Science Advancement & Outreach
A DIVISION OF PETA

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NIAMS FY 2025–2029 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 Arthritis and Musculoskeletal and Skin Diseases (NIAMS) draft strategic plan framework. NIAMS 2025–2029 strategic plan is well-structured, integrating research priorities and capacity-building within four comprehensive goals that effectively cover the essentials to advancing therapy development, fostering discoveries, and supporting infrastructure.

PETA celebrates NIAMS' mission to better support research using human-relevant methods such as iPSC-derived organoids and other human *in vitro* models, 3D bioprinting, large human datasets, omics technologies, and ML/AI approaches, and the institute's focus on equity and prevention. Recognizing the failure of animal-based research results translating into human-relevant knowledge, **our key recommendation for the NIAMS is to conduct and fund research using only human biology-based systems and not those that use other species**. Below, we expand on recommendations for some of the priorities listed in this request for public comment.

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.

This plan can be accessed at https://www.peta.org/wp-content/uploads/2023/01/peta-research-modernization-deal.pdf. We are happy to meet and discuss with NIAMS any questions related to this response or the topics covered in the Research Modernization Deal.

Priority 1: Studying Molecular and Cellular Mechanisms of Health and Disease in Humans and Understanding the Resulting Phenotypes and Endotypes

Molecular and cellular processes are key to understanding biology and improving health interventions. PETA supports NIAMS' priority to develop patient-driven tools for researching uniquely human biological mechanisms associated with phenotypes. Exposomics is a new research field focused on understanding the environmental exposures that can affect an individual's health over their lifetime. When combined with other study modalities, such as genomic tools, exposomics can significantly contribute to correlating biological aspects with phenotypes. According to Diesler and Cottin of the University of Lyon, "the interaction between genotype and environment, and especially smoking, triggers auto-immunity and inflammation in the lung," a risk factor for rheumatoid arthritis-associated lung disease, a condition that accounts for most rheumatoid arthritis mortality.[1]

As mentioned in the draft strategic plan, sex can be a determinant factor for effective health interventions, given that hormonal and physiological differences exist among the sexes. Including sex as a variable is crucial to uncover distinct pathways leading to diseases, but this must be done using human data, not by including more females of other species into animal-based study designs. Sex differences matter, but species differences are a bigger hurdle that can be avoided.

Similarly, from a social perspective, gender distinction can influence access to interventions and ultimately, clinical outcomes. A recent retrospective study on a Japanese cohort with difficult-to-treat rheumatoid arthritis (D2T RA) identified a 76% incidence of the condition in women. Interestingly, they found the presence of pulmonary and neurological diseases as risk factors associated with D2T RA and

[1] Diesler R, Cottin V. Pulmonary fibrosis associated with rheumatoid arthritis: from pathophysiology to treatment strategies. *Exp Rev of Resp Med*. 2022;16(5):541–553.

other factors as critical determinants of disease progression.[2] Rheumatoid arthritis has been shown to have genetic and environmental etiology, with smoking and pulmonary fibrosis as a major risk factor that can be reduced by behavioral changes.[3]

Although very frequent, the definition and management of these conditions remain inappropriately addressed without official guidelines available, so there is more work to be done in this field that will have a direct impact on physicians and their patients. In this regard, the European League Against Rheumatism published a D2T-RA recommendation in 2021 to be implemented in clinical practice and trials.[4] Actions like this are a first step to standardize procedures and guide research investigations and interventions adequately. NIAMS must support exclusively human-based models for studying phenotypes and endotypes related to human diseases, like D2T-RA and RA-ILD. Using other species presents significant challenges to advancing research on human diseases as they fail to replicate the complex physiology and environmental context of humans.

Priority 2: Developing Regenerative Medicine Approaches to Facilitate Repair or Restoration of Tissue

Regenerative medicine is revolutionizing treatments in fields like blood cancer and stroke therapy by using humans as sources of samples for tissue regeneration, rather than animal models. While traditional animal models cannot accurately predict and replicate multifactorial human conditions like arthritis, human-based approaches such as engineered tissues and cell transplantation are promising alternatives for more effectively translating therapies. **NIAMS should not develop animal models for the purpose of providing insights on how to facilitate regenerative versus reparative musculoskeletal and skin tissue regeneration in humans.** Historically, animal-based research has failed to provide human-relevant data in many fields, including regenerative medicine.

For NIAMS to achieve the objective of "Developing advanced physiologically relevant models and

[2] Ryu Watanabe R, Hashimoto M, Murata K, et al. Prevalence and predictive factors of difficult-to-treat rheumatoid arthritis: the KURAMA cohort. *Immunol Med*. 2021;45(1):35–44.
[3] Venetsanopoulou AI, Alamanos Y, Voulgari PV, Drosos AA. Epidemiology of rheumatoid arthritis: genetic and environmental influences. *Exp Rev of Clin Immuno*. 2022;18(9):923–931.
[4] Nagy G, Roodenrijs NM, Welsing PM, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. J *Rheum Dis*. 2021;80:31-35.

scalable and economic protocols […] for use in regenerative medicine approaches," it must invest in new approaches that use human cells and samples, authentically replicating human physiology. Fundamentally, animal models cannot mimic human biology.

