# UCSD Research May Lead to Targeted Treatment for Asthma Sufferers

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The bronchial tubes of a patient with severe asthma can become scarred due to repeated episodes of allergic inflammation in the airways. The scarring results in blocked airways, excessive production of mucus, and shortness of breath.

Researchers at the University of California, San Diego (UCSD) School of Medicine have discovered that when a single gene – IKK beta – is selectively inactivated in the membrane-lining cells of the bronchial tubes of mice that later inhale allergens, such scarring, mucus production and airway inflammation is significantly reduced.

David H. Broide, M.B.,Ch.B., Professor in UCSD's Department of Medicine, and Michael Karin, Ph.D., Professor in UCSD's Department of Pharmacology and the Laboratory of Gene Regulation and Signal Transduction, will publish their findings in the December 6 issue of the *Proceedings of the National Academy of Sciences.*

"This finding is significant because it suggests that if we can produce a drug that inhibits IKK beta – for example, a drug that is inhaled to target only the patient's bronchial tubes and not their immune cells – then the scarring, inflammation, and mucus production in asthma could be significantly reduced," said Broide.

IKK beta is a master regulator gene that is expressed in cells throughout the body including cells lining the bronchial tubes and immune cells, which are needed to fight infection. Through its effects on the transcription factor NF-kB, IKK beta also regulates the expression of many additional genes important to the induction of airway inflammation in asthma.

Using gene-targeting strategies, the UCSD team selectively inactivated the IKK beta gene only in the mouse airway membrane-lining cells, called epithelial cells, but not in other cells outside the airway that also express the gene, such as immune cells. The researchers were able to demonstrate that mice lacking the IKK beta gene in these lining cells had significantly less airway

inflammation, mucus production and scarring of bronchial tubes after repeatedly inhaling an allergen.

The researchers set out to explore selective inactivation of IKK beta in the airway because blocking IKK beta throughout the body to prevent the damaging effects of asthma could also suppress the patient's immune system, resulting in infections.

"An inhaled IKK beta antagonist could theoretically be designed that would not be absorbed into the blood stream, where it would affect the patient's immune cell function. Such a selective targeting of the drug to the airway would be able to reduce airway inflammation, mucus production, and scarring of the bronchial tubes, with reduced potential for negative side effects." said Broide.

While only about 10 percent of asthma patients have severe symptoms which lead to scarring of the bronchial tubes, new therapies to prevent scarring are needed, since these patients account for about half of the health costs associated with asthma. As patients with Chronic Obstructive Pulmonary Disease also suffer from mucus production and scarring of their lungs, an inhaled IKK beta antagonist could potentially prove beneficial in such patients.

This research was funded by a National Institutes of Health grant from the National Institute of Allergy and Infectious Diseases, and a grant from the Sandler Program for Asthma Research. Additional contributors to the paper include members of the Broide Laboratory, Jae Youn Cho, M.D., Ph,D,; Marina Miller, M.D., Ph.D.; Taylor Doherty, M.D.; Kirsti McElwain, B.S.; and Shauna McElwain, B.S., and Toby Lawrence, Ph.D. a visiting scientist in the Karin laboratory.

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