Science Advancement & Outreach
A DIVISION OF PETA

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Request for Information (RFI): Inviting Comments and Suggestions on NIAID's Strategic Plan

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We are writing on behalf of People for the Ethical Treatment of Animals—PETA entities have more than 9 million members and supporters globally—regarding the National Institute of Allergy and Infectious Diseases' (NIAID's) proposed updates on its Strategic Plan. For NIAID to meet its mission of conducting and supporting "basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases"[1] in humans, it must divest from poorly translatable experiments on animals and fully embrace research that is based in human biology. Shifting NIAID's funding in this direction, in addition to increasing focus on preventative measures and access to care, would accelerate progress towards its crucial goals.

Below, we briefly expand on recommendations related to each priority listed in this RFI. Similarly, PETA has developed thorough recommendations for the advancement of biomedical research in the U.S. with a straightforward plan of action using cutting-edge, non-animal methods that can be implemented in any research area. This plan, called the Research Modernization Deal, can be accessed at https://www.peta.org/wp-content/uploads/2023/01/peta-research-modernization-deal.pdf. Given what we know about animal sentience and the failure of experiments on animals in immunology research, it is unacceptable for NIAID to support, fund, and encourage the continued use of millions of animals to meet its mission. The most effective way to increase knowledge of humans and the pathogens and allergens which endanger them is to shift its focus back to the species it is obligated to help: Humans.

Priority 1: Advance foundational research on the immune system, host-pathogen interactions, and pathogen biology.

To provide foundational knowledge on the human immune system and the pathogens that endanger human lives and well-being, it is critical that NIAID ensure that the basic research it supports in this field be grounded in human biology and immunology—not that of other species. Past research has documented the many ways in which other animals' immune systems and responses to pathogens differ from humans.

[1] NIAID. NIAID Mission. Reviewed April 16, 2021. Accessed April 29, 2024. https://www.niaid.nih.gov/about/mission-planning-overview

As a recent example, research on COVID-19 revealed that mice[2] and monkeys[3] were not as susceptible to the virus and exhibited more minor symptoms compared to humans who contracted it.

There are many differences between mouse and human immune systems, including in the anatomy of lymphoid tissue, ratios of white blood cell types, antimicrobial peptide profiles, cytokine profiles and functions, mechanisms for crosstalk between the adaptive and innate immune systems, antibody subtypes, development and regulation of lymphocytes, and activation of clotting factors.[4] A 2014 study found fundamental differences between the species in the innate immune response, stating, "[W]hile in human blood mechanisms of immune resistance are highly prevailed, tolerance mechanisms dominate for the defense against pathogenic microorganisms in mouse blood."[5] Logically, these differences make sense: We humans "do not live with our heads a half-inch off the ground,"[6] and we have considerably longer life spans and a larger body size than mice do. Despite the glaring contrast, mice continue to be used for immunological research by NIAID. A search conducted on NIH RePORTER in April 2024 for NIAID-funded research mentioning "mouse OR mus OR murine" in the project title or abstract returned 1,963 active projects with combined funding of $1,266,539,411.[7]

The viruses used in animal studies are often adapted through serial passage in target hosts to allow for easier infection.[8] Through serial passage, the virus can adapt to the new host and become distinct from the kind that predominantly affects humans. Additionally, we now know that the gut microbiome is intimately linked to the immune system[9] and studies have demonstrated drastic differences between the microbiomes of humans and other animals. For example, 85% of bacterial species in mice don't exist in humans.[10] This evidence and more underscores the incompatibility of study human immunity in other species.

Considering the obvious failure of using other animals as surrogates in the fundamental study of human immune systems, NIAID must replace their use with increased investment in human-relevant *in vitro* and

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[2] Callaway E. Labs rush to study coronavirus in transgenic animals—some are in short supply. *Nature*. Published March 9, 2020. Accessed February 14, 2022. https://www.nature.com/articles/d41586-020-00698-x.
[3] Zimmer C. Prototype vaccine protects monkeys from coronavirus. *The New York Times*. Updated May 25, 2020. Accessed February 14, 2022. https://www.nytimes.com/2020/05/20/health/coronavirus-vaccine-harvard.html.
[4] Mestas J, Hughes CCW. Of mice and not men: Differences between mouse and human immunology. *J Immuno*l. 2004;172(5):2731-2738.
[5] Zschaler J, Schlorke D, Arhhold J. Difference in innate immune response between man and mouse. *Crit Rev Immunol*. 2014;34(5):433-454.
[6] Leist M, Hartung T. Inflammatory findings on species extrapolations: Humans are definitely no 70-kg mice. *Arch Toxicol*. 2013;87(4):563-567.
[7] NIH. RePORTER. Accessed April 29, 2024. https://reporter.nih.gov/search/DwCXcPYQVkW1TZqHtaTv_Q/projects/charts?shared=true
[8] Bouvier NM, Lowen AC. Animal models for influenza virus pathogenesis and transmission. *Viruses*. 2010;2(8):1530-1563.
[9] Wu HJ, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. *Gut Microbes*. 2012;3(1):4-14.
[10] Nguyen TLA, Vieira-Silva S, Liston A, Raes J. How informative is the mouse for human gut microbiota research? *Dis Model Mech*. 2015;8(1):1-16.

