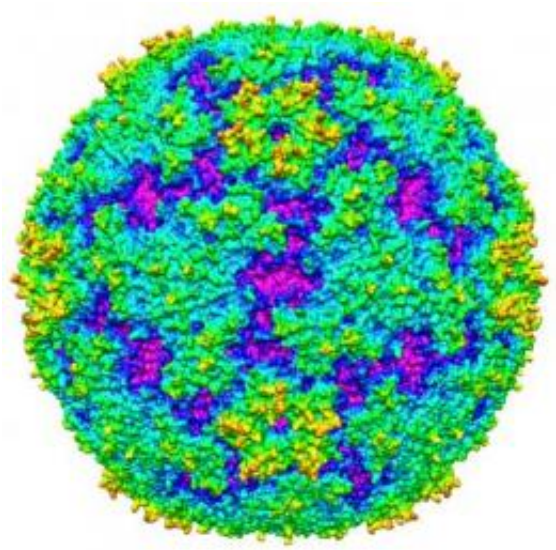
Studies reveal structure of EV71, a virus causing childhood illnesses

March 2 2012, by Emil Venere



Purdue researchers created this three-dimensional reconstruction of enterovirus 71, which causes hand, foot and mouth disease and potentially fatal encephalitis. Researchers are reporting new findings about the structure of the virus, proposing a way to design an antiviral drug to treat the infection. Credit: Department of Biological Sciences, Purdue University

Researchers have discovered critical new details about the structure of a virus that causes potentially fatal brain swelling and paralysis in children, pointing toward designs for antiviral drugs to treat the disease.

The virus, called enterovirus 71, causes hand, foot and mouth disease, and is common throughout the world. Although that disease usually is

not fatal, the virus has been reported to cause encephalitis, a potentially fatal illness found primarily in the Asia-Pacific region.

Now, two research teams are reporting new findings about the structure of the virus. One of the teams, from Purdue University, has proposed a way to design antiviral drugs to treat the infection. Findings from that team are detailed in a paper appearing Thursday (March 1) in the online Express issue of the journal *Science*. Another team, led by researchers at Oxford University, will report its findings in a paper scheduled to appear Sunday (March 4) in the journal *Nature Structural & Molecular Biology*.

"Taken together, the findings in both papers are useful when you are trying to stop the virus from infecting host cells," said Michael G. Rossmann, Purdue's Hanley Distinguished Professor of Biological Sciences. "The common theme is that they both report for the first time on the structure of this virus, and this tells us how to design compounds to fight the infection."

Rossmann is co-author of a paper written by Purdue postdoctoral research associate Pavel Plevka; Purdue research scientist Rushika Perera; Richard J. Kuhn, a professor and head of Purdue's Department of Biological Sciences; and Jane Cardosa, a researcher at Sentinext Therapeutics in Malaysia.

Both teams used a technique called X-ray crystallography to determine the virus's precise structure, showing similarities to features on related enteroviruses, including poliovirus. However, a key feature is different in that a small molecule called a "pocket factor," located within a pocket of the protective shell of the virus, is partially exposed in EV71.

When the virus binds to a human cell, the pocket factor is squeezed out of its pocket resulting in the destabilization of the virus particle, which then disintegrates and releases its genetic material to infect the cell and

replicate.

Researchers led by Rossmann have developed antiviral drugs for other enteroviruses such as rhinoviruses that cause the common cold. The drugs work by replacing the pocket factor with a molecule that binds more tightly than the real pocket factor.

This hinders infection in two ways: The drug molecule fills the pocket, making it difficult for a virus to bind to a human cell. Also, because the drug binds tightly to the pocket, it stabilizes the virus and keeps it from disintegrating and releasing its genetic material into the host cell.

However, in enterovirus 71 - or EV71 - a portion of the pocket factor sticks out of the pocket, exposing a hydrophilic tip, whereas the pocket factors in other related viruses are entirely enclosed in the pocket. In order to hinder EV71 infection, antiviral drugs must have a hydrophilic tip at one end to mimic the pocket factor.

"The major point of this paper is that it suggests how to design a drug to inhibit EV71 infection," Rossmann said.

Hand, foot and mouth disease, an infection most common among young children, sometimes arises in a daycare setting. Of the 427,278 cases of the disease recorded in mainland China between January and May 2010, 5,454 cases were classified as severe, with 260 deaths, according to the World Health Organization.

"Right now, there isn't much you can do for a child who contracts encephalitis," Kuhn said.

Future work will include research aimed at developing an antiviral drug for EV71. The research has been funded by the National Institutes of Health.

More information: Crystal Structure of the Hand, Foot, and Mouth Disease Virus, Enterovirus 71, *Nature Structural & Molecular Biology*.

ABSTRACT

Enterovirus 71 is a picornavirus associated with fatal neurological illness in infants and young children. Here we report the crystal structure of enterovirus 71 and show that, unlike in other enteroviruses, the "pocket factor," a small molecule that stabilizes the virus, is partly exposed on the floor of the canyon. Thus the structure of antiviral compounds may require a hydrophilic head group designed to interact with residues at the entrance of the pocket.

Provided by Purdue University