A better COVID treatment for the immunocompromised? Researchers create a non-toxic potential alternative to Paxlovid

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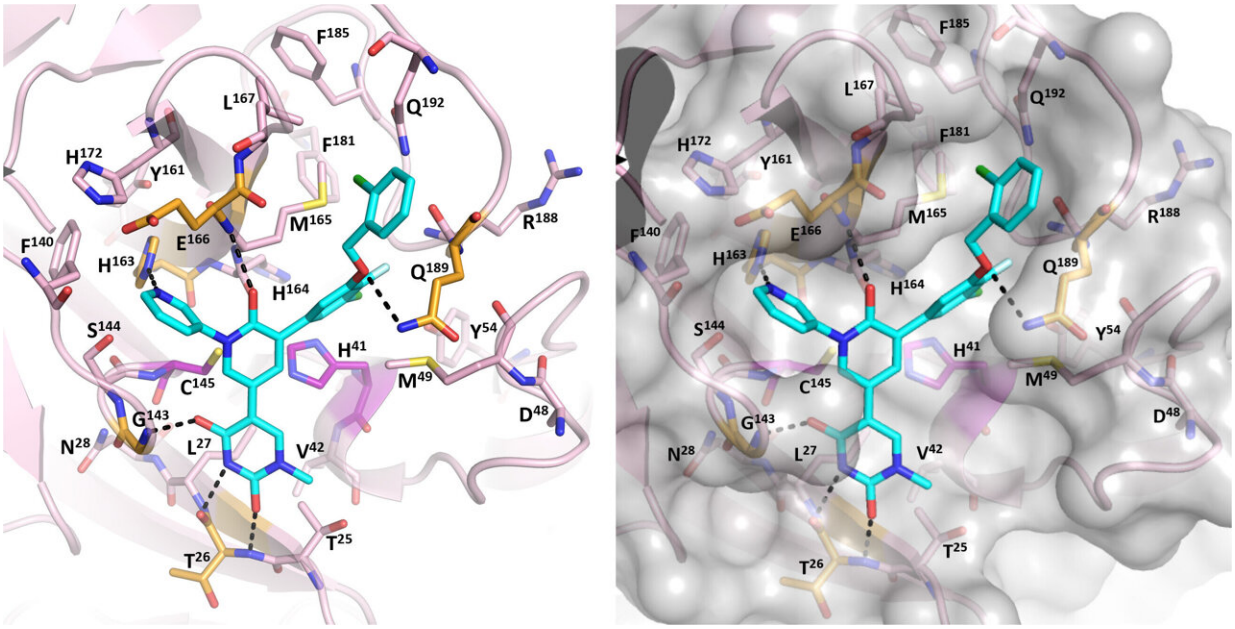

Crystal structure of compound Mpro61 bound by the SARS-CoV-2 main protease . Credit: *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2320713121

A combination of two antiviral compounds may be a promising alternative to Paxlovid when treating COVID-19 in immunocompromised patients, according to Karen S. Anderson, Ph.D., professor of pharmacology and of molecular biophysics & biochemistry

at Yale School of Medicine.

People who are infected with SARS-CoV-2, the virus that causes COVID-19, currently have two options approved by the Food and Drug Administration (FDA) for antiviral treatment. The more widely used medication is Paxlovid, a drug whose antiviral component, nirmatrelvir, is highly effective at reducing the severity of symptoms and decreasing hospitalizations, and may, Anderson believes, have helped save thousands of lives.

However, another component of Paxlovid, ritonavir, can negatively interact with anti-rejection medications taken by immunocompromised people, most notably those who have received organ transplants. This has led some patients to be hospitalized with kidney failure after taking Paxlovid due to drug-drug interactions. Meanwhile, molnupiravir—another antiviral for COVID-19 that has received Emergency Use Authorization (EUA) by the FDA—is not nearly as effective at treating the disease.

Now, in a study published in *Proceedings of the National Academy of Sciences*, Anderson and her colleagues at Yale University have created a non-toxic potential alternative to Paxlovid by combining molnupiravir with a new antiviral compound they developed in the lab.

Research scientists Christina Papini, a Ph.D. student, and Irfan Ullah, Ph.D., both at Yale School of Medicine, are the first authors of the paper. Anderson is a corresponding author along with her colleagues, William Jorgensen, Ph.D., and Priti Kumar, Ph.D.

The study found that humanized mice infected with SARS-CoV-2 universally overcame the disease when treated with the new drug combination. If replicated in clinical studies, this finding could help immunocompromised people receive better treatment for COVID-19 in

the future.

Race toward an antiviral

Progress toward the current effort at Yale to develop antivirals for COVID started with work on HIV, the virus responsible for AIDS. Anderson and her colleagues have spent much of their careers using computational and experimental methods to design better drugs that could be used to treat HIV. During the first month of lockdown in March 2020, the team wondered if they could use this same approach to find drugs to target COVID-19.

"At the time, there were really no therapies" for treating people infected with SARS-CoV-2, says Anderson. "Everyone was desperate to find something."

William Jorgensen, Ph.D., Sterling Professor of Chemistry at Yale, used computational methods to see if the structure of any existing drugs could serve as a starting point to target the main protease of SARS-CoV-2, which is essential for viral replication.

The analysis revealed that the existing compound of perampanel, an FDA-approved seizure drug, could loosely bind to the main protease. From there, Jorgensen and his lab made changes in the chemical structure of the compound until they came up with preclinical candidates that might eventually work in a clinical setting.

Preparing for future viral diseases

One of these compounds of the series was Mpro61. Priti Kumar, Ph.D., associate professor of internal medicine (infectious diseases) and of microbial pathogenesis, and her lab tested Mpro61 alone and combined

with molnupiravir in mice that were genetically engineered to replicate the worst COVID cases in people.

Promisingly, the researchers found that Mpro61 was effective at reducing viral load. But while Mpro61 helped extend mice survival, most infected animals eventually succumbed to the disease.

However, when they combined Mpro61 with the existing EUA-approved antiviral molnupiravir, the one-two-punch antiviral proved highly effective—with no noticeable traces of the virus after 14 days post-infection. All mice treated with the drug survived. By contrast, mice treated with just one antiviral showed reduced viral load but most died within 14 days post-infection.

The finding suggests that a combination of the two antivirals could make for a promising alternative to Paxlovid with limited side effects. But whether this drug is taken to the next step in clinical trials may depend on whether there is interest from the pharmaceutical industry.

"The problem is that people's attention is turned away from COVID," says Anderson. "They may no longer think it's a problem."

However, new COVID variants continue to emerge, and the disease remains especially dangerous for people who are immunocompromised. Even with vaccines, more people die from COVID-19 today than from the flu. So, a more potent alternative to molnupiravir could be important for treating immunocompromised people infected with the disease.

Other tests showed that the Mpro61 may be effective at reducing viral load for another type of coronavirus, called SARS-CoV-1, which caused the respiratory disease SARS and spread through much of Asia starting in 2002, resulting in more than 900 deaths.

Given that coronaviruses are a hotbed for new diseases, having a drug on the shelf that can be used in the case of an emergent pathogen from this family could be useful, says Anderson.

"We were so caught off guard with [the COVID- 19] pandemic in terms of having something that works," she says. "This work might put us a step forward in future pandemics."

More information: Christina Papini et al, Proof-of-concept studies with a computationally designed M pro inhibitor as a synergistic combination regimen alternative to Paxlovid, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2320713121

Provided by Yale University

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