THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

Submission by The American Association of Immunologists (AAI)
to the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH)
Request for Information (RFI): Inviting Input on an NIH-Wide Strategic Plan
for Autoimmune Disease Research

February 29, 2024

Introduction

The American Association of Immunologists (AAI), the nation's largest professional association of research scientists and physicians who are dedicated to understanding the immune system through basic, translational, and clinical research, appreciates this opportunity to submit comments in response to NOT-OD-24-049: "Request for Information (RFI): Inviting Input on an NIH-Wide Strategic Plan for Autoimmune Disease Research." AAI strongly supports this and other recent efforts to coordinate autoimmune disease research across NIH Institutes and Centers and foster multidisciplinary collaboration to improve the diagnosis, treatment, and outcomes for those living with one or more of the over 100 known autoimmune diseases. Continued investment in autoimmune disease research and better coordination across NIH is crucial to making meaningful progress against these debilitating diseases, which disproportionately affect women. We offer specific input on the four objectives outlined in the RFI:

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).*

Fully elucidating the foundational mechanisms of how central and peripheral tolerance break down in those with autoimmune diseases is crucial. Why this breakdown occurs more frequently in women is of utmost importance, as 80% of those with autoimmune diseases are women, and autoimmune diseases are the fifth leading cause of death in women younger than 65.[1] Research should continue to address, for example, hormonal changes, which are known to profoundly affect innate and adaptive immune responses, across the lifespan with emphasis on periods of acute endocrinological transitions in biological females (puberty, pregnancy, and menopause).[2] As onset of many autoimmune conditions tends to peak in early to middle adulthood, understanding age-related changes in immunity and how that affects disease susceptibility, particularly in women, is imperative. Recent data suggests altered X chromosome

[1] Melinda Wenner Moyer. "Why Nearly 80 Percent of Autoimmune Sufferers are Female." *Scientific American*. September 1, 2021. https://www.scientificamerican.com/article/why-nearly-80-percent-of-autoimmune-sufferers-are-female/

[2] Desai, M.K. and Diaz Brinton, R. 2019. Autoimmune Disease in Women: Endocrine Transition and Risk Across the Lifespan. *Frontiers in Endocrinology*. https://doi.org/10.3389/fendo.2019.00265

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inactivation (including in immune cells) may play a role in the development of autoimmunity;[3,4] more research is necessary to understand this mechanism and the additional triggers (e.g., genetic, environmental) that may result in autoimmune disease. While the great majority of individuals with autoimmune diseases are women, understanding the pathophysiology of autoimmune disease in males, and the similarities and differences in disease presentation, outcomes, response to treatments, etc., between females and males, should also be a priority.

Other areas of research that would benefit from cross-cutting collaboration include understanding how helminth infections, and the induction of Th2 responses, can prevent the onset of or treat autoimmunity. Specific analyses of the protective mechanisms may be immensely informative for the development of therapeutics, and could involve fundamental research, data science and artificial intelligence (AI)/machine learning, and bioengineering. In addition, understanding how mechanical and/or physical cues from the tissue microenvironment can affect immune cell function and autoimmunity can benefit from collaborations between immunologists and biomedical engineers.

Several studies have demonstrated that individuals with an autoimmune disease, especially young women (less than 45 years old), have an increased risk of cardiovascular disease (CVD).[5,6,7] In addition to highlighting the importance of strictly managing and treating cardiovascular issues in patients with autoimmune diseases, these studies indicate a broad link between autoimmunity and CVD that would benefit from collaborative research. Similarly, while chronic kidney disease and renal involvement is well established in lupus, less is known about kidney conditions in other autoimmune diseases.

NIH should consider providing collaborative opportunities to examine the effect of environmental factors on autoimmunity, accounting for geographic location and how environmental factors may have differential effects on distinct populations. This area is ripe for cross-cutting collaborations among basic scientists, toxicologists, environmental health researchers, population scientists, and data scientists.

Developing appropriate experimental systems will further advance the study of autoimmunity. Reliable and relevant animal models and novel alternative methods with human applicability should mimic individual diseases and be designed to uncover common mechanisms underlying autoimmunity. Creating an accessible, consistent, and comprehensive set of research tools will streamline and coordinate research across the field, lead to greater discovery, and may result in more effective treatments.

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

Advancing the understanding and treatment of autoimmune diseases will require coordinated efforts between a multitude of disciplines and scientific perspectives. New research opportunities should aim to

[3] Dou, D.R., Zhao, Y., Belk, J.A. et al. 2024. Xist ribonucleoproteins promote female sex-based autoimmunity. *Cell*. https://doi.org/10.1016/j.cell.2023.12.037

[4] Syrett, C.M., Paneru, B., Sandoval-Heglund, D. et al. 2019. Altered X-chromosome inactivation in T cells may promote sex-biased autoimmune diseases. *JCI Insight.* https://doi.org/10.1172/jci.insight.126751

[5] Conrad, N., Verbeke, G., Molenberghs, G. et al. 2022. Autoimmune diseases and cardiovascular risk: a population-based study on 19 autoimmune diseases and 12 cardiovascular diseases in 22 million individuals in the UK. *The Lancet*. https://doi.org/10.1016/S0140-6736(22)01349-6

[6] Han, J.Y., Cho, S.K., Kim, H. et al. 2024. Increased cardiovascular risk in Korean patients with systemic lupus erythematosus: a population-based cohort study. *Science Reports.* https://doi.org/10.1038/s41598-024-51546-1

[7] Moran, C.A., Collins, L.F., Beydoun, N. et al. 2022. Cardiovascular Implications of Immune Disorders in Women. *Circulation Research.* https://doi.org/10.1161/CIRCRESAHA.121.319877

bring together investigators from fundamental biology to translational and clinical research to epidemiology, and utilize data science, bioinformatics, AI, and machine learning. Drug discovery and *in silico* design of novel targeted drugs is an example of an area in which NIH should promote interdisciplinary collaborations and initiatives, particularly between fundamental immunologists and computational biologists utilizing AI/machine learning. For example, use of generative AI to identify drug targets and design candidate drugs like synthetic inhibitors can be paired with subsequent validation by cellular assays and other models. This is a promising area that may eventually bring new and more effective treatments to patients.

