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For Immediate Release

Stopping asthma in its tracks

New therapeutic "cocktails" may provide long-lasting relief for treatment-resistant asthma and other immune system inflammatory diseases

LA JOLLA, CA—Current asthma treatments don't work in all patients, and they don't provide long-term relief from potentially deadly asthma attacks.

Scientists at La Jolla Institute for Immunology (LJI) are advancing a new kind of therapy. According to a recent study published in the *Journal of Allergy and Clinical Immunology*, their approach holds promise for providing long-lasting relief for people with asthma—and it may be useful for dampening immune inflammation in general.

The researchers have developed two therapeutic "cocktails" to stop immune cells from overreacting to allergens. The cocktails inhibit key molecules (called ICOSL, OX40L, and CD30L) that they found allow specialized tissue-resident memory T cells to stay active and maintained in high numbers in tissues. Without these molecules, the T cells can't trigger asthma attacks and do not persist to trigger future asthma exacerbations.

Even better, there are two effective versions of these cocktails. The researchers demonstrated that they could treat a mouse model of severe allergic asthma using either a combination of an ICOSL and OX40L inhibitor—or an ICOSL and CD30L inhibitor.

The researchers are hopeful that these two cocktails may one day give doctors the flexibility to help patients with different forms of allergic asthma.

"If we can target these molecules in human patients, they might be able to develop long-lasting tolerance to allergens," says study first author LJI Instructor Gurupreet Sethi, Ph.D., who led the study with support from LJI's Tullie and Rickey Families SPARK Awards for Innovations in Immunology.

"This study gives us insight into what could be two terrific options for helping asthma patients, but also might be applicable to other inflammatory diseases as well as autoimmune diseases" adds LJI

Professor Michael Croft, Ph.D., senior author of the new study and a member of LJI's Center for Autoimmunity and Inflammation.

Funded entirely through philanthropy, The Tullie and Rickey Families SPARK Awards for Innovations in Immunology program follows a collective funding model. For Sethi, project support actually came directly from program co-benefactor and LJI Board Director David M. Rickey, as well as his family through The Brenda and Dave Rickey Foundation Charitable Trust. Beyond initial funding, the program also offers winner cohorts the opportunity to compete for follow-on investment. Among his cohort, Sethi was selected for the competitive second round of funding—once again made possible by the generosity of The Brenda and Dave Rickey Foundation.

Researchers track down key culprits behind asthma attacks

The new research builds on a 2022 study from the Croft Lab, which showed that blocking the T cell "co-stimulatory" molecules OX40L and CD30L at the same time could reduce asthma attacks in mice. This was an encouraging finding, but Croft suspected that additional co-stimulatory molecules contributed to asthma attacks.

The team uncovered clues in single-cell sequencing data, which revealed a lot of variation, or "heterogeneity," in T cells from human asthmatic lungs. Some of the T cells played bigger roles in lung inflammation—and they didn't all express the receptors for OX40L and CD30L in the same way.

With funding from LJI's Tullie and Rickey Families SPARK Awards for Innovations in Immunology, Sethi developed a mouse model with the same variety of T cells seen in asthmatic human lungs. Sethi was especially interested in investigating different subtypes of memory T cells. Memory T cells normally help the body by "remembering" past threats, such as viruses. But memory T cells pose a big problem for people with asthma, as well as being drivers of other inflammatory diseases.

"Memory T cells in the lungs are responsible for a patient's long-lasting, exaggerated response to an allergen," says Sethi.

Sethi discovered that a subset of memory T cells—called "tissue-resident memory T cells"—are in part controlled by another molecule, called ICOSL, that also serves as an important co-stimulatory molecule for these T cells during asthma exacerbations.

The researchers then tried blocking ICOSL activity alongside either OX40L and CD30L. Sethi found that around 50 percent of tissue-resident memory T cells remained in the lungs following treatment with a combination of OX40L and CD30L inhibitors. In contrast, only around 10 to 20 percent of

tissue-resident memory T cells persisted after treatment with combinations of ICOSL and OX40L or ICOSL and CD30L inhibitors.

This big reduction in allergic tissue-resident memory T cells made a difference. Mice were protected against asthma exacerbations for weeks after either treatment, even when they were challenged repeatedly with an asthma trigger. It was like the researchers had erased the immune system's memory of the asthma-causing allergen.

Next steps: Targeting T cells to treat autoimmune diseases

Sethi says it will be important to investigate ways to further reduce the remaining 20 percent of allergic tissue-resident memory T cells in the lungs. He also hopes to advance both therapeutic "cocktails" to clinical studies in people with asthma.

The findings may prove important beyond asthma. As Croft explains, researchers have found that the same tissue-resident memory T cells accumulate in patients with a wide range of diseases. For example, these cells gather in the brain in patients with multiple sclerosis, in the skin in patients with atopic dermatitis, and in the gut in patients with inflammatory bowel disease.

"The idea is that if you can limit the number of memory T cells that remain in those tissues, you should be able to limit the extent of the inflammatory response, and you might be able to prevent future disease exacerbations. At present no approved drug treatment has been able to do this," says Croft. "The combination therapies that we have discovered might then pave the way for durable as well as effective treatments for multiple immune system diseases."

Additional authors of the study, "ICOSL, OX40L, and CD30L Control Persistence of Asthmatic CD4 Trm cells," include Ashmitaa Logandha Ramamoorthy Premlal and Ashu Chawla.

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