

Novel molecules to combat asthma and COVID-related lung diseases discovered

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A study designed to study how the immune system impacts gut bacteria—has led to the extraordinary discovery of two molecules that can not only provide profound protection in experimental models of asthma but can also substantially reduce the severity of an attack.

Neither of these molecules, one of which is already commercially available as a [dietary supplement](#), were previously known to have an effect on asthma—and they also appear, from animal studies, to have a role in treating the respiratory illness that is prevalent, and often fatal, in people with serious COVID-19.

The researchers aim to test one of the molecules in a clinical trial in 2021 in asthmatics.

As further evidence that these two molecules could

potentially protect against asthma the Monash University researchers found, through studying the literature, that these metabolites are present in higher amounts in two studies of children without asthma compared to those with the disease, according to Professor Benjamin Marsland from the Monash University Central Clinical School, whose paper is published today in *Nature Immunology*.

Asthma is one of the most common major non-communicable diseases and it impacts 300 million people globally. The global asthma treatment market size stood at over \$18 billion US in 2019.

The team led by VESKI innovation fellow, Professor Marsland, wanted to understand how the [immune system](#) impacts the [gut microbiome](#). While it is known that [gut bacteria](#) have an effect on the immune system, "how the immune system influences the gut microbiome has to date been under studied," he said.

Studying a mouse that had a limited immune system, consisting of a single type of antibody, the researchers found the gut microbiome was changed. By transferring these gut bacteria into 'normal' mice they could identify which bacteria had an impact on the mouse immune system.

In what was an enormous surprise the researchers found that the production of a particular gut bacteria by-product, called p-cresol sulfate (PCS), led to a "profound and striking protection against asthma." Part of the serendipity of the finding is that Professor Marsland's area of expertise is in the immunology of asthma, though he suspects this metabolite may have a role in other inflammatory diseases.

The researchers found that the PCS was produced by enhanced bacterial metabolism of L-tyrosine; a well-known amino acid found in dietary supplements aimed at improving attention and alertness.

"We found that giving mice either L-tyrosine or PCS, provided significant protection against lung inflammation. PCS travels all the way from the gut, to the lungs, and acts on epithelial cells lining the airways to prevent the allergic asthma response"

The researchers also tested the metabolites in animal models of acute respiratory distress syndrome (ARDS), and found it to be protective. ARDS is a common killer of people with serious COVID-19.

While L-tyrosine has a long history of use in the clinic, as mentioned in dietary supplements, its potential use as a therapy could be fast tracked into [clinical trials](#) because it is known to be safe. Professor Marsland commented "It's very important that a thorough clinical study is performed in order to determine whether L-tyrosine is effective in people with asthma, and for us to determine what is the correct dose and treatment regime."

PCS however is known to be in high levels in people with chronic kidney disease and it's suspected to be toxic because of these patient's inability to clear it. The research group has started developing a form of PCS that is a potent protector against [asthma](#) without the potential toxic side effects.

More importantly the scientists have found that inhaling PCS provides a direct protective effect against lung inflammation, opening the way for a novel inhaled preventive therapy.

More information: Microbial metabolism of l-tyrosine protects against allergic airway inflammation, *Nature Immunology* (2021). DOI: [10.1038/s41590-020-00856-3](https://doi.org/10.1038/s41590-020-00856-3) , www.nature.com/articles/s41590-020-00856-3

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