Researchers discover first-in-class broad-inhibitor of paramyxovirus polymerases

13 July 2020

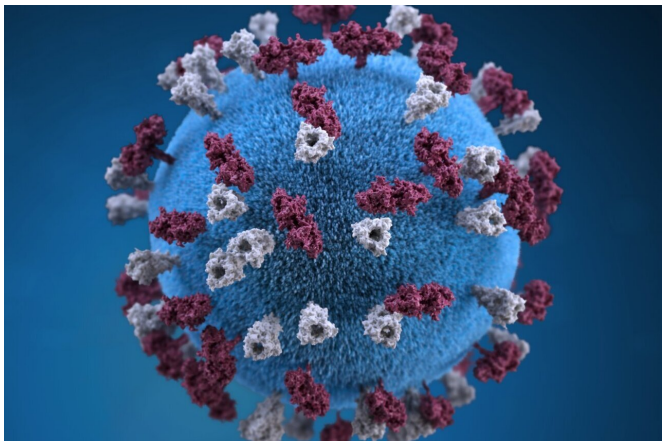

Illustration of the virus which causes measles. Credit: CDC/ Allison M. Maiuri, MPH, CHES

A new antiviral drug that is effective against a broad range of human pathogens in the paramyxovirus family, such as the human parainfluenzaviruses and measles virus, has been discovered by researchers in the Institute for Biomedical Sciences at Georgia State University.

The drug binds to and inhibits paramyxovirus polymerases, the unique viral protein complexes that are essential for virus genome replication and the expression of viral proteins. Identified at Georgia State through a high-throughput drug screen, the compound is highly potent in cultured cells and primary human airway epithelium tissues, well-tolerated and provides complete recovery from a lethal paramyxovirus infection of animals when given by mouth. These findings were published online on July 13 in *Nature Microbiology*.

"We believe that a viable drug for the treatment of paramyxovirus infection must be broad-spectrum," said Dr. Richard Plemper, senior author of the study, Distinguished University Professor in the Institute for Biomedical Sciences and head of the antiviral high-throughput screening center at Georgia State.

"Because many paramyxoviruses cause severe childhood diseases, the design of clinical trials is challenging. In this study, we aimed to solve the conundrum by hunting for a drug class that is equally active against paramyxoviruses that pose a major health threat to children and those that cause severe disease in adults to open a path to clinical development."

"To be safely given to children, this drug must also be exceptionally well-tolerated, which excludes the broad-spectrum polymerase substrate analog inhibitors developed to date," said Dr. Robert Cox, first author of the study and a postdoctoral Fellow in Plemper's lab.

The compound they identified, GHP-88309, has nanomolar potency against human parainfluenzaviruses.

"We selected human parainfluenzavirus type 3 as our screening paramyxovirus," said Plemper, "because 2-14 percent of adult hematopoietic stem cell transplant recipients in the United States suffer from life-threatening HPIV3 infection annually."

In addition to blocking HPIVs, the compound is equally active against pathogens of a different paramyxovirus subgroup that contains the measles virus.

"Broad activity of a non-nucleoside inhibitor against viruses of different subgroups is very unusual," said Cox. "This behavior indicates that we have identified a conserved druggable site in the polymerase complex."

Through a sophisticated biochemical approach, the creation of a chemical analog of the drug that can be photoactivated to permanently bind to its target, the researchers have located this site to be a

conserved pocket in the central cavity of the polymerase complex. Consistent with a conserved binding site for the drug, viral resistance to GHP-88309 was always associated with a complete loss of pathogenicity.

Due to interrupted vaccination schedules by the COVID-19 pandemic, a global spike in measles cases is feared.

"Measles is always one of the first diseases to return when vaccination coverage drops in an area, because the virus is exceptionally contagious," explained Plemper. "We must expedite the development of new drug classes such as GHP-88309 now to improve preparedness against emerging and re-emerging viral pathogens in the aftermath of the SARS-CoV-2 pandemic."

More information: Orally efficacious broad-spectrum allosteric inhibitor of paramyxovirus polymerase, *Nature Microbiology* (2020). DOI: 10.1038/s41564-020-0752-7

Provided by Georgia State University