

Serious flu damage prevented by compound that blocks unnecessary cell death

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As lung cells are killed by the influenza virus, they burst open, releasing molecular signals that trigger the immune cells that can combat the infection. This strategy can be an important red flag that something is

wrong; however, if one cell death response, called necroptosis, continues unchecked, it can cause life-threatening injury to lung tissue.

In a [study](#) published April 10 in the journal *Nature*, Tufts University School of Medicine scientists and collaborators present a newly developed compound capable of reversing the course of infection in mice by blocking necroptosis.

There are currently few therapeutic options available to reverse the course of a serious flu infection other than to manage symptoms until the body can combat the virus on its own. With prior evidence showing that lung injury can be caused by influenza-induced necroptosis, the researchers showed that a compound called UH15-38 can safely and efficiently block the key receptor in [lung cells](#) undergoing necroptosis without intolerable side effects.

"If you remove necroptosis, you still get restriction of the viral replication without causing the massive damage to the lungs," says Alexei Degterev, an associate professor of developmental, molecular and [chemical biology](#) at Tufts University School of Medicine and a co-corresponding author on the study.

"Necroptosis does not appear to be necessary for restricting a viral activity, so if we can block it, we will be able to protect the host by reducing inflammation in the lungs."

Necroptosis is triggered when a cell under duress activates its receptor interacting [protein kinase](#) 3 (RIPK3) pathway, thereby attracting [immune cells](#) to the area. UH15-38 reduces excessive inflammation by inhibiting the activation of the RIPK3 pathway.

Not only did UH15-38 prove to be well-tolerated in mice, but it successfully prevented any influenza deaths, even when administered up

to five days into the course of an [infection](#).

The researchers note that if the results from the mouse studies extend into further preclinical and [human trials](#), compounds like UH15-38 could potentially address the most severe flu infections as well as other viruses that trigger severe respiratory symptoms. The value of the approach is how it addresses the inflammation that is intended to be protective but can do more harm than good.

"While the worst of COVID-19 may be behind us, the credible expectation is that there will be another pandemic that's going to happen and we need something that is going to protect the host independent of how the host is infected," says Degterev. "This work highlights the possibility of achieving such a goal and renews interest in how [cell death](#) shapes infections."

Tufts University researchers helped organize the study and provided key insights into the UH15-38 inhibitor, but these results would not have been possible without investigators at multiple institutions—including Fox Chase Cancer Center, the University of Houston, and St. Jude Children's Research Hospital—working closely together.

Degterev and his co-collaborators are now pursuing the second generation of these inhibitors. They are also continuing to test how UH15-38 and related compounds can protect against other respiratory diseases. The commercialization of UH15-38 is being managed by Tufts University's Office for Technology Transfer and Industry Collaboration.

More information: Siddharth Balachandran, Necroptosis blockade prevents lung injury in severe influenza, *Nature* (2024). [DOI: 10.1038/s41586-024-07265-8](https://doi.org/10.1038/s41586-024-07265-8).

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