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RESEARCH NEWS

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New Ways to Disarm Deadly South American Hemorrhagic Fever Viruses

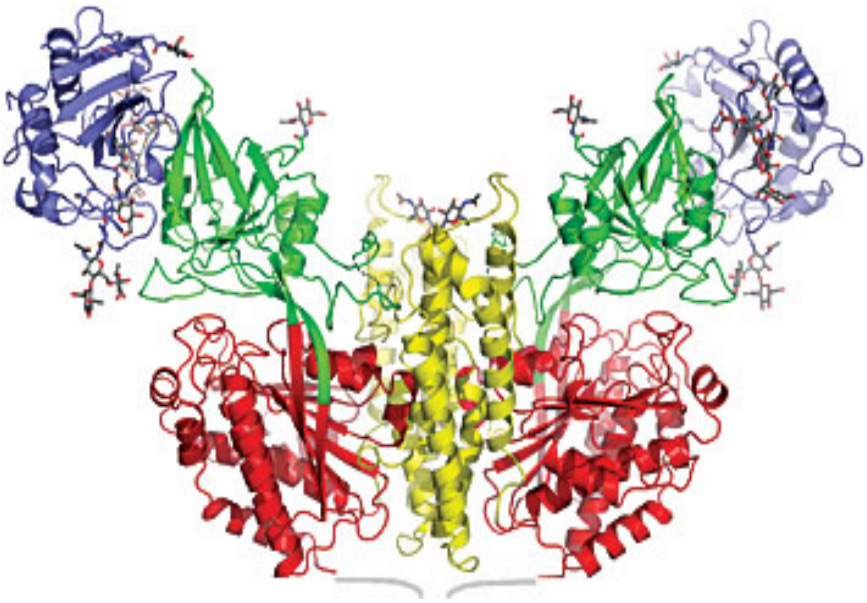

Image Title: Several viruses found in South America can cause hemorrhagic fevers when transmitted from small rodents to humans. These viruses, including the Machupo virus, attach to cells by binding transferrin receptor, a protein that regulates cellular iron uptake. Transferrin receptor is a butterfly-shaped molecule that consists of three parts, including the apical domain shown in green. The normal function of the apical domain is unknown, but Harrison and Abraham's new study shows that the Machupo virus surface protein, shown in blue, latches on to the tip of the apical domain. - Jonathan Abraham and Stephen C. Harrison

New World hemorrhagic fevers are emerging infectious diseases found in South America that can cause terrible, Ebola-like symptoms. Current treatments are expensive and only partially effective.

Now, Howard Hughes Medical Institute (HHMI) researchers have discovered exactly how one type of New World hemorrhagic fever virus latches onto and infects human cells, offering a much-needed lead toward new treatments.

“New World hemorrhagic fevers are nasty, serious, and often fatal diseases,” says Stephen C. Harrison, an HHMI investigator at Harvard Medical School and senior author of the report, published March 7, 2010, in *Nature Structural & Molecular Biology*. “The need for new interventions is high.”

Arenaviruses, the infectious agents that cause New World hemorrhagic fevers, circulate naturally in rodents and can infect people who are in close contact with the animals. Symptoms include severe inflammation and bleeding from the mouth, nose, eyes, and other orifices. Most outbreaks occur in rural regions of Bolivia, Venezuela, Argentina, and Brazil. “The outbreaks of New World hemorrhagic fever tend to be brief and brutal, with mortality rates of 20 to 30 percent,” says Jonathan Abraham, an M.D./Ph.D. candidate at Harvard University and first author of the paper. “These viruses aren’t a huge public health issue yet, but you could say the New World hemorrhagic fevers are an emerging disease threat.”

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Researchers have known about these viruses since the 1960s, but the molecular basis of the disease has only been tackled recently, says Abraham, whose graduate studies are funded by HHMI through a Gilliam Fellowship for Advanced Study. The Gilliam Fellowships program currently supports the doctoral education of 30 exceptional students from disadvantaged backgrounds.

In 2007, Abraham was working with Boston Children’s Hospital virologist Hyeryun Choe when he was co-first author on a report in *Nature* identifying the human cell surface receptor that the Machupo virus, an arenavirus, grabs to gain access to the human cell it is infecting. The receptor, called transferrin receptor 1, offers a handhold for Machupo virus as it invades cells in the body. Nearly every human cell displays the transferrin receptor, which ferries iron into cells.

Abraham then brought the project to Harrison, who had mentored the young scientist in 2004 as part of HHMI’s Exceptional Research Opportunities Program (EXROP), which places undergraduate students from disadvantaged backgrounds in the laboratories of HHMI investigators and HHMI professors. The pairing was fortuitous. In Choe’s laboratory, Abraham had developed methods to produce the Machupo virus surface protein, which links to the human transferrin receptor. Meanwhile, Harrison had stocks of purified transferrin receptor because he had previously worked to image the molecule

and understood its molecular structure.

Together, the pair made batches of the Machupo surface protein bound to the transferrin receptor and then set about creating an image showing how the two molecules connected. They used x-ray crystallography, a technique in which protein crystals are bombarded with x-ray beams. As the x-rays pass through and bounce off of atoms in the crystal, they produce a diffraction pattern, which can then be analyzed to determine the three-dimensional shape of the protein. After a data collection trip to the powerful x-ray beam at Argonne National Laboratory in Illinois, Abraham and Harrison were able to examine the atomic structure of the Machupo surface protein attached to the transferrin receptor.

The images show that the Machupo surface protein binds to the transferrin receptor in a surprising way—using a loop called the apical domain. The biological function of this loop in humans is unknown, Harrison says. Other segments of the receptor bind iron-bearing transferrin, but the apical domain appears to be uninvolved in that process. “We don’t know the normal function of the apical domain. Obviously it didn’t evolve just to give Machupo virus a way to infect humans, but that’s what the virus has evolved to latch onto,” he says.

Because the apical domain is not involved in the critical task of moving iron into cells, Harrison says it presents an attractive target for drugs. In theory, an antibody designed to attach to the apical domain would prevent the Machupo virus from attaching to cells, blocking infection. One possible treatment strategy, then, would be to infuse patients with such an antibody during the early stages of infection, which might slow the infection enough to let patients recover.

Harrison says the finding might also help virologists predict which of the 22 known arenaviruses might be capable of infecting humans. Only five are known to infect humans now—and all of those bind to the human transferrin receptor. Presumably the other 17 viruses produce surface proteins that are unable to bind to the human transferrin receptor, Harrison says.

For Abraham, the idea of finding a treatment for these New World hemorrhagic fevers is close to his heart. His family hails from Haiti, where there is a “huge burden of infectious diseases. I’d like to dedicate my career to studying pathogens in underserved parts of the world,” he says.