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Scientists reveal host- SARS-CoV-2 protein targets for drug repurposing

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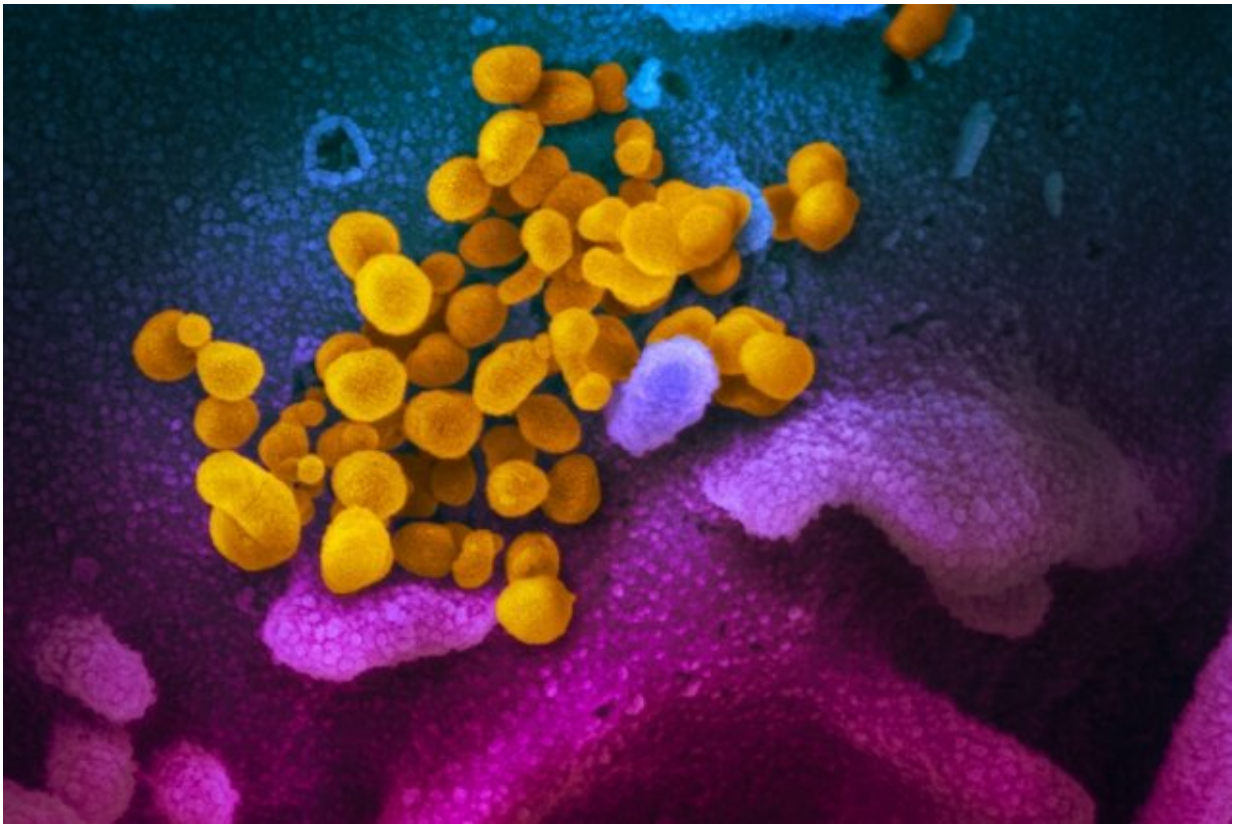

This scanning electron microscope image shows SARS-CoV-2 (yellow)—also known as 2019-nCoV, the virus that causes COVID-19—isolated from a patient, emerging from the surface of cells (blue/pink) cultured in the lab. Credit: NIAID-RML

For the first time, a team of about 100 scientists collaborated to clone

and express 26 of the 29 SARS-CoV-2 proteins in infected human cells, and then they identified hundreds of human proteins associated with each virus protein. These virus-host protein interactions are crucial to the development of coronavirus disease 2019 (COVID-19) in individuals. And so pinpointing these protein interactions could be important to developing new anti-viral drugs or repurposing known drugs to fight COVID-19.

This research, published in *Nature*, was led by scientists at UC-San Francisco and included Bryan L. Roth, MD, Ph.D., the Michael Hooker Distinguished Professor of Pharmacology at the UNC School of Medicine, Xi-Ping Huang, Ph.D., a research associate professor, and YongFeng Liu, Ph.D., a postdoctoral fellow, who worked day and night shifts to complete their work.

After using a technique called "affinity purification mass spectrometry" to identify 332 high-confidence virus-human protein interactions, the researchers identified 66 druggable human proteins and 69 compounds that target these proteins. Twenty-eight of these compounds are already FDA-approved drugs, 12 are in clinical trials, and 28 are preclinical compounds.

The researchers then screened a subset of these compounds in multiple viral assays to find two sets of pharmacological agents with antiviral activity: inhibitors of messenger RNA translation and predicted regulators of two cell receptor proteins called Sigma1 and Sigma2.

"We think some of these already-known agents or yet-to-be created compounds like them—combined with drugs that directly target viral enzymes—are worth investigating as part of a therapeutic regimen to help treat people with COVID-19," said Roth, director of the National Institute of Mental Health Psychoactive Drug Screening Program, which is housed at UNC-Chapel Hill.

The new coronavirus SARS-CoV-2 causes COVID-19 respiratory disease and has infected more than 2 million people, killed more than 200,000, and caused worldwide social and economic disruption. There are no antiviral drugs with proven clinical efficacy, though a drug called remdevisir is in clinical trials. There is no vaccine available, though several are in clinical trials. These efforts are hampered by limited knowledge of the molecular details of SARS-CoV-2 infection, which is why Roth and colleagues collaborated to delineate the host-virus interactions and screen compounds that might target these compounds.

"This was a huge effort led by Nevan Krogan's team at UCSF," Roth said. "It is amazing this team of 100 researchers completed this so fast, given that the genetic sequence of the virus was not available for study until January."

Roth said that targeting the virus-host protein interaction is a proven strategy. For instance, one of the compounds commonly used in the drug cocktail to treat HIV targets such an interaction.

He cautioned, though, that just because several known drugs target the sigma receptors or other proteins associated with SARS-CoV2 doesn't mean they will have a strong anti-viral effect in patients. All experiments for this Nature paper were conducted in vitro in the lab. But understanding these basic biological mechanisms lays important groundwork for investigating compounds that could have a strong effect.

More information: David E. Gordon et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing, *Nature* (2020). DOI: 10.1038/s41586-020-2286-9

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