Science Advancement & Outreach
A DIVISION OF PETA

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Request for Information (RFI):

Inviting Input on an NIH-Wide Strategic Plan for Autoimmune Disease Research

Submitted February 25, 2024, by:

Science Advancement and Outreach

A division of People for the Ethical Treatment of Animals

OBJECTIVE 1: *Research areas that would benefit from cross-cutting, collaborative research (these areas may include basic or translational research, clinical research, health services research, population science, data science, preventative research, biomedical engineering, and other areas of research).*

An NIH-Wide Strategic Plan to advance autoimmune disease research should focus on supporting human-relevant, non-animal methods. Animal models of human autoimmune diseases have consistently failed to lead to new treatments and cures for humans. The NIH-wide strategic plan should emphasize cross-cutting collaborations across NIH institutes and centers that facilitate transitioning away from failing animal models and establishing support for and validating human-relevant methods.

In the National Academies of Sciences, Engineering, and Medicine report "Enhancing NIH Research on Autoimmune Disease," it was disconcerting to read that much emphasis was placed on generating new animal models of these diseases to correct for where current animal models have failed. New animal models are not the answer to the problem, which is that other species fundamentally fail when it comes to modeling human conditions.

While the extensive use of mice in immunological research has resulted in little benefit to humans, it has highlighted several critical differences across species, including differences 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, activation of clotting factors, and fundamental differences between the species in the innate immune response (https://doi.org/10.4049/jimmunol.172.5.2731; https://doi.org/10.1615/CritRevImmunol.2014011600). Logically, these differences make sense: We humans "do not live with our heads a half-inch off the ground" (https://doi.org/10.1007%2Fs00204-013-1038-0) and we have considerably longer life spans

and a larger body size than mice do.

Mice and other animals fail to adequately model many human autoimmune diseases. For example, in research on inflammatory bowel diseases (IBDs), symptoms are experimentally induced in animals in ways that do not mimic human etiology. Strains of mice vary in their susceptibility to chemically-induced IBDs, don't recapitulate the nuanced and multigenic underpinnings of human IBDs, and these experiments lack important environmental factors contributing to IBDs in humans (https://doi.org/10.1155/2021/7479540). As another example, experimenters' attempts to induce endometrial disorders in animals—the vast majority of whom do not menstruate as humans do—has led to many failed clinical trials for therapies that worked in other animals, but not in humans (https://doi.org/10.1186/s12967-020-02471-0). Mouse models of multiple sclerosis have similar poor translation and don't meet clinical needs (http://dx.doi.org/10.2174/138161282166615031612270 6).

Fortunately, human biology-based autoimmune research models offer promise in areas where the use of animal models have stalled progress. As reported in a recent European Union Joint Research Centre systematic review of non-animal models for autoimmune research, "human stem cell-derived models have emerged as a highly promising tool to study autoimmune diseases in a human context, providing an exciting addition to existing animal-based methods. Indeed, stem cells can be genetically modified, retain a high degree of developmental control, and maintain the capability to replicate, allowing the generation of the high amount of tissue required for high-throughput experiments" (https://publications.jrc.ec.europa.eu/repository/handle/JRC131505). These models will be discussed in greater detail in the following response.

OBJECTIVE 2: *Opportunities to advance collaborative, innovative, or interdisciplinary areas of autoimmune disease research.*

Innovative autoimmune disease research and the use of advanced, human-relevant systems go hand-in-hand. In the recent European Union Joint Research Centre systematic review of non-animal models for autoimmune research, it was found that in vitro and in silico non-animal systems were available to model multiple facets of autoimmune conditions including, but not limited to, proinflammatory phenotypes, cytokine physiology and T cell dynamics, immune activation, autoantigen and autoantibodies pathogenesis, disease therapeutic targets, insulin production, apoptosis, cytotoxic events, and fibrosis (https://publications.jrc.ec.europa.eu/repository/handle/JRC131505).

