Science Advancement & Outreach
A DIVISION OF PETA

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Request for Information (RFI): Soliciting Input on Priorities and Progress in Alzheimer's Disease-Related Dementias Research (NOT-NS-24-132)

Submitted by email to ADRDSummit2025@ninds.nih.gov on December 6, 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, and PETA U.S. is the largest animal rights organization in the world. Our purpose is to address priorities and progress in Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRD) research.

The National Institute of Neurological Disease and Stroke's (NINDS) ADRD Summit 2022 research recommendations outlined important goals, including increasing training support and promoting career development for AD/ADRD researchers. However, the institute's approach to basic and translational research was overly reliant on ineffective animal-based models. There are well-documented issues with animal models, including failures in translation, validity, and reproducibility. Furthermore, Congress has called for both a reduction and replacement of animals used for research, and public support of animal use in biomedical research has declined.

We urge the NINDS to modernize its research recommendations for the ADRD Summit 2025 by engaging with new agency initiatives, such as the Common Fund's Complement-ARIE program. This would allow NINDS to fully leverage advancements 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 general recommendation is for NINDS to conduct and fund basic, translational, and preclinical research using only human biological systems, excluding non-human animal-based research. Below, we expand on specific recommendations and explain why these should be implemented by NINDS in the ADRD summit 2025.

Additionally, we would like to share our Research Modernization Deal, a comprehensive action plan with detailed recommendations for advancing biomedical research in the U.S., applicable across various research domains, including neurodegenerative diseases. This plan can be accessed at https://www.peta.org/wp-content/uploads/2023/01/peta-research-modernization-

[1] 42 U.S.C. § 283e(a)(1)(A)-(C)

deal.pdf and the section specific to AD research can be found on page 30. We are more than happy to meet and discuss any questions related to this response or topics covered in the Research Modernization Deal.

How can the current milestones be revised to better meet NINDS's goal of preventing and effectively treating Alzheimer's disease and related dementias by 2025?

In order to achieve its goal of effectively preventing and treating AD/ADRD by 2025, the NINDS must prioritize research that is reproducible and translatable. This can only be achieved through innovative, non-animal, human-relevant research.

The clinical failure rate for new drugs aimed at treating AD was last estimated to be 99.6%.[2,3,4] In addition, recent efforts to improve animal models of AD, such as the development of transgenic animals, have failed to replicate the human disease or lead to effective treatments.[5,6] This is unsurprising, given that AD is unique to humans, and highly variable in terms of cognitive and neurological symptoms,[7,8,9] age of onset and progression rate,[10,11,12] and the many

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genetic,[13,14,15] environmental,[16,17,18] and epigenetic[19,20] contributors. Thus, the complexity of AD in humans makes it impossible to fully recapitulate the disease using animals.

To emulate Alzheimer's-like symptoms in primates, experimenters induce long-term neuropathology using invasive methods. However, these methods only induce one or two symptoms seen in Alzheimer's patients.[21,22,23,24] Hallmarks of the disease such as neuronal loss, tauopathy, rapid cognitive decline, and dementia, are rarely observed in animals used for AD research.[25,26,27] Additional concerns regarding laboratory life, such as the physiological effects of captivity, introduce confounding variables that complicate experimental data. The altered immune system in captive laboratory animals, including changes to microbiomes and systemic inflammation, is particularly problematic for AD research, as the immune system plays a critical role in AD neuropathology.[28] Species differences in gene expression and protein function,[29]

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immune system responses,[30] neurodevelopment,[31] neuroanatomy,[32] age-related changes in hormone production,[33] and neurodegeneration[34,35] make it impossible for animal models to accurately represent AD.

Fortunately, there are non-animal research tools that are already being used to understand the complex genetic and environmental risk factors of AD, as well as its mechanisms of development. These cutting-edge technologies include AD-derived induced pluripotent stem cell models,[36] 3D cell culture organoid models,[37] organ-on-a-chip,[38] and computational biological system modeling.[39] These human-relevant methods are more accurate and are already being used to test drug efficacy and safety, but need greater support.

