Researchers race to develop Paxlovid replacement

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Researchers from Rutgers believe they are among the leaders in a race to find an oral COVID-19 treatment to supplement or replace Paxlovid—an antiviral medication that helps keep high-risk patients out of the hospital.

Their report, published in *Science*, shows that an alternative medication,

a viral papain-like protease inhibitor, inhibits disease progression in animals, a necessary step before human drug trials.

"COVID-19 remains the nation's third leading cause of death, so there's already a massive need for additional treatment options," said Jun Wang, senior author of the study and an associate professor who runs a research lab at Rutgers' Ernest Mario School of Pharmacy. "That need will grow more urgent when, inevitably, COVID-19 mutates in ways that prevent Paxlovid from working."

The Rutgers team hoped to make a drug that interfered with viral papain-like protease (PLpro), a protein that performs important functions in all known strains of COVID-19.

Creating such a drug required detailed information about PLpro's structure, which Wang's team got from the Arnold Lab at Rutgers' Center for Advanced Biotechnology and Medicine (CABM).

Precise knowledge of PLpro's structure enabled Wang's team to design and synthesize 85 drug candidates that would bond to—and interfere with—this vital protein.

"The PLpro crystal structures showed an unexpected arrangement of how the drug candidate molecules bind to its protein target, leading to innovative design ideas implemented by professor Wang's medicinal chemistry team," said Eddy Arnold, who is a professor at CABM and the Rutgers Department of Chemistry and Chemical Biology.

Laboratory testing established that the most effective of those drug candidates, a compound dubbed Jun12682, inhibited several strains of the SARS-CoV-2 virus, including strains that resist treatment with Paxlovid.

Subsequent testing on SARS-CoV-2-infected mice by the Deng lab at Oklahoma State University showed that oral treatment with Jun12682 reduced viral lung loads and lesions while improving survival rates.

"Our treatment was about as effective in mice as Paxlovid was in its initial animal tests," said Wang, who added the experimental drug appears to have at least one major advantage over the older drug.

"Paxlovid interferes with many prescription medications, and most people who face the highest risk of severe COVID-19 take other prescription medicines, so it's a real problem," Wang said. "We tested our candidate Jun12682 against major drug-metabolizing enzymes and saw no evidence that it would interfere with other medications."

Rutgers has submitted patent applications for Jun12682, along with the other 84 drug candidates, and is looking for partners to help move the drug candidate forward through further stages of testing and development.

More information: Bin Tan et al, Design of a SARS-CoV-2 papain-like protease inhibitor with antiviral efficacy in a mouse model, *Science* (2024). DOI: 10.1126/science.adm9724. www.science.org/doi/10.1126/science.adm9724

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