Statement in Response to Recent *Nature* Publication

The Lupus Research Alliance (LRA) is encouraged by the recent study, “Interferon subverts an AHR–JUN axis to promote CXCL13+ T cells in lupus”, funded in part by the LRA and published in the journal *Nature*, that identified a molecular pathway that promotes an imbalance of T cells leading to an overactive immune response in lupus.

Lupus is a highly complex and heterogeneous autoimmune disease that manifests differently in different people and symptoms can change over time. As such, the goal of the LRA is to identify as many individualized treatments as possible to meet the needs of the diverse people living with lupus.

This study is the latest testament to our rigorously vetted research portfolio that will move us closer to that goal. To date, the LRA has supported research that has contributed to the identification or further validation of more than a dozen different disease pathways in lupus, enabling the discovery, validation or testing of many different therapies for lupus.

Our research funding was instrumental in the identification of novel pathways that led to the development and approval of belimumab and anifrolumab, the only biologic medications to be approved by the U.S. FDA for systemic lupus erythematosus. The LRA has also supported pioneering research on immune therapy (CAR-T cell therapies) that has led to the most dramatic, albeit still preliminary, clinical trial benefits in lupus yet.

The Lupus Research Alliance is dedicated to unraveling the complexity of lupus to identify more novel targets that can be used to develop better, safer and more personalized treatments. We are striving for a world free of lupus and are relentless in our pursuit of a cure --- and have the track record to get there.

How does this study affect the treatment of people currently living with lupus?

It will likely take several years of additional research to confirm the findings presented in the paper above and translate them into a clinical treatment for people living with lupus. The discovery of this pathway as a regulator of T cell imbalance has the potential to lead to specific targeted therapies, which could be advantageous over treatments such as glucocorticoids that broadly suppress the immune system. It is important to note that due to the heterogeneity of the disease, it is not likely that a treatment developed based on these findings will be effective for all of the people currently living with lupus.

What additional research is needed to confirm these findings?

There are several types of additional research that may need to be done to confirm these findings. Due to the extreme heterogeneity of lupus, these findings will need to be examined in a larger number of people living with lupus, across a wide variety of populations and those with different manifestations of the disease. In addition, more specific, mechanistic studies and clinical trials of potential treatments modulating the AHR-JUN pathway will need to be performed.

Will this research lead to new therapies for lupus?

This research advances our understanding of one of the underlying causes of lupus. It has the potential to lead to new, targeted treatments for people living with lupus. However, we would like to urge caution, as there have been many other promising therapeutic targets that have not led to successful treatments of this complex disease.

Are there current therapies that target this newly identified pathway?

Not directly, no. Anifrolumab, which binds to part of the type 1 interferon receptor, is upstream of the pathway identified in this research. This study looked back at blood samples from people living with lupus who had participated in a clinical trial testing the effectiveness of anifrolumab (now approved for the treatment of lupus as Saphnelo) and found that in these patients the T cell imbalance was improved from those who did not have the treatment. In addition, there are small molecule inhibitors of the aryl hydrocarbon receptor (AHR) identified in this pathway. One was tested in this study and demonstrated to be effective in modulating the T cell imbalance in blood samples from people living with lupus. However, this inhibitor is not currently FDA approved. These AHR inhibitors may be a good place to start in developing a targeted treatment for this pathway.

How did the LRA funding impact this study?

This study was funded, in part by two LRA grants. A Lupus Mechanisms and Targets Award to Dr. Deepak Rao in 2018 and a Diversity in Lupus Research Postdoctoral Awards to co-first author Dr. Vanessa Wacleche in 2022. Dr. Wacleche was one of the inaugural award recipients of our Diversity in Lupus Research awards, which was designed to harness the collective power of diverse minds and address the underrepresentation of specific groups in lupus research.

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