in silico models. To its credit, NIAID has done some work in this area with the Human Immunology Project Consortium (HIPC) program and the NIAID Human Immunome Project, but critical funds are still being wasted in its many funded extramural animal projects. Examples of the types of basic research that NIAID should support include the use of human immune cells, which have been used to generate an immune atlas of human lung development;[11] human cell models to study pathogens like pneumonia[12,13,14] and neuroinflammation;[15] computer models of human inflammation,[16] and more.

Priority 2: Apply foundational knowledge of the complex interactions between microbes and the immune system to develop and test medical countermeasures against known infectious diseases (non-HIV/AIDS).

It is indeed of public interest to develop vaccines and therapeutics against emerging and re-emerging infectious diseases. However, prioritizing broad spectrum therapies, which is usually the case with corticosteroids, immunosuppressives and antibiotics, is contradictory to an effective approach since it typically induces drug resistance and results in considerable side-effects.[17] Efforts must be put into developing target-specific treatments and exploring combinations of already available therapies and repurposed drugs to address therapeutic gaps while minimizing resistance development.

NIAID must invest in innovative preclinical approaches such as new cellular models to test drug response and host-pathogen interaction. In 2020, the first 2D organoid model for human small intestine was characterized and validated to study immune response following Enterovirus A71 and *Listeria monocytogenes* infection.[18] More recently, immunocompetent 3D microfluidic patient-derived cancer

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[11] Barnes JL, Yoshida M, He P, et al. Early human lung immune cell development and its role in epithelial cell fate. *Sci Immunol*. 2023;8(90):eadf9988.
[12] Kopenhagen A, Ramming I, Camp B, et al. *Streptococcus pneumoniae* Affects Endothelial Cell Migration in Microfluidic Circulation. *Front Microbiol*. 2022;13:852036
[13] Holler A. The Swiss Medtech Award 2022 Goes to Alveolix. Swiss-MedTech.com. Published June 14, 2022. Accessed April 29, 2024. https://www.swiss-medtech.ch/en/news/swiss-medtech-award-2022-goes-alveolix
[14] Sempere J, Rossi SA, Chamorro-Herrero I, et al. Minilungs from Human Embryonic Stem Cells to Study the Interaction of Streptococcus pneumoniae with the Respiratory Tract. *Microbiol Spectr*. 2022;10(3):e0045322.
[15] Brown JA, Codreanu SG, Shi M, et al. Metabolic consequences of inflammatory disruption of the blood-brain barrier in an organ-on-chip model of the human neurovascular unit. *J Neuroinflammation*. 2016;13(1):306.
[16] Ehling P, Meuth P, Eichinger P, et al. Human T cells in silico: Modelling their electrophysiological behaviour in health and disease. *J Theor Biol*. 2016;404:236-250.
[17] Moingeon P. Artificial intelligence-driven drug development against autoimmune diseases. *Trends Pharmacol Sci*. 2023;44(7):411-424.
[18] Roodsant T, Navis M, Aknouch I, et al. A Human 2D Primary Organoid-Derived Epithelial Monolayer Model to Study Host-Pathogen Interaction in the Small Intestine. *Front Cell Infect Microbiol*. 2020;10:272.

models have allowed for the coculture and recruitment of donor-derived neutrophils[19] and the assessment of off-tumor toxicity drug toxicity of bi-specific antibodies.[20]

Focusing on current advancements in artificial intelligence and multiomics approaches, which are widely used in cancer research, could also be beneficial for studying infectious and immune-based diseases. For example, the introduction of virtual patients and digital twins, as described by immunologist Dr. Philippe Moingeon in 2023, offers an "organ-specific model built up from medical imaging data and physiological data," enhancing tools available for the study of human physiology and immunology. The combination of artificial intelligence tools with molecular profiling and quantitative pharmacology presents a promising approach to systematically integrate immunological data directly from human patients. Such strategies would provide a more reliable foundation for developing targeted therapeutic interventions and reducing reliance on animal models, who are poor predictors for human immune related diseases.