New research models like organoids and human induced pluripotent stem cells (hiPSCs) are growing technologies that are beginning to become more automated and scalable. For example, "[t]he differences in skin regeneration and wound healing processes between rodents and humans are evident, and mouse skin models are often poor predictors of human trial outcomes."[5] Current skin substitutes, like hydrogels and bioprinting, allow human stem cell proliferation and provide signals for skin regeneration in the extracellular matrix. Researchers are calling for more support to improve vasculature in these models for advancing regenerative potential and scalability. NIAMS can pioneer this field by supporting and creating funding opportunities exclusively for human-relevant approaches on skin and musculoskeletal regeneration while completely shifting away from animal-based research. We recommend that NIAMS invest in such human-relevant systems that can better advance tissue regeneration research and clinical applications.

Priority 3: Using Data Science, Artificial Intelligence and Machine Learning (AI/ML), and Computational Biology to Advance Knowledge and Treatments

NIAMS' priority in leveraging data science and AI to enhance regenerative medicine research is commendable. Collaborations with fields such as mathematics and bioinformatics to investigate disease mechanisms via data-driven *in silico* studies can offer more accurate insights for future preclinical testing of potential treatments using human-based models.

Preclinical research accounts for over 43% of pharma expenses and billions of public funding. The design of *in silico* preclinical studies that take advantage of 3D structural-chemical data from molecules obtained with techniques like crystallography can accelerate the R&D process. The expansion of virtual

[5] Hosseini M, Koehler KR, Shafiee A. Biofabrication of Human Skin with Its Appendages. *Adv Healthc Mater*. 2022;11(22):e2201626.

models has facilitated the discovery of new targets, for example, the REAL database is the largest virtual library offering *in silico* drug screening to find new hit molecules with 80% efficacy in a short time.[6,7] "When combined with more accurate in vitro testing, this may reduce and eventually eliminate animal test requirements (as recently indicated by FDA)." [8] Similar to other computational tools for *in silico* trials. HINT, a graph-neural-network, integrates diverse data sources (i.e. drug molecules, target diseases, and patient data) to predict clinical trial success.[9] The model was launched two years ago with over 17 thousand datasets and has been shown to outperform existing methods.[10,11] These tools help pharmaceutical companies refine trial designs or consider alternative drugs, aiming for more accurate predictions of trial outcomes.

Arthritis and musculoskeletal diseases often have genetic and immunological backgrounds and can be influenced by lifestyle, such as repetitive movements due to working conditions. The combination of longitudinal studies and using AI/ML tools such as the ones described above to integrate datasets from human patients can also provide insights into the etiology and evolution of these conditions, which is addressed in priority 4. **However, NIAMs should not support or collaborate in creating databases with animal-derived data to investigate exposomics, such as MoTrPAC, since it misleads research from producing human-relevant knowledge. On the contrary, only human data are reliable for identifying health determinants and developing more precise interventions.**

Priority 5: Translating Findings Into Interventions Through Clinical and Epidemiologic Studies

As stated by NIAMS, "this priority addresses the translation of discoveries into patient care or public health efforts," which is currently needed, especially for arthritis and musculoskeletal diseases patients, who commonly rely on symptom relief interventions due to the lack of more effective therapeutic approaches.

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[6] Enamine. REAL database. Enamine.net. Accessed July 29, 2024. https://enamine.net/compound-collections/real-compounds/real-database
[7] Grygorenko OO, Radchenko DS, Dziuba I, Chuprina A, Gubina KE, Moroz YS. Generating Multibillion Chemical Space of Readily Accessible Screening Compounds. *iScience*. 2020;23(11):101681.
[8] Sadybekov AV, Katritch, V. Computational approaches streamlining drug discovery. *Nature.* 2023;616:673–685.
[9] Hutson M. How AI is being used to accelerate clinical trials. *Nature Index*. Published March 13, 2024. Accessed July 29, 2024. https://www.nature.com/articles/d41586-024-00753-x
[10] Fu T, Huang K, Xiao C, Glass LM, Sun J. HINT: Hierarchical interaction network for clinical-trial-outcome predictions. *Patterns* (N Y). 2022;3(4):100445.
[11] Xiao C, Huang K, Fu T, Glass L, Sun J. HINT: Hierarchical Interaction Network for Clinical Trial Outcome Prediction. IQVIA. Published March 2022. Accessed July 29, 2024. https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/hint-hierarchical-interaction-network-for-clinical-trial-outcome-prediction-insight-brief.pdf

Translating molecular and cellular discoveries from the previous priorities of this strategic plan into patient care is deeply needed. A key strength is the focus on health equity and innovative clinical trial designs, which can better tailor treatments to diverse populations. However, the complexity of integrating patient-reported outcomes and precision medicine requires robust data collection and effective communication between all parties involved, which aligns with priority 10. In this regard, NIAMS has stated its commitment to sustaining timely and relevant communication and we encourage the institute to include all stakeholders (i.e. patients, researchers, and non-governmental organizations) in this communication. This will make it more possible for NIAMS to build trust with communities and encourage their members to engage in scientific research.

