Researchers use live virus to identify 30 existing drugs that could treat COVID-19

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Sumit Chanda, Ph.D., a professor at Sanford Burnham Prebys, gestures to experimental assays that test for compounds that may treat COVID-19. Credit: Sanford Burnham Prebys Medical Discovery Institute

Scientists at Sanford Burnham Prebys Medical Discovery Institute, the University of Hong Kong, Scripps Research, UC San Diego School of Medicine, the Icahn School of Medicine at Mount Sinai and UCLA have identified 30 existing drugs that stop the replication of SARS-CoV-2, the virus that causes COVID-19. Almost all of the drugs are entirely different from those currently being tested in clinical trials, and weren't previously known to hold promise for COVID-19 treatment. The new

candidates expand the number of "shots on goal" for a potential COVID-19 treatment and could reach patients faster than drugs that are created from scratch. The study was placed on bioRxiv (pronounced "bio-Archive"), an open-access distribution service for preprints of life science research.

"We believe this is one of the first comprehensive drug screens using the live SARS-CoV-2 virus, and our hope is that one or more of these drugs will save lives while we wait for a vaccine for COVID-19," says Sumit Chanda, Ph.D., director of the Immunity and Pathogenesis Program at Sanford Burnham Prebys and senior author of the study. "Many drugs identified in this study—most of which are new to the COVID-19 research community—can begin clinical trials immediately or in a few months after additional testing."

Screening a library of known drugs

The drugs were identified by screening more than 12,000 drugs from the ReFRAME drug repurposing collection—a library of existing drugs that have been approved by the FDA for other diseases or have been tested extensively for human safety. ReFRAME was created by Scripps Research with support from the Bill & Melinda Gates Foundation to accelerate efforts to fight deadly diseases. Every compound was tested against the live SARS-CoV-2 virus, isolated from patients in Washington State and China, and the final 30 drugs were selected based on their ability to stop the virus's growth.

"For us, the starting point for finding any new antiviral drug is to measure its ability to block viral replication in the lab," says Chanda. "Since the drugs we identified in this study have already been tested in humans and proven safe, we can leapfrog over the more than half decade of studies normally required to get approval for human use."

Early access to live SARS-CoV-2 virus

Chanda's team partnered with the scientist who discovered the first SARS virus, Kwok-Yung Yuen, M.D., chair of Infectious Diseases at the University of Hong Kong; and Shuofeng Yuan, Ph.D., assistant research professor in the Department of Microbiology at the University of Hong Kong, who had access to the live SARS-CoV-2 virus in February 2020. Together, the labs re-created Chanda's automated high-throughput drug screen in Yuen's lab, where it was used to identify 300 drugs from the ReFRAME library that could keep cells alive despite infection with SARS-CoV-2. These 300 drugs advanced to a second round of testing in Chanda's lab in La Jolla, Calif., where the researchers used molecular tools such as polymerase chain reaction (PCR) and immunofluorescence microscopy to pinpoint 30 compounds that were the most effective at stopping viral replication

New drugs emerge as promising candidates for COVID-19 treatment

Highlights of the scientists' discoveries follow. Each drug or experimental compound requires further evaluation in clinical trials to prove its effectiveness in treating people with COVID-19 before it can be used broadly.

Laura Riva, Ph.D., a postdoctoral research fellow in the Chanda lab at Sanford Burnham Prebys, tests for compounds that may treat COVID-19. Credit: Sanford Burnham Prebys Medical Discovery Institute

- 27 drugs that are not currently under evaluation for COVID-19 were effective at halting viral replication. 17 of these drugs have an extensive record of human safety from clinical studies in non-COVID-19 diseases, including four—clofazimine, acitretin, tretinoin and astemizole—that were previously approved by the FDA for other indications.
- Thus far, six of the 17 were shown to be effective at concentrations, or doses, likely to be effective and tolerable in humans. Four of these six drugs—apilimod, MLN-3897, VBY-828 and ONO 5334—have been tested clinically for diseases including rheumatoid arthritis, Crohn's disease, osteoporosis and cancer.
- In addition to the 27 drug candidates, three drugs currently in clinical trials for COVID-19, including remdesivir and

chloroquine derivatives, were also shown to be effective at stopping the growth of SARS-CoV-2. These results reaffirm their promise as potential COVID-19 treatments and support the continuation of ongoing clinical trials to prove their effectiveness in patients.
- Depending on regulatory guidance, the newly identified drug candidates may proceed directly to COVID-19 clinical trials or undergo further testing for efficacy in animal models.

"Based on the extensive data in this study, we believe the four drugs described above—apilimod, MLN-3897, VBY-825 and ONO 5334—represent the best new approaches for a near-term COVID-19 treatment," says Chanda. "However, we believe that all 30 drug candidates should be fully explored, as they were clearly active and effective at halting viral replication in our tests."

Chanda's team was able to work with the live virus because his laboratory is certified as biosafety level 3, or BSL-3, which means it's equipped with safeguards to protect lab personnel—as well as the surrounding environment and community—from pathogens that can cause serious or potentially lethal disease. The facility was established in 2016 to support Chanda's research on broad-spectrum antivirals—drugs that work against many viruses—for HIV, influenza, Dengue fever and West Nile virus.

Support for the research

"We were only able to generate these rapid results thanks to many years of support from the National Institutes of Health (NIH) and the Department of Defense (DoD), both funded by taxpayers, and the generosity of philanthropists," says Chanda, "This support enabled us to build the infrastructure and teams that were fully trained and ready to go when it was time to do this important work.

We have chosen to release these findings to the scientific and medical community now to help address the current global health emergency," Chanda continues. "The data from this drug screen is a treasure trove; and we will continue to mine the data from this analysis, with a goal to find additional candidate therapies—and combinations of drugs—as they are identified."

More information: Laura Riva et al. A Large-scale Drug Repositioning Survey for SARS-CoV-2 Antivirals, *bioRxiv* (2020). DOI: 10.1101/2020.04.16.044016

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