Importantly, for the development of medical countermeasures, animals in laboratories can harbor undetected infections that confound preclinical research and testing. The inability of U.S. authorities to determine whether the monkeys purchased by research facilities were illegally wild-caught or purpose-bred, and the inadequacy of current quarantine procedures, complicates this matter.[21] Between 2020-2022 the Centers for Disease Control & Prevention (CDC) confirmed that monkeys imported for use in experimentation arrived infected with four different Mycobacteria including *M. bovis, M. caprae, M. orygis, and M. tuberculosis*. According to the CDC these infections were identified up to two years post CDC-mandated quarantine. Non-human primates in U.S. research laboratories have also been found to be harboring *Burkholderia pseudomallei*,[22] *Yersinia pseudotuberculosis*, *Yersinia enterocolitica*, *Shigella*, *Campylobacter*, simian retrovirus, and *Macacine herpesvirus 1*, as well as undetermined pathogens that caused hemorrhagic gastroenteritis and erosive colitis with serositis (Letter from Lisa Jones-Engel, Ph.D. to Daniel Jernigan, December 18, 2022). These confounds not only make preclinical research using these animals unreliable but are also a risk to zoonotic disease spillover and threaten public health. 2023 already saw a 15% increase in tuberculosis cases in humans compared to the previous year.[23]

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[19] Kromidas E, Geier A, Weghofer A, Liu HY, Weiss M, Loskill P. Immunocompetent PDMS-Free Organ-on-Chip Model of Cervical Cancer Integrating Patient-Specific Cervical Fibroblasts and Neutrophils. *Adv Healthc Mater*. 2023.
[20] Harter MF, Recaldin T, Gerard R, et al. Analysis of off-tumour toxicities of T-cell-engaging bispecific antibodies via donor-matched intestinal organoids and tumouroids. *Nat Biomed Eng*. 2024;8(4):345-360.
[21] Martindale D. The US uses endangered monkeys to test drugs. This law could free them. Vox.com. Published January 31, 2024. Accessed April 29, 2024. https://www.vox.com/future-perfect/24055003/long-tailed-macaques-biomedical-testing-ozempic-covid-endangered-species-act-cambodia
[22] Speiser LJ, Graf EH, Seville M, et al. Burkholderia pseudomallei Laboratory Exposure, Arizona, USA. *Emerging Infectious Diseases*. 2023;29(5):1061-1063
[23] Williams PM, Pratt RH, Walker WL, Price SF, Stewart RJ, Feng PI. Tuberculosis — United States, 2023. *MMWR Morb Mortal Wkly Rep*. 2024;73:265–270.

Priority 3: Apply knowledge of HIV/AIDS to reduce HIV incidence through the development of safe and effective prevention, treatment, and cure strategies.

Incidence of HIV infection has declined 12% from 2017 to 2021 but remains high in some populations.[24] Therefore, preventive strategies and investments should be focused on high-risk groups. Especially men who have sex with men, who accounted for 86% of estimated infections among all males, and Black/African-American individuals who represented 40% of new HIV cases in 2021.[23;25] On December 1, 2021, the Executive Branch launched the National HIV/AIDS Strategy (2022-2025) with a commitment to reduce HIV infection by 90% in 2030.[26] A detailed strategic plan[27] is available with the objectives and strategies to achieve this goal that could be accessed by the NIAID.

Unfortunately, all HIV vaccine candidates developed over the past three decades have failed,[28] in part because studies were conducted using nonhuman primates, who do not develop AIDS upon infection by HIV. If scientific efforts and funding continue to be directed toward using animals as models to replicate human AIDS and other infectious diseases, as suggested in Priority 1, the Executive Branch's goal of overcoming HIV by 2030 will be impossible to achieve.

