626,847 in taxpayer spending.[5]

The NIA should also retain its 2020-2025 goal to "Recruit and retain a highly qualified and diverse workforce." The Strategic Directions for Research, 2025-2030 should concentrate on providing training and other critical tools that the NIA's intramural and extramural researchers and staff will need to compete in the human-focused future of aging research, which will include training in non-animal technologies.

A plan to conduct or commission systematic reviews for the research models that the NIA uses and funds in each disease area

In its Strategic Directions for Research, 2020-2025, one of the NIA's goals was to "Effectively steward public resources." The NIA should retain this goal and provide more concrete objectives as to how it should be achieved. To "Optimally manage research funds through careful planning and priority-setting, scientific review, and evaluation of investments," the Strategic Directions for Research, 2026-2030 should include conducting or commissioning systematic reviews for the research models that NIA uses and funds in each disease area. Systematic reviews will allow the institute to find, evaluate, and synthesize all the evidence relating to a model's fit-for-purpose and inform the institute's evidence-based decision making, while minimizing bias.

[3] Yang Z, Wen J, Erus G, et al. Brain aging patterns in a large and diverse cohort of 49,482 individuals. *Nat Med*. Published online August 15, 2024. doi:10.1038/s41591-024-03144-x
[4] Mosconi L, Nerattini M, Matthews DC, et al. In vivo brain estrogen receptor density by neuroendocrine aging and relationships with cognition and symptomatology. *Sci Rep*. 2024;14(1):12680. Published 2024 Jun 20. doi:10.1038/s41598-024-62820-7
[5] Search Results. NIH RePORTER. Accessed September 6, 2024. https://reporter.nih.gov/search/pDv76tKSGU6RCAKKhcmuNw/projects/charts?shared=true

A plan to develop, maintain, and share research resources by investing in new, non-animal research infrastructure, or convert existing animal use infrastructure into non-animal facilities

Developing, maintaining, and sharing research resources should remain a goal of the NIA and the institute should expand its work to "Make available cell cultures and tissue, cell, and blood banks for basic and epidemiological research," ensuring that these materials are of human origin only. This would also align with the 2020-2025 objective to "Encourage innovation across all areas of our mission," making work with human samples more abundant and accessible for researchers to engage in cutting-edge, human-relevant work. The Strategic Directions for Research, 2026-2030 should include investing in new, non-animal research infrastructure, or convert existing animal use infrastructure into non-animal facilities, to facilitate the transition toward non-animal approaches, aid in assisting the NIA's mission, and reduce harms to animals.

A plan to assess whether methodological biases, such as animal methods bias, are affecting the fair consideration of proposals using non-animal research methods; A plan to ensure that review groups include members that have experience using non-animal methods and to allow for adequate evaluation of their suitability for the specific research question or context of use

In its Strategic Directions for Research, 2020-2025, the NIA planned to "continually identify and recruit expert reviewers and where necessary revise processes to ensure efficient, seamless grant review and award." For its 2026-2030 iteration, the NIA should also take steps to assess whether animal methods bias, defined as the preference for animal-based research methods or the lack of expertise to adequately evaluate nonanimal methods,[6] is affecting the fair consideration of proposals using non-animal research methods. The NIA should undertake an internal study or safely open internal data to external meta-researchers to evaluate whether 1) there is balanced representation of non-animal methods expertise among its reviewers and 2) non-animal methods that are sufficiently scientifically rigorous are not being given lower scores simply because they lack an animal model. Additional recommendations are provided in the final section of this response.

What research needs and opportunities reflected in the Strategic Directions for Research, 2020-2025 document should be modified or removed because of progress over the past five years?

In the NIA's Strategic Directions for Research, 2020-2025, many of the approaches included explicit mentions of supporting the use of animal models in research intended to understand and help human aging. However, data has shown that the success rate for new treatments for age-related conditions in humans developed from basic, "translational," and preclinical animal experimentation is appalling. It has not translated in the ways that funders, researchers, and patients have hoped. The complex interaction between genetics, hormones, diet, and pre-existing

[6] Kavanagh O, Krebs CE. Mitigating animal methods bias to reduce animal use and improve biomedical translation. *Sci Prog*. 2024;107(2):368504241253693. doi:10.1177/00368504241253693

physical and mental health status on aging and age-related conditions in humans is far too complex to be "simulated" in a laboratory. It is illogical to attempt to understand human aging using species with such substantial differences in longevity and key physiological systems.

