

# Coronavirus and cancer hijack the same parts in human cells to spread: Existing cancer drugs could fight COVID-19

June 29 2020, by Nevan Krogan

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SARS-CoV-2 turns on a cellular switch to build the tubes in this photo – called filopodia – that might help viral particles – the little spheres – spread more easily. Credit: [Dr Elizabeth Fischer, NIAID NIH / Bouhaddou et al. © Elsevier 2020, CC BY-ND](#)

Most antivirals in use today [target parts of an invading virus itself](#).

Unfortunately, SARS-CoV-2—the virus that causes COVID-19—has proven hard to kill. But viruses rely on cellular mechanisms in human cells to help them spread, so it should be possible to change an aspect of a person's body to prevent that and slow down the virus enough to allow the immune system to fight the invader off.

I am a quantitative biologist, and [my lab](#) built a [map of how the coronavirus uses human cells](#). We used that map to find already existing drugs that could be repurposed to fight COVID-19 and have been working with an international group of researchers called the [QBI Coronavirus Research Group](#) to see if the drugs we identified [showed any promise](#). Many have.

For years, researchers have suspected that kinases—biological [control switches that viruses use to take over cells](#) – could be [targeted to fight infections](#). Over the last few months, we built a second, more detailed map looking specifically for the kinases that the coronavirus is hijacking.

Using this map, we identified a few already existing cancer drugs which alter the function of the kinases that SARS-CoV-2 hijacks, and began testing them in coronavirus-infected cells. The [results of these early tests](#) are promising enough that we are working with some groups and have already begun human clinical trials.

## **Kinases in disease and as drug targets**

Kinases are proteins found in every cell of our body. There are [518 human kinases](#), and they act as major control hubs for virtually all processes in the body. They are able to add a small marker—a process called phosphorylation—to other proteins and thus change how, if and when a phosphorylated protein can do its work.

For example, if a cell is preparing to grow—say to heal a cut on your finger—specific kinases will turn on and start telling proteins involved in cell growth what to do. Many cancers are caused by overactive kinases leading to uncontrolled cell growth, and [drugs that slow kinases down](#) can be highly effective at treating cancer.

This map shows how the coronavirus changes the function of kinases – cellular switches involved in most biological processes – and the proteins they control. It guided researchers from UCSF to cancer drugs that could fight COVID-19.

Credit: [Bouhaddou et al. © Elsevier 2020, CC BY-ND](#)

Kinases are central players in cellular function as well as in most diseases, so researchers and [pharmaceutical companies have studied them in great detail](#).

Kinases are also fairly easy to target with drugs because of [how they add phosphorylation markers to proteins](#). Researchers have developed a huge

number of drugs, particularly cancer drugs, that work by essentially throwing a wrench into the mechanics of specific kinases in order to stop cell growth.

So what does this have to do with the coronavirus? Well, viruses and cancer actually have more in common than you might think. Cancer is essentially a [malfunctioning of cellular machinery](#) that causes runaway cell growth.

Viruses also change the function of cellular machinery—albeit on purpose—but instead of causing cell growth, the machinery is repurposed to produce more viruses. Not surprisingly, [viruses take control](#) over many kinases to do this.

## **Coronavirus at the controls**

This idea—that SARS-CoV-2 is using kinases to hijack cellular machinery—is why we wanted to build a map of every kinase that is taken over by the coronavirus. Any virus–kinase interaction could be a potential target for drugs.

To do this, we first infected green monkey cells—which are fairly good surrogates for human cells [when it comes to virus infection](#) – with SARS-CoV-2. We then ground up these infected cells and used a device called a [mass spectrometer](#) to see which proteins were phosphorylated in these infected cells. We then did the same thing with healthy cells.

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It is impossible to actually see which kinases are activated at any time, but since each kinase can [attach phosphorylation markers to only a few specific proteins](#), researchers can look at the phosphorylated proteins to determine what kinases are active at any time.

We made two lists: one list of phosphorylated proteins in healthy cells and one list of phosphorylated proteins in infected cells. We then compared the two, and by looking at the differences between the infected and uninfected lists, we were able to determine which kinases the coronavirus uses to reproduce.

Because researchers still [don't fully understand what all 518 human kinases do](#), we were able to look for effects in only 97 of the ones we know most about. But that turned out to be more than enough. Of those 97 kinases, we found 49 that the virus affects.

Some of the more interesting ones include [Casein Kinase 2](#), which is involved in controlling how a cell is shaped. We also identified several kinases that work together in what is called the [p38/MAPK signaling pathway](#). This pathway responds to and controls our body's inflammation reaction. It is possible these kinases could be involved in the cytokine storm—a dangerous immune system overreaction—that some patients with severe COVID-19 experience.

While identifying the kinases involved in SARS-CoV-2 replication, we

were also able to learn a lot about how the virus changes our bodies. For example, CK2 becomes much more active during the course of coronavirus infection and causes the growth of little tubes that extend from the surface of the cell. Under a microscope, it looks as if the cell has a full head of hair. We think SARS-CoV-2 might be using these long cell outgrowths – [called filopodia](#) – as viral highways to get new viruses closer to neighboring cells, thereby making infection easier.

## **Kinases inhibitors in the lab and clinical trials**

Learning more about the virus's function is interesting for a biologist like me and could be useful down the road, but the ultimate goal of our project was to find drugs to treat COVID-19.

Testing the promising cancer drugs in the lab was the first step, and after dozens showed promise, we began the process of starting clinical trials. Credit: [QBI UCSF, CC BY-ND](#)

Once we knew which kinases SARS-CoV-2 uses to replicate and the proteins they change, we looked through a [database of around 250 kinase-inhibiting drugs](#) to see if any of them targeted the kinases used by the virus. To increase our chances, we also looked for drugs that hit some of the proteins the kinases act on. And sure enough, we found some.

There are 87 existing drugs that change the kinase-controlled pathways used by the coronavirus. Most of these drugs are already approved for human use or are currently in clinical trials to treat cancer, and could be quickly repurposed to treat COVID-19 patients.

With these leads, our collaborators in [New York](#) and [Paris](#) tested the effect of 68 of those drugs on cells infected with SARS-CoV-2. Several of these were effective in killing the virus in cells. A few that we are especially excited about—silmitasertib, gilteritinib, ralimetinib, apilimod and dinaciclib—are either approved for treatment, in clinical testing or under preclinical development for various diseases.

Silmitasertib stops Casein Kinase 2, the kinase that causes cells to grow the virus spreading filopodia tubes. As soon as the company that makes silmitasertib heard this news, they announced that they wanted to [test the drug against COVID-19 in the clinic](#).

Drugs hitting kinase pathways have been on the radar of researchers as potential powerful antivirals for years, but none have come to fruition. By looking to this new area of drug applications and using our new

mapping approach, our team has added dozens of drugs to the growing list of potential tools to help fight this pandemic.

It is still too early to say whether any of these will work to treat COVID-19 in patients, but the more chances we have, the better.

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