

Could this Molecule be ‘Checkmate’ for Coronaviruses like SARS-CoV-2?

Powerful drug candidates perform better than Paxlovid against SARS-CoV-2 and could head off future coronavirus pandemics.

April 25, 2025 By Levi Gadye and University of California San Francisco

A team at the University of California San Francisco [UCSF] and Gladstone Institutes has developed new drug candidates that show great promise against the virus that causes COVID-19 and potentially other coronaviruses that could cause future pandemics.

In preclinical testing, the compounds performed better than Paxlovid against SARS-CoV-2 and the Middle East Respiratory Syndrome (MERS) virus, which periodically causes deadly outbreaks around the world.

“In three years, we’ve moved as fast as a pharmaceutical company would have, from start to finish, developing drug candidates against a totally new pathogen,” said [Charles Craik](#), PhD, UCSF professor of pharmaceutical chemistry and co-corresponding author of the paper, which appears April 23 in [Science Advances](#).

“These compounds could inhibit coronaviruses in general, giving us a head start against the next pandemic,” Craik said. “We need to get them across the finish line and into clinical trials.”

The work was funded by a grant from the National Institute of Allergy and Infectious Diseases (NIAID) to prepare for the next coronavirus epidemic — work that pharmaceutical companies have largely abandoned. But the grant to UCSF has since been terminated by the National Institutes of Health (NIH) and the group’s antiviral drug candidates face an uncertain future.

The discovery came out of [UCSF’s Antiviral Drug Discovery \(AViDD\) Center for Pathogens of Pandemic Concern](#), which funded the work of several hundred scientists at UCSF and beyond. It is one of nine centers that NIAID created in 2022 to bolster the nation’s pandemic preparedness.

From virtual to real-world drug candidates

Three years ago, the UCSF AViDD grant supercharged the efforts of the UCSF Quantitative Biosciences Institute (QBI) [Coronavirus Research Group](#) (QCRG). QCRG, which was founded in 2020 by QBI’s director, [Nevan Krogan](#), PhD, brought together 800 scientists from more than 40

institutions across the world.

From this group, he assembled hundreds of scientists from 43 labs across UCSF, Gladstone Institutes, and a wide range of domestic and international institutions — including the Icahn School of Medicine at Mount Sinai, Northwestern University, the Massachusetts Institute of Technology (MIT), the University of Toronto, the University of Alberta, University College London, Institut Pasteur, and others — and obtained one of the nine AViDD center grants in the country.

“COVID was our wake-up call to apply all our resources and know-how toward new therapies and future pandemic preparedness,” said Krogan, UCSF professor of cellular and molecular pharmacology, co-author of the paper, and a leading expert on the biology of infectious disease. “The AViDD funding, which is now in peril, was poised to help us produce potent and necessary antivirals in record time.”

For the project that led to the new SARS-CoV-2 drug candidates, Craik, who had experience designing drugs against HIV, partnered with the UCSF labs of [Brian Shoichet](#), PhD; [Adam Renslo](#), PhD; [Kliment Verba](#), PhD; and Krogan, as well as [Melanie Ott](#), MD, PhD (Gladstone Institutes).

The group focused on the major protease (MPro), a type of enzyme, that breaks proteins into smaller pieces like a pair of molecular scissors. SARS-CoV-2 uses MPro to trim viral proteins into usable parts, which the virus then uses to replicate in human cells. Viral proteases have often been the target of attempts to make antiviral drugs, most notably for HIV.

Shoichet’s [molecular docking program](#), a virtual system to test how different molecules interact with proteins, helped the team identify a few dozen molecular structures, out of millions, that mildly blocked MPro — a starting point for developing real-world drug candidates.

The Renslo lab then synthesized hundreds of new molecules based on the virtual molecules, which the Craik lab tested against MPro in the laboratory. Tyler Detomasi, PhD, a post-doctoral researcher in the Craik Lab, showed that two molecules named AVI-4516 and AVI-4773 had bonded to the MPro active site. These molecules were a perfect fit for MPro. Fortunately, neither blocked human proteases, which are important for human health.

“This was our lucky break and gave us some very special molecules,” Craik said. “They only react when they’re already inside this viral protease, but not to any of our own human proteases, giving us hope that they could have minimal side effects in people.”

A new generation of effective antivirals

With rising confidence that AVI-4516 and AVI-4773 so effectively blocked MPro, Ott, a virologist, tested them against live SARS-CoV-2, first in petri dishes and then in mice. Ott had tested hundreds of drug candidates against SARS-CoV-2 by this point.

“It’s very challenging to fight viruses in general, let alone SARS-CoV-2, but these new compounds were some of the best, if not the best, we had ever seen, in terms of eliminating infection,” said

Ott, who is a co-corresponding author of the paper.

The two drug candidates looked promising as disease therapies. They potently blocked their target; they traveled efficiently through the body, ensuring they reached their target; and, at least in mice, they appeared safe.

In a tantalizing follow-up experiment, a further-optimized version of the molecules effectively blocked variants of SARS-CoV-2 like Delta, as well as MERS, a related coronavirus that continues to cause small but deadly outbreaks worldwide. The team believes their drug candidates, once shepherded through clinical trials to demonstrate safety in humans, could be kept “on the shelf” ready to fight the next pandemic caused by a coronavirus.

“These compounds are easy to modify and should be easy to manufacture,” Renslo said. “AViDD enabled us to discover important new counter measures for an important class of viral pathogens. It’s critical that we see this project through to clinical studies to ensure we’re better prepared for the next pandemic.”

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