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Researchers pinpoint promising inhibitors that could lead to new antiviral drugs to treat COVID-19

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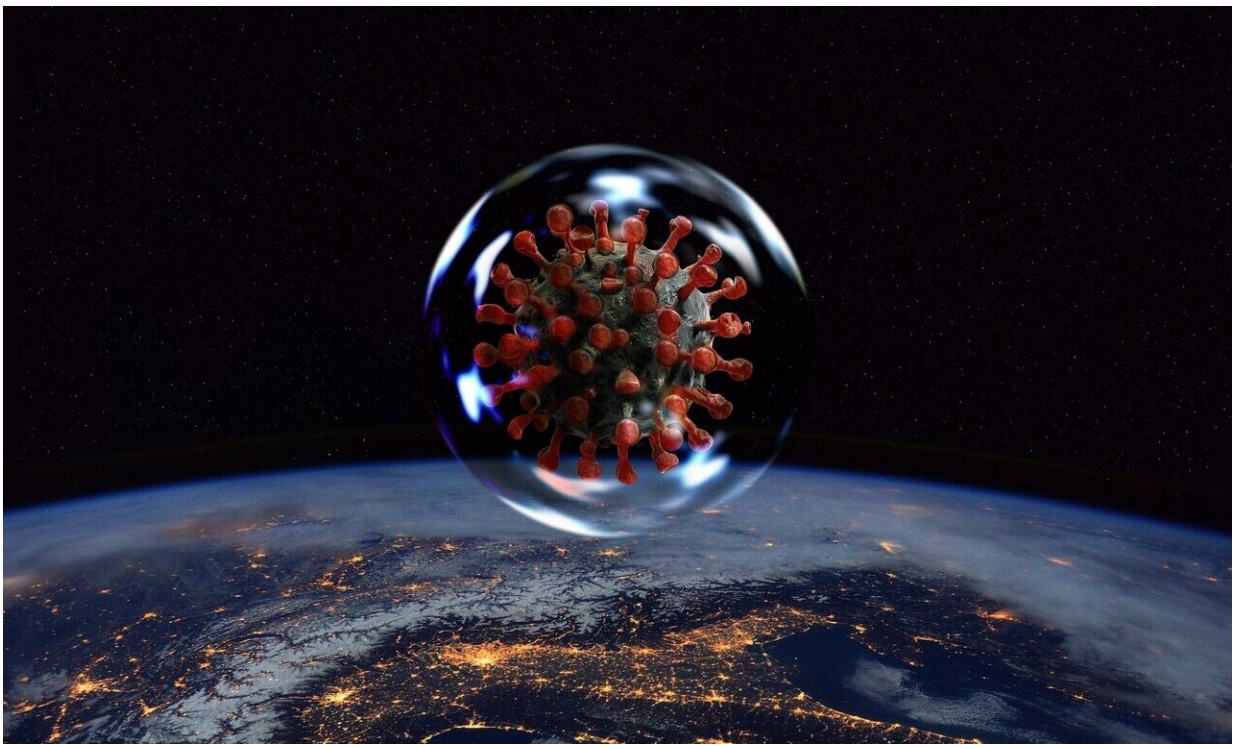

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The rapid development of safe and effective COVID-19 vaccines has been a major step forward in helping bring the pandemic under control. But with the rise of variants and an uneven global distribution of

vaccines, COVID-19 is a disease that will have to be managed for some time.

Antiviral drugs that target the way the virus replicates may be the best option for treating outbreaks of COVID-19 in unvaccinated and undervaccinated populations.

Using the Canadian Light Source (CLS), a national research facility at the University of Saskatchewan, researchers from the University of Alberta isolated promising inhibitors that could be used to treat COVID-19 infections. The scientists used the synchrotron at CLS remotely during the facility's special COVID-19 call for proposals, an initiative created to support research to help fight the pandemic.

"With the help of the CLS and the multiple teams here at the U of A, including our lab and the Young lab in the Department of Biochemistry, the Vederas lab in the Department of Chemistry and the Tyrrell team in the Department of Medical Microbiology and Immunology, we've been very efficient at developing a group of inhibitors that is very promising," said Joanne Lemieux, a professor in the U of A's Faculty of Medicine & Dentistry.

The synchrotron creates light millions of times brighter than the sun that helps researchers to find very detailed information about their samples. Lemieux and colleagues used the CMCF beamline at the CLS to search for molecules that could stop SARS-CoV-2—the virus that causes COVID-19—from replicating inside human cells.

The team found inhibitors that target a special kind of protein called a protease, which is used by the virus to make more copies of itself. Proteases act like an ax and help the virus chop up large proteins. Without this protein, the virus would be unable to multiply and harm human health.

"One of the inhibitors that we used as our benchmark starting point was one that was developed to treat a feline coronavirus," Lemieux said. "This was not an optimal inhibitor given the dosage for humans, which is why new derivatives needed to be made in order to provide patients with a lower dosage."

While COVID-19 and its cousins SARS and MERS cause serious respiratory diseases, coronaviruses are also responsible for a wide range of illnesses in humans and animals. Lemieux said the proteases are very similar among the different coronaviruses.

"It's likely that any antiviral that is developed for one coronavirus would also be a broad specificity inhibitor that could treat a variety of coronavirus infections, including those found in animals," Lemieux said.

Over the past decade, oral antiviral medication has become more accessible to patients in need. There are oral protease inhibitors that treat and manage symptoms for diseases like HIV and hepatitis C. The research team wants to help make SARS-CoV-2 inhibitors available in a pill form, which would make it easier to treat COVID-19.

Lemieux's team is not alone in their quest for antivirals that will help treat diseases like COVID-19. Pfizer, the pharmaceutical company behind the successful mRNA vaccine, is moving its antivirals to Phase 1 clinical trials. Lemieux sees this as a sign that her group has been headed in the right direction.

"With many people working around the world developing antivirals targeting proteases, there is very likely to be one or more antivirals on the market," Lemieux said. "This would enable ease of accessibility for people around the world, especially in regions or populations where vaccines are not an option."

The team's findings were recently published in the *European Journal of Medicinal Chemistry*.

More information: Wayne Vuong et al, Improved SARS-CoV-2 Mpro inhibitors based on feline antiviral drug GC376: Structural enhancements, increased solubility, and micellar studies, *European Journal of Medicinal Chemistry* (2021). DOI: 10.1016/j.ejmech.2021.113584