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Stephen Bradt
University of Pennsylvania

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Scientists Pinpoint a Protein Critical to the Function of the Ebola Virus

By Steven Bradt

Scientists at the University of Pennsylvania's School of Veterinary Medicine have identified a sequence of just four amino acids in a key viral protein that may be critical to the spread of the Ebola virus. Their findings, reported in the Dec. 5 issue of the *Proceedings of the National Academy of Sciences*, offer the promise of future treatments for Ebola outbreaks that prove fatal for up to 90 percent of victims.

Ebola hemorrhagic fever is one of the most dangerous and ghastly viral diseases known to humans, but much about the underlying virus continues to elude researchers, said lead author Ronald N. Harty, Ph.D, assistant professor of microbiology. Like all viruses, Ebola requires a host in order to replicate, invading host cells and using them as factories to crank out countless copies of its own genetic material.

Harty's work indicates that after this newly created RNA is packaged into viral protein coats, the newborn viruses rely on the little-known VP40 protein to traverse the cell's membrane, exiting the cell by simply budding off from it. These viruses proceed to infect other host cells until the cumulative effect of this explosive viral proliferation overwhelms the body.

The function of VP40, found directly under the virus's external coat, had previously been unknown. Harty worked with the isolated protein and single mammalian cells to discover that a short segment of VP40 appears to be what enables Ebola to slip out of host cells.

"This new understanding of the role VP40 plays in Ebola's replication cycle could be a critical first step in the development of new antiviral drugs to combat Ebola," said Harty. "Now that we've identified this vital region of this key protein, we may have a target for new Ebola-fighting medications."

Because Ebola hemorrhagic fever occurs only in relatively small, sporadic outbreaks, Harty said antiviral drugs represent a logical approach to controlling the disease. There is currently no specific treatment other than the administration of intravenous fluids to combat severe dehydration.

Harty's findings implicate a proline-rich sequence of amino acids within VP40 as the key to its ability to bud efficiently from cell membranes. This segment of the protein – dubbed a PPxY motif because of its signature sequence of two prolines (P) and a tyrosine (Y) separated by any single amino acid – interacts physically and functionally with cell enzymes known as ubiquitin ligases. Such a virus-host interaction is thought to be crucial

for the virus to escape from the cell.

One of just seven proteins produced by Ebola, VP40 was significantly impaired in its ability to exit mammalian cells by even the slightest mutations affecting the PPxY motif, Harty found.

"Motifs similar or identical to PPxY are also common in other viruses, including HIV and the virus responsible for rabies," Harty said. "In each case, they function in virus release from infected cells, and they may carry out this function by mediating interactions with host cell proteins."

Harty was joined in the research by Melissa E. Brown and Felicia P. Hayes at Penn and by Guangli Wang and Jon Huibregtse at the University of Texas at Austin. The work was funded by the University of Pennsylvania Research Foundation.

About Ebola hemorrhagic fever

World Health Organization statistics indicate that Ebola hemorrhagic fever has killed 793 of 1,100 known victims since it was first identified in Sudan and Zaire in 1976. Ebola is believed to originate in the jungles of Africa and Asia, although it's not known where, how or in what carrier species the virus lies dormant between outbreaks.

Ebola is transmitted through close contact with bodily fluids, such as mucus, saliva and blood. Ebola hemorrhagic fever can take days or weeks to incubate, manifesting itself only with the sudden onset of fever, weakness, muscle pain, headache and sore throat, followed by vomiting, diarrhea, rashes and reduced kidney and liver functions. Later, victims start to hemorrhage and bleed through the nose, mouth, eyes and other orifices. Blood and other bodily fluids also begin seeping through the skin, producing painful blisters.

The last major Ebola outbreak was in 1995 in Zaire, with as many as 300 lives lost; the most recent outbreak, in Uganda, killed more than 100 people several months ago. Because the virus typically kills its victims faster than it can spread, outbreaks have usually been extinguished before spreading very far.

On the cover

Linda, a 13 year old African elephant, was seen at New Bolton Center for diagnostic radiographs of her leg. To keep her content, her two constant companions, Shanna, a 17 year old African elephant, and Cora, a 44 year old Asian elephant, accompanied her. All three went to radiology, and the two older ones watched while technicians took the radiographs of the younger elephant's leg. Once the procedure was complete the "family group" walked back to the trailer in a line, trunks holding tails.

