A new class of drugs could prevent resistant COVID-19 variants, study finds

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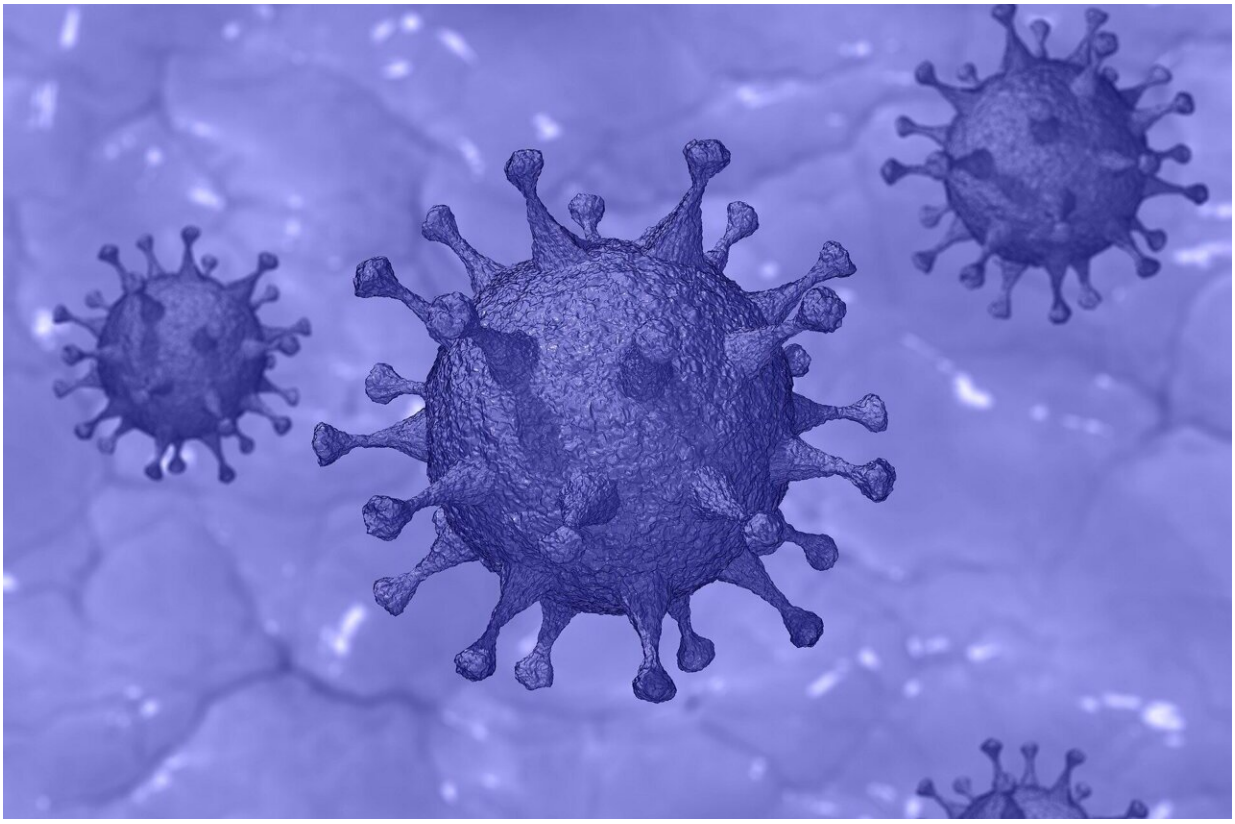

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The constant evolution of new COVID-19 variants makes it critical for clinicians to have multiple therapies in their arsenal for treating drug-resistant infections. Researchers have now discovered that a new class of

oral drugs that acts directly on human cells can inhibit a diverse range of pathogenic SARS-CoV-2 strains.

In their newly published study, the team found a novel mechanism through which the gene that expresses angiotensin converting enzyme-2 (ACE-2)—the cellular receptor to which SARS-CoV-2 binds so that it can enter and infect the cell—is turned on. They also found that a class of oral drugs currently in human clinical trials can block this pathway and potentially be a therapeutic for all SARS-CoV-2 variants, as well as any newly emerging SARS-like viruses. The team published its findings in *Nature Genetics*.

"Because of drug-resistant variants, we're down to only one drug, Paxlovid, as far as our oral options," says Craig Wilen, MD, Ph.D., associate professor of laboratory medicine and of immunobiology, and a member of Yale Cancer Center.