Other potential research collaborations with those who study autoimmunity and autoimmune diseases may include, but are not limited to, immunologists and infectious disease specialists, scientists who study the microbiome, metabolomics, and/or genetics and epigenetics, and those who study diseases that affect specific organs including the kidneys, heart, lungs, and skin. Consideration should also be given to the fact that many autoimmune diseases are systemic and can affect multiple organs and organ systems at once. These areas of research can be advanced by leveraging current and next generation technologies like single-cell transcriptional profiling, spatial transcriptional profiling, multiplex tissue imaging, and whole-genome sequencing.

By creating the opportunities outlined above, underlying mechanisms of disease etiology and pathology of individual autoimmune diseases can be determined, and common aspects and mechanisms across autoimmunity can be elucidated. Bringing together scientists who study, for example, microbiome changes or epigenetic changes in individual disease states can find commonalities that may inform broad pathways of autoimmunity that can be targeted for prevention or treatment. Given that autoimmunity is often familial, and families tend to suffer from multiple autoimmune diseases, significant consideration should be given to studying not only commonalities within each family, but across multiple families to determine common markers, genes, pathways, and more. Collaborations to generate multidimensional datasets from a sizeable number of patient samples of this nature will allow for large scale analysis and discovery.

NIH should create concrete collaborative opportunities through programs, initiatives, and grants that emphasize cross-cutting partnerships between disciplines. Such opportunities should encourage new and unique collaborations to investigate novel and big picture hypotheses, and NIH should urge partnerships between well-resourced laboratories and those with less funds, resources, and accessibility to patients.

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.*

Improving outcomes for all people living with autoimmune diseases is an area of high priority. To do so, it is first necessary to gain a comprehensive understanding of the prevalence of autoimmune diseases across all populations and geographical areas. Improved methods of diagnosis, including enhanced biomarker discovery, can aid in uncovering the true burden of autoimmune disease in the U.S. It is also important to understand heterogeneity of disease presentation, response to treatment, and outcomes in different populations. An initiative focused on awareness, education, diagnosis, treatment options, and access to specialists/clinical trials targeted to populations with health disparities and those that have been historically underrepresented, and to areas of the U.S. with less data about patients with autoimmune diseases (e.g., parts of the South and Midwest, as well as Alaska) would help increase the accuracy of data and access to healthcare. Patient education, support, and regular and reliable access to care, including

mental health care, is essential to improving outcomes and quality of life for those living with autoimmune diseases.

Currently, most approved therapies are broadly immunosuppressive, leaving patients susceptible to a wide range of side effects, infections, and cancer. More targeted and specific treatments are necessary to decrease these risks and improve patient outcomes. Recent data from clinical trials testing immunotherapy (e.g., CAR-T cells and PD-1 agonists) for treating some autoimmune diseases are encouraging and should continue to be an area of investigation.[8,9] Innovation in personalized medicine, especially for those with rare diseases, should continue to be at the forefront of potential therapeutic options for those with autoimmunity.[10]

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.*

Increased availability and use of trustworthy datasets will maximize hypothesis-driven and discovery-driven research. NIH can play a role in this by establishing a well-curated central repository for autoimmune disease research data that is easily accessible to all. In addition, NIH should foster and help generate an integrated system of shared research tools to aid in the generation of reliable data and a coordinated effort to elucidate common and distinct mechanisms of autoimmune disease.

NIH should work closely with the Centers for Disease Control and Prevention and other epidemiological sources to prioritize the use and maintenance of accurate information on the prevalence of autoimmune diseases in the U.S., and the demographics of those who suffer from them, which would require increasing education and access to accurate medical information and diagnoses, and innovation in diagnostic tools.

Consideration of sex, ancestry, and gender, as well as other demographics like age, geographical location, and social determinants of health, should be prioritized in research, clinical trial design, and data analysis. To broaden inclusion and enhance diversity in participants, study design should consider factors related to the ease of participation, including clinical trial study location, language barriers, study duration, and the frequency of sample collection.

In addition, NIH should consider incorporating patients in study design to inform which outcomes are most important to – and would most benefit – those suffering from autoimmunity. Utilizing digital health technologies to gather real-time data throughout the study can improve data collection and enhance participation. Further, long term follow-up and assessment is important to determine treatment durability, late-onset side effects, and disease progression in chronic autoimmune diseases.

[8] Mullard, Asher. 2023. CAR T cell therapies raise hopes – and questions – for lupus and autoimmune disease. *Nature Reviews Drug Discovery.* https://www.nature.com/articles/d41573-023-00166-x

[9] Mullard, Asher. 2023. PD1 agonist antibody passes first phase II trial for autoimmune disease. *Nature Reviews Drug Discovery.* https://www.nature.com/articles/d41573-023-00087-9

[10] Miner, J.J., Fitzgerald, K.A. 2023. A path towards personalized medicine for autoinflammatory and related diseases. *Nature Reviews Rheumatology.* https://www.nature.com/articles/s41584-022-00904-2