Medical Xpress

Flu virus variants resistant to new antiviral drug candidate lose pathogenicity, study finds

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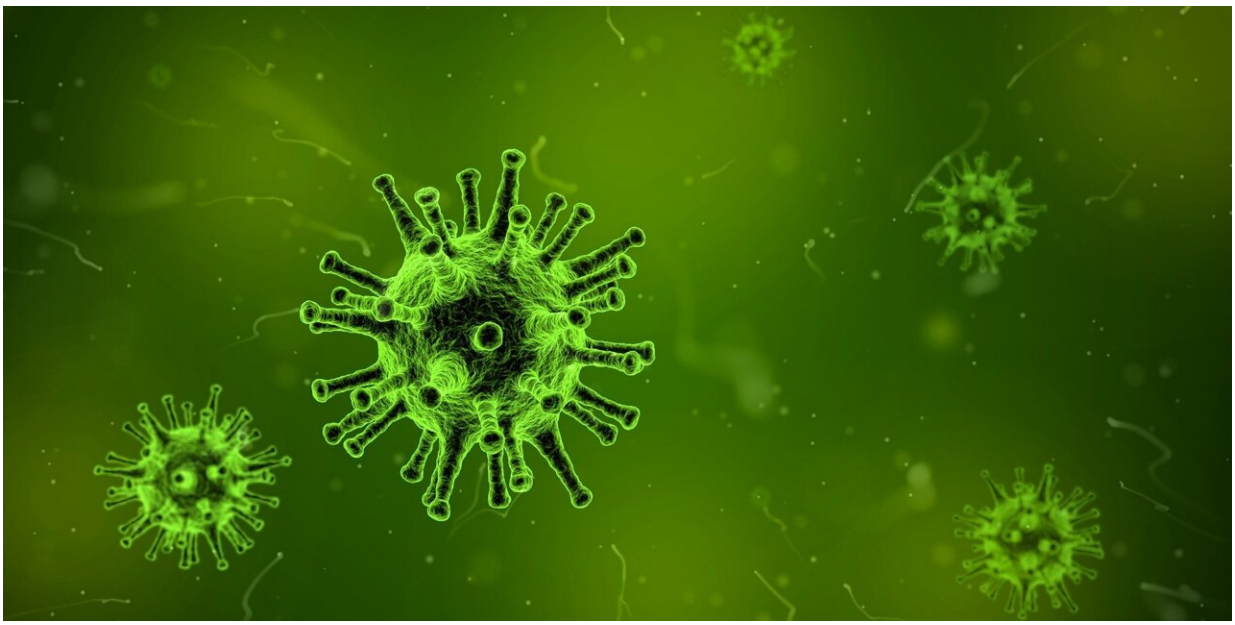

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Influenza A viruses with induced resistance to a new candidate antiviral drug were found to be impaired in cell culture and weakened in animals, according to a study by researchers in the Center for Translational Antiviral Research at Georgia State University.

In a study published in *PLOS Pathogens*, the authors explored the

developmental potential of 4'-fluorouridine (4'-FlU), a clinical drug candidate, for influenza therapy. They resistance-profiled the compound against influenza viruses and mapped possible routes of viral escape, addressing specifically whether resistance affects viral pathogenicity and ability to transmit.

In previous studies, 4'-FlU demonstrated broad oral efficacy against seasonal, pandemic and highly pathogenic avian influenza viruses in cell culture, human airway epithelium cells and two animal models, ferrets and mice.

Seasonal influenza viruses pose a major public health threat, infecting nearly 1 billion people worldwide each year and causing millions to require hospitalization and advanced care. Annual flu vaccines provide moderate protection, but the benefit is marginal when vaccines are poorly matched with circulating virus strains or when novel pandemic virus strains emerge.

While three different classes of antivirals are approved by the U.S. Food and Drug Administration for use against influenza, they each have a low genetic barrier against viral resistance. One of these classes is no longer recommended by the Centers for Disease Control and Prevention due to widespread presence of resistance mutations in circulating human and animal influenza A virus strains. Resistance has also been frequently observed to the other two classes of antivirals in human viruses.

"Developing novel therapeutics to mitigate seasonal influenza and improve preparedness against future influenza pandemics is an urgent priority because of pre-existing or rapidly emerging resistance of influenza viruses to approved antivirals," said Carolin Lieber, first author of the study and a postdoctoral fellow in the Center for Translational Antiviral Research in the Institute for Biomedical Sciences at Georgia State.

"In this study, we tested the potential of 4'-FlU as an influenza drug and found that resistant influenza A virus variants are severely weakened in mice. In ferrets, these resistant variants are impaired in their ability to invade the lower respiratory tract and cause viral pneumonia, in addition to being transmission-defective or compromised," Lieber said.

In cell culture, six different escape lineages with distinct mutations were found. The mutations adhered to three distinct structural clusters that are all predicted to affect the active site of the viral RNA-dependent RNA polymerase complex, leading to moderately reduced viral sensitivity to the drug, according to the study's findings.

The study also found that oral 4'-FlU administered at the lowest efficacious dose (2 mg/kg) or elevated dose (10 mg/kg) overcame moderate resistance when mice were infected with a lethal amount of influenza virions. This was demonstrated by significantly reduced virus load and complete survival, the authors reported.

"We discovered that we could fully mitigate lethal infection with the resistant variants and viral spread with standard or five-fold elevated oral dose of 4'-FlU," said Richard Plemper, senior author of the study, Regents' Professor in the Institute for Biomedical Sciences and director of the Center for Translational Antiviral Research at Georgia State. "These results demonstrate that partial CA09 escape from 4'-FlU is feasible in principle, but escape mutation clusters are unlikely to reach clinical significance or persist in circulation."

More information: Carolin M. Lieber et al, Influenza A virus resistance to 4'-fluorouridine coincides with viral attenuation in vitro and in vivo, *PLOS Pathogens* (2024). DOI: 10.1371/journal.ppat.1011993