Some examples of work being done in this field, which often involves collaborations between clinicians and in vitro researchers across disciplines, fostering collaborations across investigators working with different patient groups or different methodologies, include the following:

- A large European project called 3TR set out to "fundamentally increase our knowledge of the molecular pathways and mechanisms linked to response and non-response to therapy in seven different immune-mediated, allergic and inflammatory diseases" by using real-world data (https://www.3tr-imi.eu/).
- A review summarizing the progress of immune-competent human skin disease models recognized the failures of animal studies to translate into effective treatments for autoimmune diseases such as psoriasis. The authors describe how co-culture, three-dimensional organotype

systems, and organ-on-a-chip technology will "enable human models of well-controlled complexity, yielding detailed, reliable data; thus providing a fitting solution for the drug development process" (https://doi.org/10.1016/j.drudis.2016.05.008).

- A human vascularized synovium-on-a-chip can improve the understanding of conditions like rheumatoid arthritis and osteoporosis (https://doi.org/10.1088/1748-605x/acf976).
- Patient-specific cerebral organoids have revealed insights into the progression of multiple sclerosis (https://doi.org/10.1242/bio.059845).
- A human genetic study revealed links between COVID-19 severity and systemic lupus erythematosus (https://doi.org/10.1371/journal.pgen.1010253).
- Population genetics was combined with single-cell RNA (scRNA)-seq data using blood samples from healthy human volunteers to "uncover drivers of interindividual variation in the immune system" (https://doi.org/10.1126/science.abf3041).
- Using patient cells, researchers identified a previously unreported genetic mechanism for hemophagocytic lymphohistiocytosis (https://doi.org/10.1182/blood.2020008738).
- "By connecting human microphysiological systems of the gut, liver, and circulating Treg and Th17 cells," a multi-organ, ex vivo model of ulcerative colitis (UC) was developed "to study causality and the fundamental entanglement of immunity, metabolism, and tissue homeostasis" (https://doi.org/10.1016/j.cels.2020.02.008).
- A human in vitro study of Graves' orbitopathy identified modulators of sphingolipid SP1 as a potential target for treating this condition (https://doi.org/10.1167/iovs.18-25466).
- For autoimmune endometrial diseases, organoids, assembloids, microfluidic models, and human "omics" data have the potential to dramatically improve research in this field (https://doi.org/10.1055/s-0040-1719084; https://doi.org/10.1093%2Fbiolre%2Fioaa124).

NIH's Strategic Plan for autoimmune disease research must prioritize the support for these types of models and the development of more like them. The Strategic Plan could pave the way for institutes to develop concepts for Program Project Grants or Center Grants to investigators interested in establishing centers for non-animal methods at their institutions or grant supplements to investigators who want to switch to non-animal methods mid-funding. Training opportunities, such as Institutional Training Grants and Continuing Education Training Grants, can be developed to train autoimmune researchers to use these human-relevant systems.

OBJECTIVE 3: *Opportunities to improve outcomes for individuals living with autoimmune diseases including NIH-designated health disparities populations, populations and individuals with rare diseases, and specific populations that have been historically underrepresented in research and clinical trials.*

Shifting toward human-relevant autoimmune research, and away from animal models, will not only better serve patients, including those in populations experiencing health disparities and underrepresentation, but will also better support investigators in these populations. A study by the NIH Office of Portfolio Analysis revealed that applications from African-American/Black investigators were

more likely to propose studies involving human subjects and that this topic choice contributed to lower funding rates for individuals in this demographic. The new NIH-Wide Strategic Plan for autoimmune disease research should correct this, in part, by prioritizing human-centered research.

OBJECTIVE 4: *Cross-cutting areas that are integral to advancing autoimmune disease research at NIH including development of a publicly accessible central repository for autoimmune disease research, sex- and gender-intentional research design across all stages of research, and engagement of all populations in research and clinical trials.*

Under NIH's Strategic Plan for autoimmune disease research, the agency should mandate that data obtained through NIH-funded projects, including data from non-animal research methods, be made publicly available and that results be published in open access scientific journals. Greater transparency and data availability will enable additional use and dissemination of this critical information, allow for additional collaboration, and foster greater transparency.