"Targeting these master regulatory complexes complements existing approaches and fills a need for a new drug class that can be exploited to help combat drug resistance and infection." Wilen and Cigall Kadoch, Ph.D., of Dana-Farber Cancer Institute, were co-senior authors of the study.

Researchers identify mSWI/SNF complexes and as potential anti-viral targets

In a previous study published in 2021, Wilen's team at Yale performed genetic screening to identify host factors that are essential for SARS-CoV-2 infection. One of the key players was the mammalian switch/sucrose non-fermentable (mSWI/SNF, also called BAF) chromatin remodeling complex, a group of over a dozen very conserved proteins that allow certain genes to turn on.

"At that point, I'd never heard of it in the setting of virus infection, and we couldn't understand why it was important for coronaviruses," says Wilen. Thus, the group teamed up with experts on this complex, the Kadoch Lab at the Dana-Farber Cancer Institute and Harvard Medical School to find out how the protein complex acts to make cells susceptible to infection and if newly emerging drugs against these complexes could stunt viral infection.

At the time they embarked on their collaborative work, the U.S. Food and Drug Administration had authorized six monoclonal antibody treatments for emergency use, yet none of these treatments work against the newest Omicron variants.

This leaves clinicians with remdesivir, which can only be administered through an IV, limiting its use; molnupiravir, an oral drug that works similarly to remdesivir but only has 30 percent efficacy; and Paxlovid, an oral antiviral that works through inhibiting the viral protease. Paxlovid, Wilen says, is the mainstay of current treatment.

"It's a great drug that works well, but there has been some emerging drug resistance to it," he says. "And currently, that is the only drug in our toolbox that we can give as an oral form." The dwindling of effective treatments further highlights the critical need for a new class of drugs to add to the toolbox, and ideally, ones that are less susceptible to quick-acting resistance mechanisms.

Blocking mSWI/SNF protects cells against SARS-CoV-2

First, the team discovered that disrupting mSWI/SNF complexes prevented viral entry into human cells. Because mSWI/SNF is known to regulate genes turning on and off, they then hypothesized that it might also play a role in activating the ACE-2 receptor. Next, they uncovered

its mechanism: mSWI/SNF binds to another protein called HNF1A, a transcription factor, which directs it to the gene that encodes ACE-2.

Upon disrupting mSWI/SNF complexes, the cell could no longer make ACE-2 and became resistant to infection by any virus that uses that receptor. This includes many coronaviruses.

Small molecule inhibitors that target mSWI/SNF have already been developed by Kadoch-founded Foghorn Therapeutics and are in phase I clinical trials as a therapeutic for several cancers. Wilen and Kadoch found that this class of drugs was effective against multiple variants of SARS-CoV-2—including a remdesivir-resistant strain isolated from a Yale patient—without any adverse effects on the cell. "This is proof of principle that this can be a really important first- or second-line tool to combat drug resistance," says Wilen.

"Further, this speaks to the wide, multi-disease potential for pharmacologic modulation of chromatin remodeling complexes," says Kadoch. "These molecular machines sit at the top of the pyramid in governing gene expression programs that go awry in many different human diseases—we are just at the tip of the iceberg in identifying and exploring their utility."

Wilen believes the drugs in these clinical trials can potentially be repurposed to inhibit both current and future coronaviruses. Furthermore, Wilen and Kadoch hope the work can provide insight into why certain people and specific cell types may be more susceptible to coronavirus than others. "Future work is needed to look at the underlying biology of why some people are asymptomatic while others experience severe infection and death," Wilen says.

COVID-19 will not be the last severe viral outbreak. Wilen's lab studies coronaviruses circulating in wild bats, which he believes pose the highest

risk for infecting humans and causing the next pandemic. Many of these viruses use ACE-2 as a receptor, which means that this new study may hold the key to slowing or stopping the next outbreak.

"We're going to have another pandemic, whether it's in a few years or a decade. And we're underprepared for it," he says. "The best way to prepare is to have as many vaccines and drugs as possible ready to go so that we can combat the outbreak early with maximum effectiveness."

More information: Cigall Kadoch, Pharmacological disruption of mSWI/SNF complex activity restricts SARS-CoV-2 infection, *Nature Genetics* (2023). DOI: 10.1038/s41588-023-01307-z. www.nature.com/articles/s41588-023-01307-z

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