

# THE CONVERSATION

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There are 20,000 FDA approved drugs. One of them might fight COVID-19, if we can find it. Peter Dazeley/The Image Bank via Getty Images

## COVID-19 treatment might already exist in old drugs – we're using pieces of the coronavirus itself to find them

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Why don't we have drugs to treat COVID-19 and how long will it take to develop them?

SARS-CoV-2 – the coronavirus that causes the disease COVID-19 – is completely new and attacks cells in a novel way. Every virus is different and so are the drugs used to treat them. That's why there wasn't a drug ready to tackle the new coronavirus that only emerged a few months ago.

As a systems biologist who studies how cells are affected by viruses during infections, I'm especially interested in the second question. Finding points of vulnerability and developing a drug to treat a disease typically takes years. But the new coronavirus isn't giving the world that kind of time. With most of the world on lockdown and the looming threat of millions of deaths, researchers need to find an effective drug much faster.

This situation has presented my colleagues and me with the challenge and opportunity of a lifetime: to help solve this huge public health and economic crisis posed by the global

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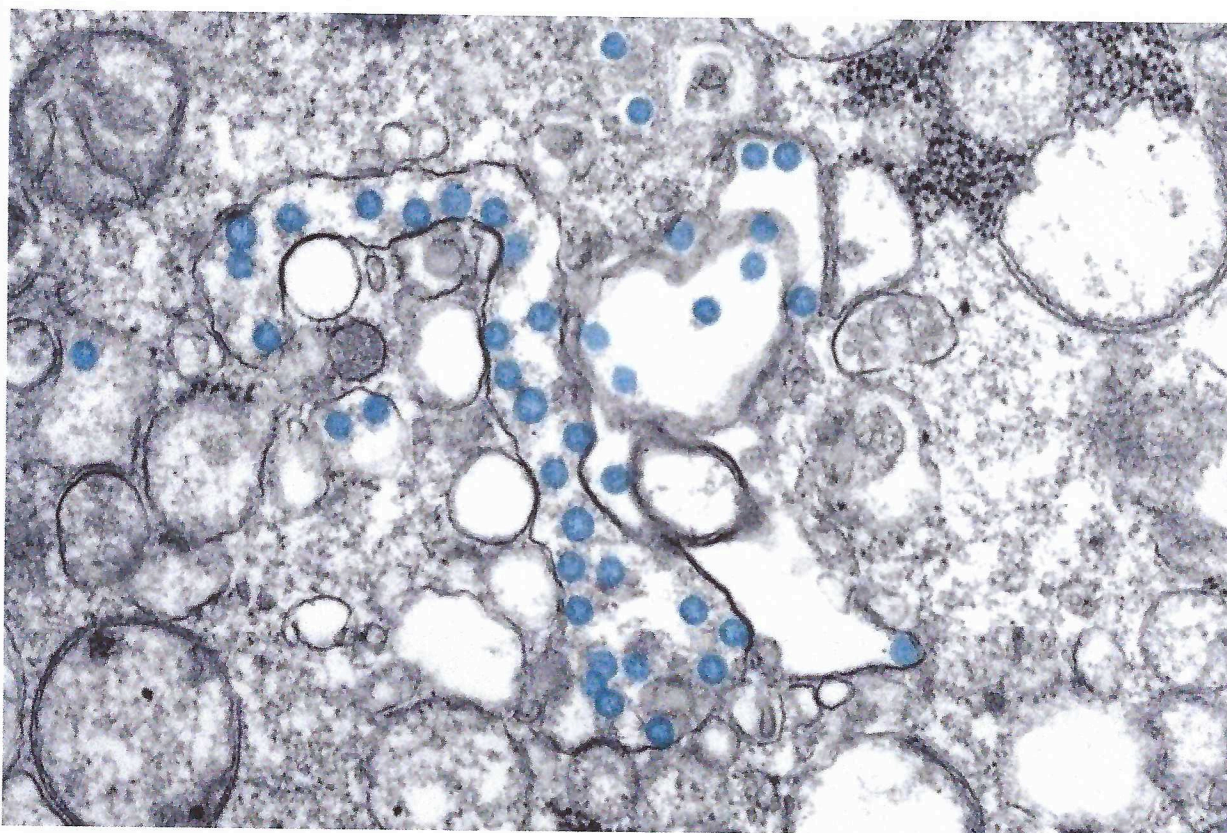
### Languages

- Français
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pandemic of SARS-CoV-2.

