Press Release

April 11, 2024

Dear All

University of Yamanashi
Alivexis, Inc.

Joint Research on Novel Anti-Allergic Disease Drug Candidate Published by Alivexis, Inc. and University of Yamanashi

Alivexis, Inc., and the University of Yamanashi announce the publication of a joint research article entitled “A highly selective KIT inhibitor MOD000001 suppresses IgE-mediated mast cell activation”, published in JACI: Global, an open-access online journal from the American Association of Allergy, Asthma and Immunology (AAAAI).
The research, led by Associate Professor Yuki Nakamura and Professor Atsuhito Nakao of the Department of Immunology, Graduate School of Medicine, University of Yamanashi, in collaboration with Alivexis, was performed on a new small molecule compound, MOD000001, to investigate its use as a treatment for allergic diseases, including hay fever, asthma, and chronic hives. This compound targets a cellular receptor molecule called KIT, thereby suppressing the activation and reducing the number of mast cells, which are the root cause of allergy symptoms. In the published study, administration of MOD000001 not only suppressed mast cell activation but also reduced the survival of mouse and human primary mast cells and alleviated symptoms in a mouse model of skin allergic reaction. Currently, Alivexis is further optimizing similar compounds for early clinical application as an oral anti-allergy medication. The paper was published in JACI: Global on April, 2nd.

Summary

Background:

Allergic diseases such as hay fever (allergic rhinitis), asthma, food allergies, atopic dermatitis, and hives (urticaria) occur when a particular type of immune cell known as mast cells are activated by allergens in the environment. Mast cells then release molecules including histamine, triggering inflammation, itching, and other allergic symptoms. Existing anti-allergic drugs such as antihistamines and corticosteroids target and inhibit the reaction against these molecules. However, these treatments only provide symptomatic relief because they do not directly inhibit the activation of mast cells by allergens, thus allergic symptoms return quickly after stopping medication.
Mast cell activity and survival are regulated by a receptor molecule called KIT, which is expressed on the surface of mast cells. The research groups at University of Yamanashi and Alivexis hypothesized that specific suppression of KIT function would reduce the activity and number of mast cells in the body, potentially leading to the development of a new anti-allergic medication. Since the number of mast cells are increased in the nasal mucosa, bronchi, skin, and intestines of patients with allergic diseases, reducing the number of mast cells in those tissues could achieve strong and long-lasting relief of allergy symptoms. Although several KIT inhibitors have been developed to date for the treatment of diseases such as leukemia and cancer, these drugs are not highly specific to KIT and come with many side effects.

Results of this study:
The research group used a proprietary drug discovery platform, which includes molecular dynamics simulations using state-of-the-art supercomputers, to accurately and rapidly perform compound selection through predicting binding affinity of the compounds to target proteins, and subsequently identified several small molecule compounds that selectively bind to the KIT receptor. Through in vitro experiments, they further identified MOD000001 as a strong selective inhibitor of KIT enzyme activity, which plays an important role in the activity and the survival of mast cells.
Further studies using mouse bone marrow-derived mast cells and peripheral blood hematopoietic stem cell-derived human mast cells showed that MOD000001 significantly and specifically inhibited the activation and the survival of mast cells induced by SCF (a molecule that binds to and activates the KIT receptor) and allergens, as well as the migration activity of mast cells. In addition, studies using a mouse model of chronic urticaria showed that oral administration of MOD000001 significantly alleviated allergy-induced urticaria. Furthermore, long-term oral administration of MOD000001 was confirmed to reduce the number of mast cells in mouse skin. No adverse effects were observed in mice treated with MOD000001 even for a long period of time.

Significance of this study's results:
Until now, treatments for allergic diseases have mainly focused on the mediator molecules of allergic reaction produced by immune cells such as mast cells, rather than directly targeting mast cells themselves. Therefore, MOD000001 can be considered as a compound which tackles allergy in a new and distinct way. Since this compound has higher specificity for KIT than currently available KIT inhibitors, it is expected to have a better safety profile. Additionally, since MOD000001 affects the mast cell survival mechanism, the number of mast cells in the body should decrease, resulting in a more potent and sustained reduction in allergic reactions, anti-allergic effects in patients who do not respond to existing drugs, and reduction in the dosage of existing anti-allergy drugs.
Alivexis, Inc. has already identified and is evaluating optimized oral KIT-specific inhibitors based on MOD000001, aiming for early clinical application as anti-allergy drugs. In addition to delivering a new allergy therapy, they are also considering the possible application to other diseases that involve mast cells, such as cancer, arteriosclerosis, fibrosis and others.