NIAID must invest in advancing AIDS research using human biology as the model. Evidence with so-called "HIV elite controllers," who are infected with HIV but never develop symptoms without any medication, supports the imperative that humans themselves are the model needed to discover HIV treatment and, hopefully, a cure.[29,30,31,32] New vaccines candidates require human-specific testing methods and cutting-edge tools, not unreliable and potentially unsafe experiments on animals. Only this way will therapeutic approaches be effective in reducing incidence and improving detection of HIV. Please also see

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[24] HIV.gov. U.S. Statistics. Reviewed December 7, 2023. Accessed April 19, 2024. https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics

[25] Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States 2017–2021. HIV Surveillance Supplemental Report 2023;28(3). Reviewed March 26, 2024. Accessed April 19, 2024. https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-28-no-3/index.html

[26] The White House. Fact Sheet: The Biden-Harris Administration Marks World AIDS Day 2021 With Renewed Commitments to Ending the HIV/AIDS Epidemic by 2030. Accessed April 19, 2024. https://www.whitehouse.gov/briefing-room/statements-releases/2021/12/01/fact-sheet-the-biden-%e2%81%a0harris-administration-marks-world-aids-day-2021-with-renewed-commitments-to-ending-the-hiv-aids-epidemic-by-2030/

[27] HIV.gov. National HIV/AIDS Strategy (2022-2025). Reviewed December 1, 2023. Accessed April 19, 2024. https://www.hiv.gov/federal-response/national-hiv-aids-strategy/national-hiv-aids-strategy-2022-2025

[28] NIAID. History of HIV vaccine research. Updated October 22, 2018. Accessed April 19, 2024. https://www.niaid.nih.gov/diseases-conditions/hiv-vaccine-research-history.

[29] Galperin M, Farenc C, Mukhopadhyay M, et al. CD4+ T cell-mediated HLA class II cross-restriction in HIV controllers. *Sci Immunol*. 2018;3(24):eaat0687.

[30] Shi Y, Su J, Chen R, et al. The Role of Innate Immunity in Natural Elite Controllers of HIV-1 Infection. *Front Immunol*. 2022;13:780922.

[31] David Cox. The 'elite controllers' who can naturally suppress HIV. *The Guardian*. Published April 4, 2021. Accessed April 19, 2024. https://www.theguardian.com/society/2021/apr/04/the-elite-controllers-who-can-naturally-suppress-hiv

[32] Jiang C, Lian X, Gao C, et al. Distinct viral reservoirs in individuals with spontaneous control of HIV-1. *Nature*. 2020;585(7824):261-267.

our March 19, 2024 comment on the Office of AIDS Research's recent RFI for further discussion of how the agency can move forward in this area: https://headlines.peta.org/wp-content/uploads/2024/04/2024-03-19-rfi-nih-hiv-strategic-plan-sao.pdf.

Priority 4: Apply knowledge of basic immunology to develop and enhance intervention strategies for asthma, allergic and immune-mediated diseases, and transplantation.

This priority outlines the key roles of the NIAID's division of Allergy, Immunology, and Transplantation (DAIT). For instance, addressing challenges related to immune tolerance is essential to improve the success rates of immune-based therapies and transplantation, which currently pose obstacles to long-term safety and efficacy.[33] NIAID should integrate emerging technologies and foster interdisciplinary collaborations among immunologists, bioengineers, and data scientists to develop innovative approaches that leverage human models for disease research. Moreover, NIAID should discourage the use of animal models for investigating human immune-mediated diseases as the practice is inherently limited due to unique human immune characteristics impossible to replicate in other animals.[34;35]

Allergies and asthma management primarily revolves around reducing exposure and alleviating symptoms through pharmacological therapy. Specifically in the context of asthma, the approach involves cyclic symptom assessment, treatment adjustment, and response review.[36] As outlined on the Asthma and Allergy Foundation of America's website,[37] the CDC's National Asthma Control Program and interventions strategies (EXHALE and CCARE) aim to reduce 500,000 asthma-related emergencies by August 31, 2024 through education and training of professionals and patients in self-management.

However, a growing body of evidence emphasizes the role of lifestyle in asthma incidence and severity, aspects currently overlooked in the healthcare system.[38] For example, asthmatic individuals often avoid physical activity, leading to a higher likelihood of exercise-induced bronchoconstriction, affecting 90% of asthmatic patients.[36] A large interventional Danish study in 2022 demonstrated that a daily 20-minute breathing exercise program provided by respiratory specialists improved the health and quality of life of moderate to severe asthmatics with sustained effects over one-year.[39] Given the need for additional