The ADRD summit 2022 research recommendations have already taken important steps in this direction. We support the NINDS's Vascular Contributions to Cognitive Impairment and Dementia (VCID) 1(1) milestone, which calls for the development of *in vitro* models to study the molecular mechanism of VCID. We also support the Multiple Etiology Dementias (MED) 3(1) milestone, which promotes "human tissue, sample or data-based translational studies" for identifying biomarkers for AD.

While these are important first steps, there are still many milestones in the ADRD research recommendations that rely on animals to answer questions related to Alzheimer's prevention and treatment. Below are specific recommendations for updating the approaches in the ADRD Summit 2025 document:

<u>Frontotemporal Dementia (FTD)</u>

5(1): "At least three new ~~animal and/or~~ *human* cell-based models that replicate key aspects human FTD."

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[39] Jones D, Lowe V, Graff-Radford J, et al. A computational model of neurodegeneration in Alzheimer's disease. *Nat Commun*. 2022;13(1):1643. doi:10.1038/s41467-022-29047-4

5(1): “Develop and/or validate at least two ~~in vivo functional~~ assays for FTD translational research, including with endpoints in ~~animal~~ *human-based* models that are relevant for FTD biology and/or clinical outcomes.

7(3): “Develop at least 2 human ~~or humanized~~ cell-based models that recapitulate cell-specific vulnerability or resilience to FTD disease mechanisms.”

Vascular Contributions to Cognitive Impairment and Dementia (VCID)

1(1): ~~“Establish at least 2 new small vessel VCID animal models suited for VCID and mixed dementias of aging research that reproduce small vessel disease and other key pathogenic processes thought to result in human VCID.”~~ Only include “At least two new in vitro models to study specific molecular mechanisms of VCID that are not feasible in animal models.”

Lewy Body dementias (LBD)

7(3): “At least two new *human-based* models of LBD that reproduce key features of LBD pathology and/or symptoms and are translatable for human LBD drug development.”

MED Special Topic: Post-TBI AD/ADRD (MED post-TBI)

4(4): “To facilitate translational research, develop at least one new TBI *human-relevant preclinical system* ~~animal model~~ that *can model* ~~has~~ sustained cognitive decline and progressive changes in the brain associated with AD/ADRD cognitive impairment and dementia outcomes in humans following TBI.”

MED Special Topic: LATE (TDP-43 in Common Late-Onset Dementias) (MED-LATE)

3(3): Two or more validated ~~animal~~ *human biology-based* models, available to the research community, that exhibit brain TDP-43 pathology aligned with the affected anatomical sites and ~~with~~ *represent* functional changes that occur in common human dementias that include TPD-43 pathology.

What are some additional research activities your organization has supported that are in alignment with the ADRD research milestones?

As mentioned above, we commend NINDS for including training for AD/ADRD scientists in health equity research and for providing career development resources to scientists from diverse backgrounds at all career levels. The ADRD research milestones should extend this support to include training and career development resources for using non-animal methods in AD/ADRD research. This is to ensure that both emerging scientists and established professionals can develop the skills necessary to contribute to impactful, human-relevant neurological discoveries for Alzheimer’s treatment. Additionally, it will help to ensure that the U.S. Alzheimer's research community remains competitive with international developments.

Since many educational programs lack sufficient courses on animal-free research methods, separate entities have developed programs to fill this gap, such as the summer school on non-

animal approaches held by the European Commission Joint Research Center.[40] There are also resources available from experts in the field, including those offered by the Physicians Committee for Responsible Medicine.[41] These resources could serve as a foundation for NINDS to develop and implement training on non-animal methods for AD/ADRD research.

Another research activity that would be beneficial to incorporate into the ADRD Summit 2025 research recommendations is the conduct or commissioning of systematic reviews that examine the research models currently used in AD/ADRD research. Systematic reviews will inform AD/ADRD research policy and priorities to ensure that only rigorous models are used and also identify potential biases in favor of existing models, regardless of whether they are the most appropriate for the research question. There are many resources available for conducting systematic reviews.[42,43]

We would be happy to meet or provide resources on any of the topics covered in this response. You may reach us at info@scienceadvancement.org.

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