Facing this crisis, we assembled a team here at the Quantitative Biosciences Institute (QBI) at the University of California, San Francisco, to discover how the virus attacks cells. But instead of trying to create a new drug based on this information, we are first looking to see if there are any drugs available today that can disrupt these pathways and fight the coronavirus. So far, we've identified 27 FDA-approved drugs that we hope will narrow and speed up the search.

The team of 22 labs, that we named the QCRG, is working at breakneck speed – literally around the clock and in shifts – seven days a week. I imagine this is what it felt like to be in wartime efforts like the Enigma code-breaking group during World War II, and our team is similarly hoping to disarm our enemy by understanding its inner workings.



The coronavirus is simple biologically, but complicated in how it infects a host. CDC/ Hannah A Bullock; Azaibi Tamin

## A stealthy opponent

Compared with human cells, viruses are small and can't reproduce on their own. The coronavirus has about 30 proteins, whereas a human cell has more than 20,000.

To get around this limited set of tools, the virus cleverly turns the human body against itself. The pathways into a human cell are normally locked to outside invaders, but the coronavirus uses its own proteins like keys to open these "locks" and enter a person's cells.

Once inside, the virus binds to proteins the cell normally uses for its own functions, essentially hijacking the cell and turning it into a coronavirus factory. As the resources and mechanics of infected cells get retooled to produce thousands and thousands of viruses, the cells start dying.

Lung cells are particularly vulnerable to this because they express high amounts of the “lock” protein SARS-CoV-2 uses for entry. A large number of a person’s lung cells dying causes the respiratory symptoms associated with COVID-19.

There are two ways to fight back. First, drugs could attack the virus’s own proteins, preventing them from doing jobs like entering the cell or copying their genetic material once they are inside. This is how remdesivir – a drug currently in clinical trials for COVID-19 – works.

A problem with this approach is that viruses mutate and change over time. In the future, the coronavirus could evolve in ways that render a drug like remdesivir useless. This arms race between drugs and viruses is why you need a new flu shot every year.

Alternatively, a drug can work by blocking a viral protein from interacting with a human protein it needs. This approach – essentially protecting the host machinery – has a big advantage over disabling the virus itself, because the human cell doesn’t change as fast. Once you find a good drug, it should keep working. This is the approach that our team is taking. And it may also work against other emergent viruses.

## Learning the enemy’s plans

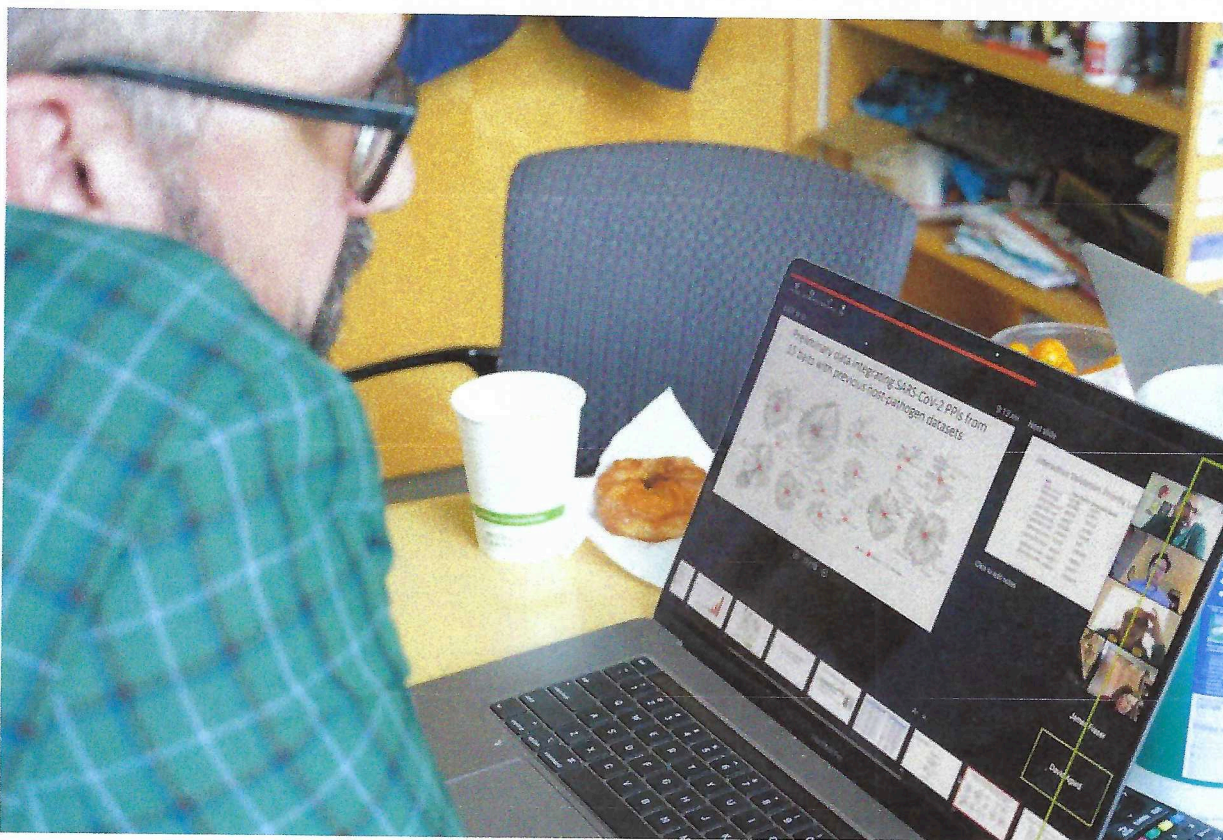
The first thing our group needed to do was identify every part of the cellular factory that the coronavirus relies on to reproduce. We needed to find out what proteins the virus was hijacking.

