

## Cellular quality-control system identified as a culprit in coronavirus infection

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Color-enhanced scanning electron micrograph of mammalian cells infected with Middle East Respiratory Syndrome coronavirus. Credit: National Institute of



Allergy and Infectious Diseases, NIH

By studying a disease caused by a close cousin of the virus behind COVID-19, a team of scientists has identified a compound that shows potential in easing the symptoms of coronavirus infections.

The team, from the Department of Energy's Pacific Northwest National Laboratory and the University of North Carolina at Chapel Hill, studied the virus that causes Middle East Respiratory Syndrome (MERS), which is caused by a <u>coronavirus</u>. MERS is much less common but much more lethal than COVID-19.

The team set out to learn more about how the virus that causes MERS damages the lungs and harms patients. In <u>laboratory studies</u>, the team analyzed tens of thousands of measurements of proteins, molecular messengers and other signals that occur after infection. They pinpointed a molecular process, part of the body's quality-control machinery, that plays a central role in causing damage from a coronavirus infection.

Then, the team searched a vast database of compounds and identified one—known as AMG PERK 44—that put a halt to virus replication in human tissue in the laboratory. They also found the compound has a strong effect in mice infected with the virus. The compound boosted lung function and reduced lung damage and weight loss in the mice, particularly in male mice.

## The broad fight against respiratory diseases

Battelle, which operates PNNL, and UNC have filed for a patent on the use of a PERK inhibitor to treat coronavirus infections. But the scientists emphasize that it's far too soon to know whether the compound could



help patients. It's not currently used as a drug.

Rather, they say that the results of their study, published in the journal *mBio*, are most useful as part of a broader effort to learn more about respiratory diseases.

"Studies like this help us learn more about how deadly respiratory viruses operate—how they do what they do, why they attack certain parts of the lung and not others," said PNNL virologist Amy Sims, one of two first coauthors of the paper, along with PNNL scientist Hugh Mitchell.

"Studying how these viruses work helps us understand why patients exhibit the symptoms they do and ultimately how to treat or prevent disease," Sims added.

Sims has been studying coronaviruses for more than 20 years. She and her collaborators began the current study eight years ago, before the coronavirus that causes COVID-19 appeared. Years after Sims and colleagues crafted the study, its results could have relevance for the millions of people who have been infected with SARS-CoV-2, the virus that causes COVID-19.

"Consider how fast a vaccine to protect against COVID-19 was created and how quickly new drugs were found to treat the disease," said Sims. "The success wasn't because scientists started from scratch when the virus appeared. They were able to build upon years and years of research understanding how the <u>immune system</u> works and how it responds to coronaviruses. You never know when a certain bit of knowledge will prove crucial in the future."





A veterinarian in Yemen takes a blood sample from a camel, part of a program to help detect diseases like MERS locally and prevent their spread. Credit: Awadh Mohammed Ba Saleh and CDC Public Health Image Library

## **Emergency response—for damaged proteins**

The team's studies led to proteins, molecules that are the workhorses of the body's cells. Proteins carry out myriad functions to keep organisms, like people, alive and well. The body keeps close tabs, making sure that its proteins are intact and functioning.

When the body begins producing proteins that aren't up to standard for



whatever reason, including infection, <u>protein</u>-repair machinery in a cell's endoplasmic reticulum goes into emergency response mode. The organelle can function like a triage center for damaged proteins in times of stress. When it's swamped with misfolded proteins, the unfolded protein response, or UPR, kicks in. The UPR puts a temporary stop to all cellular activity related to making new proteins. This buys time for the cell to make the necessary repairs to misfolded proteins.

If too many proteins are damaged and the protein-repair and folding machinery cannot recover, the system triggers other proteins to kill the cell.

It's this system that the PNNL-UNC team discovered is very active in certain lung cells when the body responds to a MERS infection.

For the current study, the handling of lung tissue and mice was done at UNC, in a laboratory headed by one of the world's top coronavirus researchers, Ralph Baric. Scientists at PNNL measured and interpreted vast amounts of data about molecular messages. Sims worked in the Baric lab while at UNC and joined PNNL early last year; the two institutions have worked together for years.

"Coronavirus infections cause complex disease phenotypes, and new strategies are needed to disentangle which host pathways are contributing to the development of severe, life-threatening outcomes," said Baric.

In addition to Sims and Mitchell, authors from PNNL include Katrina Waters, a senior author of the paper, and Jennifer Kyle, Kristin Burnum-Johnson, Richard D. Smith and Thomas Metz. From UNC, authors include Lisa Gralinski, Mariam Lam, M. Leslie Fulcher, Ande West and Scott Randell, along with senior authors Ralph Baric and Timothy Sheahan.



**More information:** Amy C. Sims et al, Unfolded Protein Response Inhibition Reduces Middle East Respiratory Syndrome Coronavirus-Induced Acute Lung Injury, *mBio* (2021). <u>DOI: 10.1128/mBio.01572-21</u>

## Provided by Pacific Northwest National Laboratory

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