It is particularly relevant to understand and appreciate that, for research that seeks to understand neurological conditions, the human brain is unique in its relative size, cellular diversity and cytoarchitecture, coding and non-coding gene expression patterns, neurotransmitter pathways and functions, expanded association cortices, and metabolic rates. The protracted and intricate nature of human neurodevelopment increases our social, cognitive, and emotional capacity, complexity, and flexibility. It also increases the susceptibility of the human brain to environmental, genetic, and epigenetic influences across the lifespan, and subsequently, our susceptibility to neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis, and amyotrophic lateral sclerosis (ALS), *which only affect humans*. Current projections estimate the prevalence of these debilitating conditions will increase significantly in the coming decades, meaning there is an urgent need to get the research right.

In a bioinformatic analysis comparing transcriptional signatures of human AD, PD, HD, and ALS with mouse models of these diseases, Stanford scientists made the following findings:

> [M]ost available mouse models of neurodegenerative disease fail to recapitulate the salient transcriptional alterations of human neurodegeneration and … even the best available models show significant and reproducible differences compared to human neurodegeneration. Although the reasons for the poor transcriptional performance of mouse models varied, the unifying theme was the failure of mouse models to exhibit the variety and severity of diverse defects observed in human neurodegeneration.[7]

These molecular discrepancies underscore the artificial ways in which such models are created. Physical and chemical lesioning and systemic administration of toxins are often used. These are acute stressors, not long-term degenerative processes, and as such, they initiate events in animal models that are not present in human patients. The acute and immediate nature of particular disease models fail to capture the progressive nature of the degenerative disorders that they aim to mimic. Genetically modified mouse models of neurodegenerative disease exhibit an inconsistent range of pathological and behavioral phenotypes, in part because of the transgenes used, inconsistencies in transgene insertion and expression, and mouse background strains.[8] In PD, even nonhuman primate studies do not "constitute a valid scientific modality for the complete understanding of PD and for the development of future neuromodulation therapeutic strategies."[9]

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[7] Burns TC, Li MD Mehta S, Awad AJ, Morgan AA. Mouse models rarely mimic the transcriptome of human neurodegenerative diseases: A systematic bioinformatics-based critique of preclinical models. *Eur J Pharmacol*. 2015;759:101-117.
[8] Ehrnhoefer DE, Butland SL, Pouladi MA, Hayden MR. Mouse models of Huntington disease: Variations on a theme. *Dis Model Mech*. 2009;2(3-4):123-129.
[9] Menache A, Beuter A. Commentary: Lessons from the analysis of non-human primates for understanding human aging and neurodegenerative diseases. *Front Hum Neurosci*. 2016;10:33.

Growing awareness of the limitations of using animals to study human neurodegenerative conditions, continuing advancements in human biology-based models and technologies are driving a paradigm shift in how we study these diseases. Scientists and policymakers are realizing that research strategies should be more human-relevant. Following a review of AD research, an interdisciplinary panel recommended that funding be allocated away from experiments on animals and toward more promising techniques involving patient-derived induced pluripotent stem cell models, "omic" technology (genomics, proteomics, etc.), *in silico* models, neuroimaging, and epidemiological studies.[10]

The same is true for research on other conditions of interest to the NIA, including the biological process of aging, cancers, cardiovascular diseases, and diabetes. Relevant to the biological process of aging, humans and other animals differ in their production of reactive oxygen species, phospholipid compositions of their biomembranes, metabolic stability, mechanisms of senescence, variabilities in life histories (including age of sexual maturity, size of progeny, and reproductive span), and more.[11] Cancer experiments on animals are poorly reproducible[12] and do not mimic the nature of human tumors nor their microenvironment.[13,14] Clinical trials for new cancer drugs fail 96.6% of the time,[15] despite promising results in experiments on animals. For cardiovascular disease research, humans and other animals differ in their resting heart rate, action potentials, myofilament protein isoforms, excitation-contraction coupling, force-frequency relations, calcium-handling proteins, profile of ventricular repolarization, susceptibility to arrhythmia and atherosclerosis, relevant microRNA expression profiles, and other complex genetic and environmental factors associated with cardiovascular health and disease.[16,17,18,19,20,21] Relevant to type II diabetes research, humans and rodents differ on every tier of glucose regulation and in terms of disease progression.[22,23]

