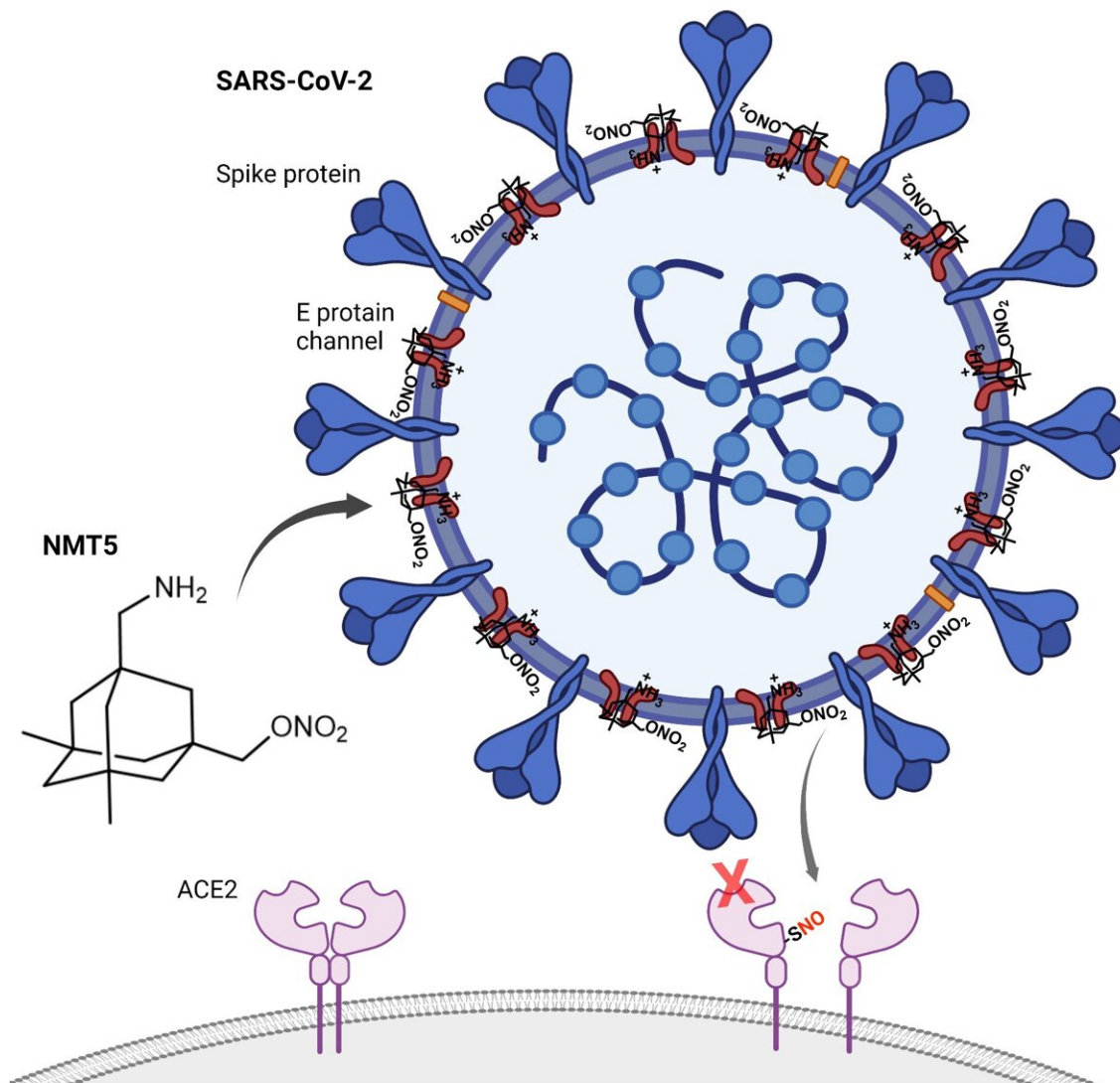


New drug has potential to turn SARS-CoV-2 virus against itself

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A drug developed by Scripps Research scientists prevents SARS-CoV-2 (blue) from binding to ACE2 receptors (pink) to infect human cells. The drug latches on to the virus and then adds a “nitro group” similar to nitroglycerin to ACE2 whenever the drug-coated virus approaches the receptor. Credit: Scripps Research

A new drug designed by scientists at Scripps Research can turn the COVID-19 virus into a harbinger of its own doom.