For its goals in developing and testing device-based interventions for pain that can provide long-lasting, non-opioid-based relief and innovative precision medicine approaches that integrate patients' biology and behaviors, human-based research, not experiments on animals, will be essential. Research on human pain must be conducted in the ways that are most relevant to human physiology and neurobiology. For example, researchers at Queen's University Belfast used *in vitro* and *in vivo* human neuronal models to study a molecular basis for the modulation of nociception in human peripheral nerves.[12] Biotechnology companies like AxoSim, NETRI, and others have developed human neuronal *in vitro* models that can be used by NIAMS grantees for pain research. Precision medicine, by definition, necessitates the use of patient-derived samples and data and would benefit from increases in funding for the use of patient iPSCs and other cells in microphysiological and other advanced human *in vitro* systems.

Chronic musculoskeletal pain (CMP) affects around one-third of the global population[13] and usually requires multimodal interventions.[14] Virtual reality (VR) application during rehabilitation shows promise for pain management, offering benefits like enhanced feedback and improved coping

[12] McMillan H, Lundy FT, Dunne OM, et al. Endogenous Mas-related G-protein-coupled receptor X1 activates and sensitizes TRPA1 in a human model of peripheral nerves. *FASEB J*. 2021;35(5):e21492.
[13] World Health Organization. Musculoskeletal Conditions. WHO.int. Published 2019. Accessed July 29, 2024. https://www.who.int/news-room/fact-sheets/detail/musculoskeletal-conditions.
[14] El-Tallawy SN, Nalamasu R, Salem GI, et al. Management of Musculoskeletal Pain: An Update with Emphasis on Chronic Musculoskeletal Pain. *Pain Ther*. 2021;10:181–209.

strategies.[15] Clinical studies combining VR with exercises like kinetic training and sensorimotor activities report reduced pain and improved range of motion.[16,17] However, studies are needed to assess VR's effectiveness in CMP rehabilitation. This opens opportunities for NIAMS to develop interventional studies that gather patient data from clinical trials and wearable devices and translate it into unique therapeutic protocols, a current gap indicated by practitioners "who see wearables' potential in trials, but do not know how to use them for highest impact."[9]

Additionally, the World Health Organization has created a Package of Interventions for Rehabilitation 2030 targeting musculoskeletal conditions, including osteoarthritis, for integration into national health services worldwide.[18] NIAMS can refer to this resource to identify research gaps, intervention strategies, and implementation guidance.

Priorities 7: Capacity-Building Priorities; 8: Supporting Interdisciplinary Research, Team Science, and Partnerships; 9: Promoting Training and a Robust, Inclusive Workforce

These three priorities collectively aim to advance scientific understanding, accelerate medical breakthroughs, and build a solid inclusive research community. **NIAMS' plans to achieve this goal, particularly its support of the 2023 recommendations of the NIH Advisory Committee to the Director, are commendable and we look forward to seeing the institute's progress in this area.**

NIAMS' vision of fostering interdisciplinary teams and partnerships between researchers and patient advocacy groups will aid in its goal of advancing patient care towards a personalized approach. Individuals suffering from chronic conditions, such as arthritis, need long-term support, which consequently requires professional training and infrastructure to provide essential care. Building a multidisciplinary team of professionals, researchers, and institutions can improve healthcare and access

[15] Bilika P, Karampatsou N, Stavrakakis G, Paliouras A, Theodorakis Y, Strimpakos N, Kapreli E. Virtual Reality-Based Exercise Therapy for Patients with Chronic Musculoskeletal Pain: A Scoping Review. *Healthcare*. 2023; 11(17):2412.
[16] Bahat HS, Takasaki H, Chen X, Bet-Or Y, Treleaven, J. Cervical kinematic training with and without interactive VR training for chronic neck pain—A randomized clinical trial. *Man. Ther*. 2015;20:68–78.
[17] Bahat HS, Croft K, Carter C, Hoddinott A, Sprecher E, Treleaven J. Remote kinematic training for patients with chronic neck pain: A randomised controlled trial. *Eur. Spine J*. 2018;27:1309–1323.
[18] World Health Organization

to it. In its support of training, NIAMS must ensure that its workforce is prepared for the further use and development of the non-animal research models, as mentioned in our comments, and offer transitional support for established researchers to become familiar with these methods.

To promote health and translate the knowledge gained with the previous priorities from this strategic plan, we recommend that NIAMS only use human-based approaches in its areas of interest. In addition, NIAMS should facilitate the integration of *in silico* and *in vitro* methods into research by creating exclusive funding opportunities and training for early-career scientists and health professionals to use these models. To ensure U.S. international competitiveness and achieve a tangible, positive impact on human health, NIAMS must go further in its move toward human-relevant research and away from poorly predictive animal models.