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[10] Pistollato F, Ohayon EL, Lam A, et al. Alzheimer disease research in the 21st century: Past and current failures, new perspectives and funding opportunities. *Oncotarget*. 2016;7(26):38999-39016.
[11] Demetrius L. Aging in mouse and human systems: a comparative study. *Ann N Y Acad Sci*. 2006;1067:66-82. doi:10.1196/annals.1354.010
[12] Errington TM, Mathur M, Soderberg CK, et al. Investigating the replicability of preclinical cancer biology. *Elife*. 2021;10:e71601.
[13] 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.
[14] Ben-David U, Ha G, Tseng YY, et al. Patient-derived xenografts undergo mouse-specific tumor evolution. *Nat Genet*. 2017;49(11):1567-1575.
[15] Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. *Biostatistics*. 2018;kxx069.
[16] Liao J, Huang W, Liu G. Animal models of coronary heart disease. *J Biomed Res*. 2015;30(1):3-10.
[17] Janssen PML, Elnakish MT. Modeling heart failure in animal models for novel drug discovery and development. *Expert Opin Drug Discov*. 2019;14(4):355-363.
[18] Milani-Nejad N, Janssen PM. Small and large animal models in cardiac contraction research: Advantages and disadvantages. *Pharmacol Ther*. 2014;141(3):235-249.
[19] Vegter EL, Ovchinnikova ES, Silljé HHW, et al. Rodent heart failure models do not reflect the human circulating microRNA signature in heart failure. *PLoS One*. 2017;12(5):e0177242.
[20] Zaragoza C, Gomez-Guerrero C, Martin-Ventura JL, et al. Animal models of cardiovascular diseases. *J Biomed Biotechnol*. 2011;2011:497841.
[21] Chandrasekera PC, Pippin JJ. The human subject: An integrative animal model for 21st century heart failure research. *Am J Transl Res*. 2015;7(9):1636-1647.
[22] Chandrasekera PC, Pippin JJ. Of rodents and men: Species-specific glucose regulation and type 2 diabetes research. *ALTEX*. 2014;31(2):157-176.
[23] Bunner AE, Chandrasekera PC, Barnard ND. Knockout mouse models of insulin signaling: Relevance past and future. *World J Diabetes*. 2014;5(2):146-159.

The NIA's Strategic Directions for Research, 2026-2030 should avoid approaches that seek answers for human aging by using other animals, focusing instead on supporting non-animal, human-relevant research in these areas. Here are some specific recommendations for how the approaches in the 2020-2025 document could be updated:

A-1: "…NIA will support research to identify additional factors and to clarify their roles both in ~~animal~~ *human biology-based* models of aging and in humans.

A-2: "…NIA will encourage research in both the loss and maintenance of functions during the aging process and will foster studies both in humans and in ~~animal models~~ *human cellular systems* to investigate the health- and disease-related effects of manipulating aging-related processes at the *human* molecular or cellular level.

A-3: "…In addition, we will test interventions in ~~animal models~~ *human-relevant preclinical systems* and, *if safe,* ultimately in humans that have ~~been shown~~ *the potential* to increase lifespan and healthspan ~~in animals~~ to determine their effect on cognitive function."

A-6: "…In this and other research the NIA promotes studies in ~~both female and male organisms~~ *humans and human-relevant systems of all sexes.* ~~Similar studies are supported in the Caenorhabditis Interventions Testing Program, a multi-institutional study that investigates interventions that might extend lifespan or healthspan using diverse species and strains of the worm Caenorhabditis, to explore the impact of genetic diversity on the efficacy of interventions.~~ We support studies on the mechanisms of action of ~~these~~ *human genetic diversity and proposed* interventions which will facilitate their translation to benefit healthy aging in humans."

A-8: "Use ~~comparative~~ *human* biology to understand how ~~adaptations in diverse~~ *characteristics unique to our species* ultimately affect aging. Lifespan is a complex biological trait resulting from multiple genetic interactions. In fact, we have identified roughly 400 genes involved in human lifespan. Comparing processes at the molecular, cellular, *and* structural~~, and organismal~~ levels across ~~animal species and~~ diverse human populations can provide important information about how these genes interact and illuminate critical molecular pathways that determine both lifespan and healthy function at older ages."

C-1: "…Epidemiological studies ~~— and, in some cases, studies in animals —~~ have shown clear positive effects of lifestyle choices such as healthy diet and physical activity, as well as the negative effects of obesity, malnutrition, and less-than-optimal sleep patterns on health and age-related morbidity. We will use these and other *human biology-based* findings to launch clinical trials of dietary and other behavioral measures and adherence strategies for the prevention or delay of disease and disability."

C-3: "Conduct clinical studies and encourage the translation of new interventions to the clinical setting. As mechanisms, pathways, and processes of disease are better defined, and as potential healthspan-extending interventions are validated in *human biology-based* model systems, development and testing of clinical applications in humans can begin. We will pursue the use of novel, flexible research designs where appropriate, and we will work with others to facilitate the

navigation of barriers to the translation of promising compounds into clinical trials and ultimately approval by the U.S. Food and Drug Administration, *including becoming involved in the agency's New Alternative Methods Program*."