[Publication Information]
JACI: Global (Open access journal of the American Academy of Allergy, Asthma & Immunology)
[Title]
A highly selective KIT inhibitor MOD000001 suppresses IgE-mediated mast cell activation
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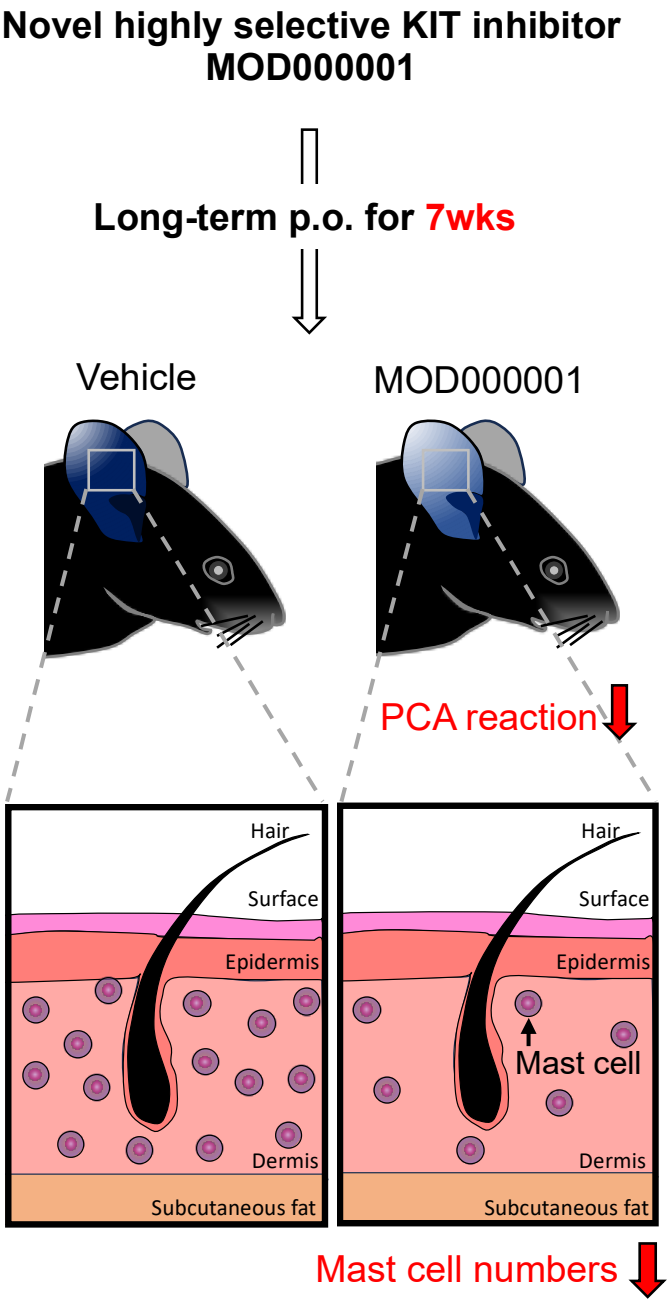
[DOI] https://doi.org/10.1016/j.jacig.2024.100249

[Reference diagram]



The novel KIT-specific inhibitor MOD000001 strongly suppresses allergic reactions even with a single oral dose. When orally administered to mice for 7 weeks, as shown in the figure, the number of mast cells in the skin significantly decreases. Furthermore, the PCA reaction (a mouse model of hives, which evaluates the intensity of plasma leakage (symptoms) caused by allergen-induced mast cell activation by measuring the amount of blue dye leakage administered intravenously prior to mast cell activation. A darker shade of blue indicates stronger symptoms) is alleviated.

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