To do this, a team in my lab went on a molecular fishing expedition inside human cells. Instead of a worm on a hook, they used viral proteins with tiny chemical tags attached to them - termed a “bait.” We put these baits into lab-grown human cells and then pulled them out to see what we caught. Anything that stuck was a human protein that the virus hijacks during infection.

By March 2, we had a partial list of the human proteins that the coronavirus needs to thrive. These were the first clues we could use. A team member sent a message to our group, “First iteration, just 3 baits ... next 5 baits coming.” The fight was on.



The first step to discovering a treatment is to understand the virus. Jiewei Xu at the Krogan lab prepares samples for the mass spectrometer. Jacqueline Fabius, CC BY-ND



Once the first protein targets were found, we needed to search the massive FDA drug database for potential matches. Alexa Rocourt, CC BY-ND

## Counterattack

Once we had this list of molecular targets the virus needs to survive, members of the team raced to identify known compounds that might bind to these targets and prevent the virus from using them to replicate. If a compound can prevent the virus from copying itself in a person's body, the infection stops. But you can't simply interfere with cellular processes at will without potentially causing harm to the body. Our team needed to be sure the compounds we identified would be safe and nontoxic for people.

The traditional way to do this would involve years of pre-clinical studies and clinical trials costing millions of dollars. But there is a fast and basically free way around this: looking to the nearly 2,000 FDA-approved drugs that have already been safety-tested. Maybe there is a drug in this large list that can fight the coronavirus.

Our chemists used a massive database to match the approved drugs and proteins they interact with to the proteins on our list. They found 10 candidate drugs last week. For example, one of the hits was a cancer drug called JQ1. While we cannot predict how this drug might affect the virus, it has a good chance of doing something. Through testing, we will know if that something helps patients.

Facing the threat of global border shutdowns, we immediately shipped boxes of these 10 drugs to three of the few labs in the world working with live coronavirus samples: two at the Pasteur Institute in Paris

and Mount Sinai in New York. By March 13, the drugs were being tested in cells to see if they prevent the virus from reproducing.


## Dispatches from the battlefield

Our team will soon learn from our collaborators at Mt. Sinai and the Pasteur Institute whether any of these first 10 drugs work against SARS-CoV-2 infections. Meanwhile, the team has continued fishing with viral baits. So far we have found 332 human proteins that the coronavirus co-opts, and there are drugs that interact with 66 of those proteins. We published the results of our work, which has not yet been peer-reviewed, on March 22 in the hope that labs around the world can start to test these drugs and find a treatment as fast as possible.

The good news is that so far, our team has found 69 existing drugs that bind the human proteins we've identified. 27 of these are FDA approved, and 42 are in clinical or pre-clinical trials. This large number makes me hopeful that we'll be able to find a drug to treat COVID-19. If we find an approved drug that even slows down the virus's progression, doctors should be able to start getting it to patients quickly and save lives.

*This is an updated version of an article originally published on March 20, 2020.*

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