D-1: "Improve our understanding of normal brain aging. Changes in brain structure and function may continue throughout life, and studies in ~~model organisms~~ *human biology-based systems* and humans are helping to define the normal trajectory of changes in the brain over the adult lifespan. Structural neuroimaging and anatomical studies of brain have shown declines in total gray and white matter, along with shrinkage or atrophy and synaptic changes in certain regions of the brain in aging. Functional imaging studies are defining the workings of large-scale neural and cognitive networks in the aging human brain. ~~Human and animal studies suggest that adaptive or resilient processes (i.e., brain plasticity) may be needed for maintenance of brain structure and function during normal aging. At the molecular and cellular level of analysis in animal models, brain aging is associated with changes in gene and epigenetic expression, mitochondrial and energy metabolism, calcium regulation, protein homeostasis, glia, and neural plasticity and synaptic function.~~ We will continue to work to elucidate the processes that occur during "normal" *human* brain aging and to identify and find ways to activate the cellular processes that protect the brain from damage and promote its repair."

D-2: "Refine our knowledge of genetic, molecular, and cellular changes involved with the development of AD and other dementias of aging. Studies of the neurobiology of aging have given us increasing insight into the ways brain aging itself is associated with the development of AD/ADRD. However, key questions remain. We will encourage a *human* systems-based approach to investigate the pathological changes associated with the preclinical development of AD/ADRD, including accumulation of abnormal proteins, loss of synapses, and death of neurons. We will also explore the impact of genetic and inflammatory processes on the development of AD. We will promote further characterization of these pathological changes in *human* tissue culture~~, animal models,~~ and humans."

D-4: "…Stimulate *non-animal, human biology-based* translational research aimed at discovery and preclinical development of new candidate drugs and biologics."

F-4: "…We will accelerate research on the basic biology driving health differences ~~between~~ *among human* sexes."

F-4: "…basic and preclinical biomedical research frequently focuses on male animals and cells, which may obscure understanding of key sex *and species* influences on health processes and outcomes. NIH has adopted a stringent "Sex as a Biological Variable" policy stating that ~~the organism's~~ sex will be factored into research designs, analyses, and reporting in ~~vertebrate animal and~~ human studies.

G-5: "Support ~~colonies of aged animal models~~ *biobanks of human specimens and non-animal technology hubs* that are necessary for research on *human* aging processes and specific age-related diseases."

G-5: "Support candidate drug evaluation programs, facilities, and related resources for ~~animal~~ *human biology-based preclinical* and clinical studies."

Please provide any additional input not captured above that may be relevant to the development of NIA's Strategic Directions for Research, 2026-2030 document.

For neurodegenerative disease research specifically, the NIA should consult a report prepared by the European Commission's Joint Research Centre which cataloged 567 non-animal models for neurodegenerative disease research, including biochemical and computational approaches, various *in vitro* techniques, and the use of *ex vivo* human material. The report "supports increased adoption and acceptance of alternative methods in neurodegenerative disease research and provides insights into emerging trends and promising areas for further development."[24] It is available in full at https://joint-research-centre.ec.europa.eu/reference-measurement/european-union-reference-laboratories/eu-reference-laboratory-alternatives-animal-testing-eurl-ecvam/biomedical-research/neurodegenerative-diseases_en.

Related to detecting and mitigating animal methods bias, the NIA should also take the following actions:

- Invest in non-animal methods-specific funding streams and do not exclude non-animal methods from funding opportunities or seek animal-only proposals.
- Implement required bias mitigation training that includes information on scholarly biases, including how to recognize and address biases in the evaluation of research methods and implement bias reporting mechanisms.
- Implement evaluation criteria that assess methods based on their suitability for the research question, context of use, translatability, and human relevance.
- Ensure that review groups include members that have experience using non-animal methods and to allow for adequate evaluation of their suitability for the specific research question or context of use and open review groups to early career researchers, especially those who have experience in innovative, human-relevant technologies.
- Consult the Coalition to Illuminate and Address Animal Methods Bias (www.animalmethodsbias.org) to help the NIA detect and mitigate animal methods bias during grant review.

[24] Witters H, Verstraelen S, Aerts L, Miccoli B, Delahanty A, Gribaldo L. *Advanced Non-animal Models in Biomedical Research – Neurodegenerative Diseases*. Publications Office of the European Union; 2021. Accessed September 9, 2024. https://joint-research-centre.ec.europa.eu/reference-measurement/european-union-reference-laboratories/eu-reference-laboratory-alternatives-animal-testing-eurl-ecvam/biomedical-research/neurodegenerative-diseases_en