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[33] Hoffman HM. Therapy of autoinflammatory syndromes. *J Allergy Clin Immunol*. 2009;124(6):1129-1140.
[34] Abdolahi S, Ghazvinian Z, Muhammadnejad S, Saleh M, Asadzadeh Aghdaei H, Baghaei K. Patient-derived xenograft (PDX) models, applications and challenges in cancer research. *J Transl Med*. 2022;20(1):206.
[35] De La Rochere P, Guil-Luna S, Decaudin D, Azar G, Sidhu SS, Piaggio E. Humanized Mice for the Study of Immuno-Oncology. *Trends Immunol*. 2018;39(9):748-763.
[36] Papi A, Blasi F, Canonica GW, Morandi L, Richeldi L, Rossi A. Treatment strategies for asthma: reshaping the concept of asthma management. *Allergy Asthma Clin Immunol*. 2020;16:75.
[37] AAFA. CHI-ASMA Project. Accessed May 13, 2024. https://aafa.org/programs/chi-asma/
[38] Stoodley I, Williams L, Thompson C, Scott H, Wood L. Evidence for lifestyle interventions in asthma. *Breathe (Sheff)*. 2019;15(2):e50-e61.
[39] Andreasson KH, Skou ST, Ulrik CS, et al. Breathing Exercises for Patients with Asthma in Specialist Care: A Multicenter Randomized Clinical Trial. *Ann Am Thorac Soc*. 2022;19(9):1498-1506.

research, NIAID has the opportunity to implement and support interventional studies in the coming years to assess the impact of these lifestyle changes and expand national asthma programs beyond symptom management.

With regards to transplantation, there are inherent risks of human infection from animal xenotransplantation, a concern raised over 20 years ago[40] and recently highlighted by a tragic incident involving the transplantation of an infected porcine heart into a human. Porcine cytomegalovirus was detected in the patient's blood 20 days post-surgery, which doctors initially assumed to be an error "since the pigs were supposedly guaranteed free of the germ."[41] The patient passed away 40 days after the transplant. Even with strict laboratory conditions, "porcine endogenous retroviruses are unavoidable."[42] Therefore, NIAID should not support xenotransplantation research or clinical trials.

Reforms to the organ donation system, such as adopting a "presumed consent" policy where organ donation is the default option as seen in other countries, could enhance donation rates. Another compelling approach is the Spanish organ donation system, considered the gold standard globally. The system operates on a three-tiered governance model comprising structural support, professional training, and the cultivation of public trust. Spain's successful strategies for achieving the best organ donation rates show that it is possible to rectify inefficient systems. These strategies are extensively discussed in recent research by Streit et al. (2023)[43] and Martinez-Lopes et al. (2023)[44] and can provide insights for improvements to the U.S system. For further recommendations on how NIAID can improve its autoimmune disease research portfolio, please see our February 25, 2024 response to a recent RFI: https://headlines.peta.org/wp-content/uploads/2024/03/2024-02-25-rfi-nih-autoimmune-strategic-plan-sao.pdf.

Priority 5: Support innovative research efforts to prepare for and respond to nationally or internationally significant biological incidents affecting public health.

Improving access to human clinical samples for research should be supported for this priority and can also be applied to all previous priorities presented for NIAID's strategic plan. Ensuring public health requires not only preparedness but also proactive prevention from biological risks. As highlighted earlier, various

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[40] Boneva RS, Folks TM. Xenotransplantation and risks of zoonotic infections *Ann Med*. 2004;36(7):504-517.
[41] Regalado A. The gene-edited pig heart given to a dying patient was infected with a pig virus. Archived May 4, 2022. Accessed May 12, 2024. https://www.technologyreview.com/2022/05/04/1051725/xenotransplant-patient-died-received-heart-infected-with-pig-virus/
[42] Xi J, Zheng W, Chen M, Zou Q, Tang C, Zhou X. Genetically engineered pigs for xenotransplantation: Hopes and challenges. *Front Cell Dev Biol*. 2023;10:1093534.
[43] Streit S, Johnston-Webber C, Mah J, et al. Ten Lessons From the Spanish Model of Organ Donation and Transplantation. *Transpl Int*. 2023;36:11009.
[44] Martínez-López MV, McLaughlin L, Molina-Pérez A, et al. Mapping trust relationships in organ donation and transplantation: a conceptual model. *BMC Med Ethics*. 2023;24(1):93.

monkey species used in research may be illegally trafficked from the wild, which poses a significant threat of zoonotic diseases to human health. For an example on this issue, refer to PETA's investigation into the trafficking of endangered long-tailed macaques from Asia by Charles River Laboratories: https://headlines.peta.org/what-charles-river-laboratories-doesnt-want-you-to-know/#monkey-business. To prepare for and respond to biological incidents, NIAID must support training scientists in modern, non-animal methods that can streamline research and enhance the international competitiveness of the U.S. biomedical workforce. Additionally, promoting multidisciplinary collaborations to apply emerging technologies in public health contexts, such as immune disease sample databases and innovative non-animal approaches with potential for large-scale commercialization, can significantly enhance preparedness against emerging biosecurity risks.