New compound shows great potential for patients with neutrophil-associated inflammation

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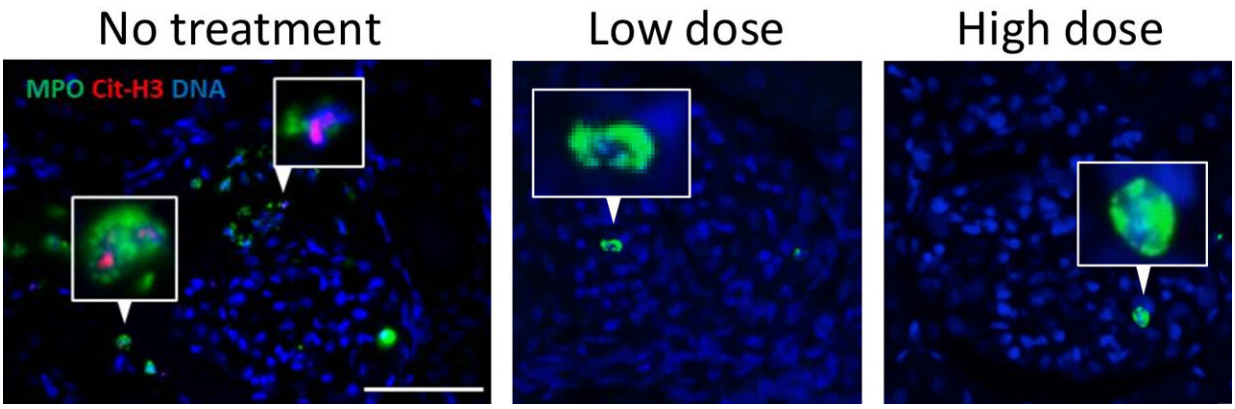


Improvement effects of MOD06051. In the glomeruli of the disease group, neutrophils (green) that are positive for the NETs marker citrullinated histone H3 (Cit-H3; red) are observed. Cit-H3 was not observed in neutrophils infiltrating in the low-dose and high-dose treatment groups. (Yuka Nishibata, et al. *Nature Communications*. August 22, 2024). Credit: (Yuka Nishibata, et al. Nature Communications. August 22, 2024)

A newly developed compound that reduces harmful inflammation caused by overactive neutrophils in rats shows great potential as a safer treatment for various inflammatory diseases in humans.

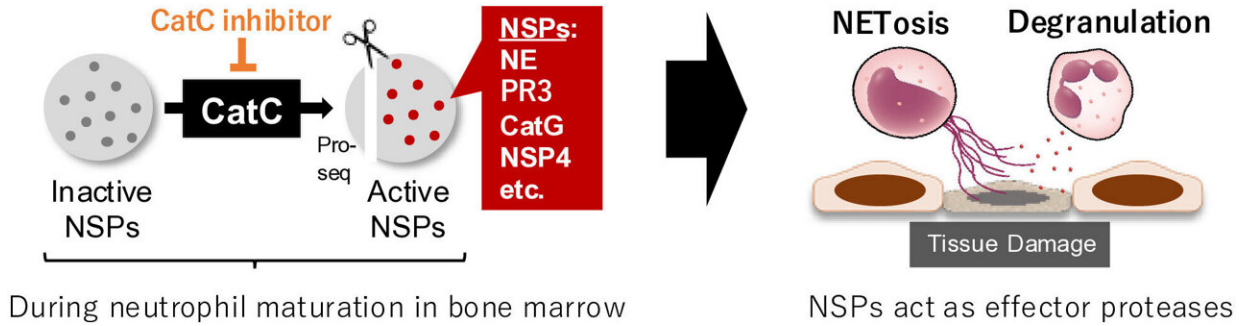
Neutrophils are the most abundant type of white blood cells in the

human body, and they play a crucial role in immune response. These immune cells help fight infections by engulfing pathogens and releasing enzymes that kill the invaders.

But although they're essential for fighting infections, neutrophils can also become overactive, leading to various inflammatory diseases. When they are activated by infection, neutrophils can release neutrophil extracellular traps (NETs), web-like structures consisting of DNA and proteins, which trap and kill pathogens as a part of the normal host defense mechanism. However, too much NET formation can significantly damage tissues, thus contributing to inflammation.

A team of researchers from Hokkaido University and Alivexis, Inc., has investigated a recently-developed drug candidate, MOD06051, which reduces harmful inflammation in rat models by targeting neutrophils. The results of their joint research appear in *Nature Communications*.

"We found that MOD06051 works as a selective inhibitor for Cathepsin C (CatC), a key regulator that activates multiple enzymes inside of neutrophils known as neutrophil serine proteases (NSPs)," explains Yoh Terada, co-author from Alivexis, Inc. "One such NSP is neutrophil elastase, an enzyme involved in killing pathogens but also an essential factor for NET formation."



Blocking the enzyme CatC can reduce harmful neutrophil activity and alleviate diseases caused by overactive neutrophils. (Yuka Nishibata, et al. *Nature Communications*. August 22, 2024). Credit: (Yuka Nishibata, et al. Nature Communications. August 22, 2024)

The scientists found that inhibiting CatC reduces the active form of neutrophil elastase and decreases the ability of neutrophils to form NETs. Excessive NET formation has been linked to several diseases, including vasculitis, lupus, rheumatoid arthritis, and diabetes.

"When we tested the compound in rats that have a specific type of vasculitis, it decreased the disease severity, which was evident by reduced inflammation and damage in the blood vessels, especially in their kidneys and lungs," says Professor Akihiro Ishizu, who led the study.

"Our findings suggest that CatC inhibition shows promise as a new treatment strategy to reduce neutrophil overactivation and improve conditions in diseases where overactive neutrophils and excessive NET formation play a critical role. This approach differs from current treatments that may have broader immunosuppressive effects."

Current treatments for inflammatory diseases often involve the use of glucocorticoids and immunosuppressive drugs which suppress the immune system's activity as a whole and can lead to secondary immunodeficiency, increasing the risk of opportunistic infections. By specifically targeting the activation of multiple NSPs through CatC inhibition without broadly suppressing the immune system, MOD06051 potentially offers a safer alternative that could reduce the risk of infections and other side effects.

These findings pave the way for further research and clinical trials to evaluate the safety and efficacy of MOD06051 in humans. The team is optimistic that this novel approach holds the promise of providing safer and more effective therapies for patients around the world suffering from a variety of inflammatory diseases, improving their quality of life.

More information: Cathepsin C inhibition reduces neutrophil serine protease activity and improves activated neutrophil-mediated disorders, *Nature Communications* (2024). DOI: 10.1038/s41467-024-50747-6

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