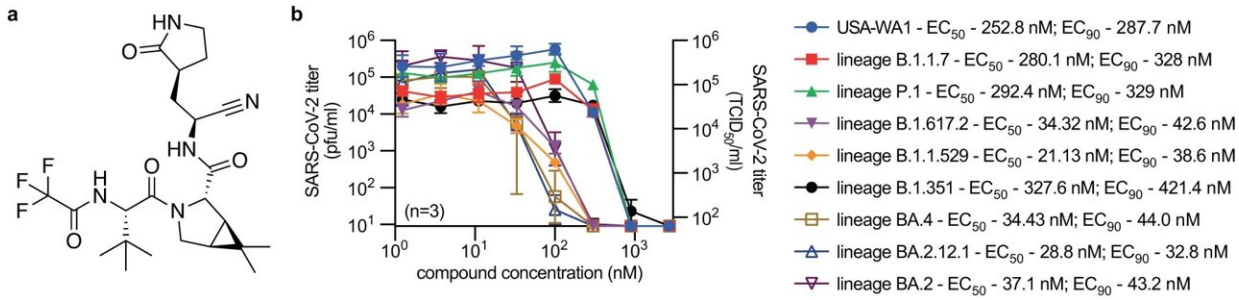
Molnupiravir administered at human effect size-equivalent dose found to block SARS-CoV-2 transmission in ferrets

August 9 2023



In vitro antiviral activity of nirmatrelvir. **a** Structure of nirmatrelvir. **b** Nirmatrelvir dose-response assays against SARS-CoV-2 WA1, and lineages B.1.1.7 (VOC α), B.1.351 (VOC β), P.1 (VOC γ), B.1.617.2 (VOC δ), B.1.1.529, BA.2, B1.2.12.1, and BA.4 on VeroE6-TMPRSS2 cells. The number of independent repeats (*n*) used in each experiment is shown (*n* = numbers of biologically independent samples). Symbols represent, and lines intersect, group geometric means ± SD; numbers denote 50 and 90% inhibitory concentrations (EC_{50} and EC_{90}, respectively), determined through non-linear 4-parameter variable slope regression modeling. Source data are provided as a Source data file. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-40556-8

Two oral drugs, molnupiravir and paxlovid (nirmatrelvir/ritonavir), provide equivalent therapeutic benefit in preventing severe COVID-19 in animal models, but only molnupiravir efficiently blocked SARS-

CoV-2 transmission when administered at a human effect size-equivalent dose, according to a study led by researchers at Georgia State University's Center for Translational Antiviral Research in collaboration with the Emory University Institute for Drug Development.

The study published in the journal *Nature Communications* compared the efficacy of two licensed drugs, molnupiravir and paxlovid (nirmatrelvir/ritonavir), and the effects on SARS-CoV-2 transmission in dwarf hamster and ferret animal models. The researchers established correlations for animal and human dose levels, which can be complex.

Both drugs have received emergency use authorization, but therapeutic options against SARS-CoV-2 are underutilized. Effective treatments against SARS-CoV-2 are critical because extensive viral spread continues, despite the development of vaccines and antivirals. Also, the rise of new SARS-CoV-2 variants of concern that can escape preexisting immunity have reduced the possibility of rapidly ending the pandemic through large-scale vaccination campaigns.

"This study affirms previous clinical analyses that early treatment of older adult patients at elevated risk of progression to severe COVID-19 with either paxlovid or molnupiravir will provide significant therapeutic benefit," said Richard Plemper, Ph.D., a Regents' Professor and Distinguished University Professor and the director of the Center for Translational Antiviral Research at Georgia State University's Institute for Biomedical Sciences.

"We demonstrate in two animal model species, one rodent and one non-rodent, that infectious particle titers, but not viral RNA copy numbers, should be assessed to determine efficacy of a viral mutagen such as molnupiravir. Using reduction of viral RNA copies as biomarker available across all animal models and human patients, we demonstrate that molnupiravir, but not paxlovid, prevents all SARS-CoV-2

transmission when drugs were administered at human effect size-equivalent doses."

The researchers compared both drugs in two animal models, the Roborovski dwarf hamster model for severe COVID-19-like lung infection and the ferret SARS-CoV-2 transmission model.

"Recent data has indicated another uptick in COVID-19 infections in a broad cross-section of the population. Antiviral drugs can play an important role in not only treating COVID-19 infection but also in controlling its transmission and spread," said George Painter, Ph.D., Distinguished Professor of Pharmacology and Chemical Biology at Emory University School of Medicine, CEO of DRIVE (Drug Innovation Ventures at Emory) and director of the Emory Institute for Drug Development where molnupiravir was developed.

"This collaborative study shows that molnupiravir treatment completely suppresses transmission at all dose levels tested. We look forward to continued studies to verify these exciting results."

More information: Robert M. Cox et al, Comparing molnupiravir and nirmatrelvir/ritonavir efficacy and the effects on SARS-CoV-2 transmission in animal models, *Nature Communications* (2023). DOI: 10.1038/s41467-023-40556-8

Provided by Georgia State University