CDMRP
Department of Defense

Lupus Research Program

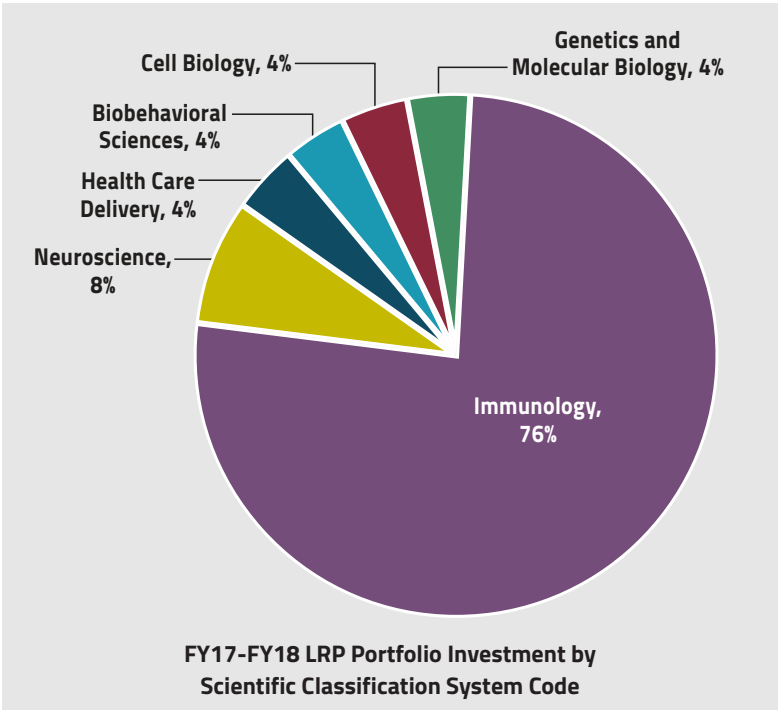
Vision: To cure lupus, through partnership of scientists, clinicians, and consumers

Mission: Fund research to understand, prevent, and diagnose lupus and to improve treatments and quality of life of patients, including Service members, Veterans, and beneficiaries

Program History

Lupus is a chronic, heterogeneous autoimmune disease that is difficult to diagnose and treat. Approximately 90% of lupus patients are women, and the disease is more common in women of African American, Hispanic, Asian, and Native American descent than in Caucasian women. Lupus causes inflammation in the skin, joints, kidneys, lungs, heart, and brain. Because it affects numerous parts of the body, people living with lupus experience a wide range of symptoms, including fatigue, arthritis, headaches, weight loss, organ damage, seizures, and strokes. The severity of symptoms can be exacerbated if a patient is experiencing a lupus flare.

Treatment options for lupus are highly dependent on an individual patient's symptoms and can include nonsteroidal anti-inflammatory drugs and corticosteroids. Patients are frequently treated with a combination of drugs. Because the symptoms of lupus vary from person to person, the disease is difficult to diagnose. There is currently no single test available capable of diagnosing lupus.



FY17-FY18 LRP Portfolio Investment by Scientific Classification System Code

The Congressionally Directed Medical Research Programs (CDMRP) funded lupus research as a topic area within the Peer Review Medical Research Program (PRMRP) from fiscal year 2005 (FY05)-FY16. During this time, the PRMRP funded 21 lupus research awards for a total of $20.6 million (M). In FY17, the Lupus Research Program (LRP) was established with an appropriation of $5M. Since then, a total of $15M has been appropriated to the program, including $5M in FY19. The LRP has funded 25 awards through FY18 to support innovative, high-risk, high-reward studies that offer the promise of shifting current paradigms with the hope of improving treatments and quality of life for those living with lupus.

Improving Lupus Treatment Options

Targeting IRF5 Hyperactivation in SLE as a Driver of Disease Risk and Pathogenesis

Betsy Barnes, Ph.D., Center for Autoimmune, Musculoskeletal, and Hematopoietic Diseases, The Feinstein Institute for Medical Research

Systemic lupus erythematosus (SLE) is an autoimmune disorder that causes inflammation in numerous tissues within the body and a wide range of symptoms including fatigue, arthritis, headaches, organ damage, seizures, and strokes. Because of the variety of symptoms a patient with SLE may experience, it is often difficult to diagnose and treat. This issue is exacerbated by the fact that the physiological mechanisms underlying SLE are still largely unknown. While the specific causes of SLE remain unclear, genetic risk factors and environmental stressors have been identified that are known to contribute to the disease's development and progression.

Previous research has suggested that there is a genetic association between certain genetic variants of interferon regulatory factor 5 (IRF5), a protein that controls inflammatory and immune responses, and SLE. Specific variants are associated with elevated IRF5 expression and pro-inflammatory cytokine production. The variants are strongly associated with an increased risk of developing SLE and contribute to what is referred to as the *IRF5*-SLE risk haplotype. In 2010 and 2012, Dr. Betsy Barnes and her colleagues investigated the relationship between the risk haplotype and IRF5 expression and activation. The results of her two studies showed that IRF5 expression was enhanced by the risk haplotype and that IRF5 was significantly activated in specific immune cells of patients with SLE.[1,2] Taken together, these results suggest that genotype is not the sole driver of IRF5 activation in SLE. Further research is required to understand how IRF5 activation contributes to SLE disease symptoms and severity.

In FY17, Dr. Barnes was awarded an LRP Impact Award to build upon her previous work and investigate whether IRF5 hyper-activation is a driver of SLE onset and severity and whether or not its inhibition will mediate protective effects in a spontaneous murine lupus model. To answer these questions, Dr. Barnes will investigate three major hypotheses: (1) whether the IRF5 risk haplotype is cell-specific and drives hyperactivation of IRF5; (2) whether inhibition of IRF5 activation will mediate protection against the IRF5 risk haplotype and SLE disease severity; and (3) whether treatment of a spontaneous lupus murine model with an inhibitor of IRF5 activation will improve disease outcomes long-term. The results of this project have the potential to make a significant impact on the lives of individuals living with lupus. In addition to providing functional and mechanistic insight into SLE progression, the findings of this project will provide clarity into the molecular drivers of SLE disease onset and mortality. Of critical importance to lupus patients, this study may provide the first evidence to support targeting IRF5 hyperactivation as a novel treatment for SLE.

References

[1] Feng D, Stone RC, Eloranta ML, et al. 2010. Genetic Variants and Disease-Associated Factors Contribute to Enhanced Interferon Regulatory Factor 5 Expression in Blood Cells of Patients With Systemic Lupus Erythematosus. *Arthritis Rheum.* 62(2):562-573. doi: 10.1002/art.27223

[2] Stone RC, Feng D, Deng J, et al. 2012. Interferon Regulatory Factor 5 Activation in Monocytes of Systemic Lupus Erythematosus Patients is Triggered by Circulating Autoantigens Independent of Type I Interferons. *Arthritis Rheum.* 64(3):788-798. doi: 10.1002/art.33395

"Consumer reviewers provide a unique perspective in peer review that is both rewarding and essential to the process. I think my role there is to provide the layman report of how each study will affect the patient."

Molly McCabe, Lupus Research Alliance, Consumer Peer Reviewer

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