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Engineered enzyme prevents lupus in mice, shows promise for patients with the disease

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An enzyme-based treatment developed by Yale researchers mitigated autoimmunity and reduced death rates in both genetic and non-genetic mouse lupus models, a new study reveals.

The findings, which were published June 18 in the journal *JCI Insight*, represent a significant advancement in autoimmune disease therapeutics, said the researchers. Lupus is a chronic autoimmune disease that can cause inflammation and pain in any part of the body.

"Although lupus was recently recognized as among the leading causes of death in young females in the U.S., we don't really understand what causes the disease, which affects up to 1.5 million Americans," said Dr. Demetrios Braddock, associate professor of pathology at Yale School of Medicine and lead author of the study.

"We were interested in an ultra-rare form of lupus reported in only 40 patients worldwide who lacked an enzyme called DNAse1L3. Because all children without the enzyme developed lupus, we thought it could tell us about both disease mechanisms and new therapies."

Weekly doses of the long-acting enzyme—which was engineered to replicate the activity of DNAse1L3 and be absorbed and used by the body—prevented autoimmunity from developing in a mouse model of genetic lupus for a year, essentially halting lupus development. When dosing started after the initiation of the disease, the enzyme reduced death rates.

Although initially conceived for a rare pediatric population, the therapeutic—which was developed in the Braddock lab by lead scientist Paul Stabach—may also be effective in many more patients with lupus. This includes an estimated 35,000 patients with a pathogenic variant of DNAse1L3 that reduces the enzyme's activity by about 80%. It also includes patients with lupus who have autoantibodies that neutralize DNAse1L3, which were characterized in the laboratory of Dr. Felipe Andrade at Johns Hopkins University in 2023. Andrade is co-author of the new study.

"We recently became aware that about one-third of patients with lupus have autoantibodies that block the function of DNAse1L3, mirroring patients who were born without the enzyme," Andrade said. "Patients with antibodies to DNAse1L3 exhibited a more severe form of lupus with significant damage to organ systems, such as the kidneys. Although these patients may benefit from DNAse1L3 replacement therapy, the presence of autoantibodies precludes this option."

To determine whether the new enzyme therapeutic could benefit the patients studied by Andrade, the Braddock lab sent him the human version of its enzyme for testing. Andrade's lab found no evidence that the enzyme was recognized by neutralizing autoantibodies present in patients with lupus.

"The lack of recognition by neutralizing autoantibodies in the lupus population to our potential therapy bodes well that our approach would also help these patients," Braddock said.

More information: Paul R. Stabach et al, A dual-acting DNASE1/DNASE1L3 biologic prevents autoimmunity and death in genetic and induced lupus models, *JCI Insight* (2024). DOI: 10.1172/jci.insight.177003

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