The [drug](#), NMT5, described in *Nature Chemical Biology* on September 29, 2022, coats SARS-CoV-2 with chemicals that can temporarily alter the human ACE2 receptor—the molecule the virus normally latches onto to infect cells. That means that when the virus is near, its path into [human cells](#) via the ACE2 receptor is blocked; in the absence of the virus, however, ACE2 can function as usual.

"What's so neat about this drug is that we're actually turning the virus against itself," says senior author Stuart Lipton, MD, Ph.D., the Step Family Endowed Chair and Scripps Research professor. "We're arming it with little molecular warheads that end up preventing it from infecting our cells; it's our revenge on the virus."

Before the COVID-19 pandemic, Lipton and his colleagues had long been studying variations of the drug memantine, which Lipton developed and patented in the 1990s for treating [neurological diseases](#) like Alzheimer's. While memantine originated from an anti-influenza drug used in the 1960s, clinicians began investigating it for additional diseases after they noticed a woman with Parkinson's symptoms improved when she took the drug for the flu.

"My team had made these [antiviral drugs](#) better for the brain, and when COVID-19 emerged, we wondered whether we had also, in the process, made any of them better antivirals," says Lipton.

Lipton and his team tested a library of compounds similar to memantine in overall structure but covered with additional pharmacological warheads. They pinpointed the drug candidate designated NMT5 as

having two key properties: It could recognize and attach to a pore on the surface of SARS-CoV-2, and it could chemically modify human ACE2 using a fragment of nitroglycerin as the warhead. The group realized this could turn the virus into a delivery vehicle for its own demise.

In the new paper, Lipton's group characterized and tested NMT5 in isolated cells as well as animals. They showed how NMT5 attaches tightly to SARS-CoV-2 viral particles as the viruses move through the body. Then, they revealed the details of how the drug adds a chemical (similar to nitroglycerin) to certain molecules if it gets close enough. When the virus gets near ACE2 to infect a cell, that translates into NMT5 adding a "nitro group" to the receptor. When ACE2 is modified in this way, its structure temporarily shifts—for about 12 hours—so that the SARS-CoV-2 virus can no longer bind to it to cause infection.

"What's really beautiful is that this only knocks down availability of ACE2 locally when the virus is coming at it," says Lipton. "It doesn't knock down all the function of ACE2 elsewhere in the body, allowing for normal function of this protein."

In cell culture experiments testing how well the Omicron variant of SARS-CoV-2 can attach to human ACE2 receptors, the drug prevented 95% of viral binding. In hamsters with COVID-19, NMT5 decreased virus levels by 100-fold, eliminated blood vessel damage in the animals' lungs, and ameliorated inflammation. The drug also showed effectiveness against nearly a dozen other variants of COVID-19, including alpha, beta, gamma and delta strains.

Most anti-viral drugs work by directly blocking part of a virus—which can pressure the virus to evolve resistance to the drug. Since NMT5 is only using the virus as a carrier, the researchers think the drug is likely to be effective against many other variants of SARS-CoV-2.

"We expect this compound would continue to be effective even as new variants emerge, because it doesn't rely on attacking parts of the [virus](#) that commonly mutate," says Chang-ki Oh, a senior staff scientist and first author of the new paper.

Though they have only studied the compound in animal models, the team is now making a version of the drug to evaluate for [human use](#), while carrying out additional safety and effectiveness trials in animals.

"These exciting findings suggest a new avenue for [drug development](#) that requires drug combinations for effective [pandemic preparedness](#)," says co-author Arnab Chatterjee, Ph.D.

In addition to Lipton, Oh and Chatterjee, authors of the new paper are Tomohiro Nakamura, Nathan Beutler, Xu Zhang, Juan Piña-Crespo, Maria Talantova, Swagata Ghatak, Dorit Trudler, Lauren N. Carnevale, Scott R. McKercher, Malina A. Bakowski, Jolene K. Diedrich, Amanda J. Roberts, Ashley K. Woods, Victor Chi, Anil K. Gupta, Namir Shaabani, Hejun Liu, Ian A. Wilson, Dennis R. Burton, John R. Yates III and Thomas F. Rogers of Scripps Research; Mia A. Rosenfeld, Fiona L. Kearns, Lorenzo Casalino and Rommie E. Amaro of UCSD; and Cyrus Becker of EuMentis Therapeutics, Inc.

More information: Stuart Lipton, Targeted protein S-nitrosylation of ACE2 inhibits SARS-CoV-2 infection, *Nature Chemical Biology* (2022). [DOI: 10.1038/s41589-022-01149-6](https://doi.org/10.1038/s41589-022-01149-6).
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