

Experimental treatment approach counters allergic asthma without weakening flu defenses

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Blocking the action of calcium signals in immune cells suppresses the

most common form of asthma, but without compromising the body's defenses against flu viruses, a new study finds.

Led by researchers at NYU Grossman School of Medicine, experiments showed that removing the gene for a [calcium channel](#)—specifically the calcium release-activated calcium (CRAC) channel made up of ORAI1 proteins—thoroughly reduced asthmatic [inflammation](#) in the lungs of mice caused by house dust mite feces, a common cause of allergic [asthma](#). Blocking signals sent through this channel with an investigational new drug called a CRAC channel inhibitor had a similar effect.

The study revolved around the use of charged particles, mainly calcium, by human cells to send signals and flip biological switches. When triggered—whether by viral proteins or allergens—immune cells called T cells open channels in their outer membranes, letting calcium rush in to turn on signaling pathways that control [cell division](#) and secretion of cytokine molecules that help T cells communicate with other immune cells.

Past work had found that CRAC channels in T cells regulate their ability to multiply into armies of cells designed to fight infections caused by viruses and other pathogens.

Published online in *Science Advances* on October 7, the new study showed that the CRAC channel inhibitor reduced allergic asthma and mucus build-up in mice without sabotaging their immune system's ability to fight influenza, a main worry of researchers seeking to tailor immune-suppressing drugs for several applications.

"Our study provides evidence that a new class of drugs that target CRAC channels can be used safely to counter allergic asthma without creating vulnerability to infections," says senior study author Stefan Feske, MD,

the Jeffrey Bergstein Professor of Medicine in the Department of Pathology at NYU Langone Health. "Systemic application of a CRAC channel blocker specifically suppressed [airway inflammation](#) in response to allergen exposure."

[About 25 million Americans](#) suffer from asthma, with repeated episodes of wheezing, breathlessness, chest tightness, and coughing, according to the Centers for Disease Control and Prevention. The majority of those have asthma related to inhaled allergens, say the study authors.

Targeting calcium channels

Allergic asthma is characterized by increased type 2 (T2) inflammation, which involves a subset of T cells called T helper (Th) 2 cells, say the study authors. Th2 cells produce cytokines that play important roles in both normal immune defenses, and in disease-causing inflammation that occurs in the wrong place and amount. In allergic asthma, cytokines promote the production of an antibody type called IgE and the recruitment to the lungs of inflammation-causing [immune cells](#) called eosinophils, the hallmarks of the disease.

In the new study, the research team found that genetic deletion of ORAI1 in T cells, or treatment of mice with the CRAC channel inhibitor CM4620, thoroughly suppressed Th2-driven airway inflammation in response to house dust mite allergens. CM4620 is under development by the company CalciMedica, which partnered with NYU Langone in the current study, and is in phase 2 clinical trials for COVID-19 associated pulmonary inflammation and [acute pancreatitis](#).

Treatment with CM4620 significantly reduced airway inflammation when compared to an inactive control substance, with the treated mice also showing much lower levels of Th2 cytokines and related gene expression. Without calcium entering through CRAC channels, T cells

are unable to become Th2 cells and produce the cytokines that cause [allergic asthma](#), the authors say.

Conversely, ORAI1 gene deletion, or interfering with CRAC channel function in T cells via the study drug, did not hinder T cell-driven antiviral immunity, as lung inflammation and immune responses were similar in mice with and without ORAI1.

"Our work demonstrates that Th2 cell-mediated airway inflammation is more dependent on CRAC channels than T cell-mediated antiviral immunity in the lung," says study co-first author Yin-Hu Wang, Ph.D., a post-doctoral fellow in the Feske lab. "This suggests CRAC channel inhibition as a promising, potential future treatment approach for allergic airway disease."

More information: Yin-Hu Wang et al, Distinct roles of ORAI1 in T cell-mediated allergic airway inflammation and immunity to influenza A virus infection, *Science Advances* (2022). [DOI: 10.1126/sciadv.abn6552](https://doi.org/10.1126/sciadv.abn6552). www.science.org/doi/10.1126/sciadv.abn6552

Provided by NYU Langone Health

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