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

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[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

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 neurologists, pulmonologists, 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