# Discovery advances fight against phleboviruses

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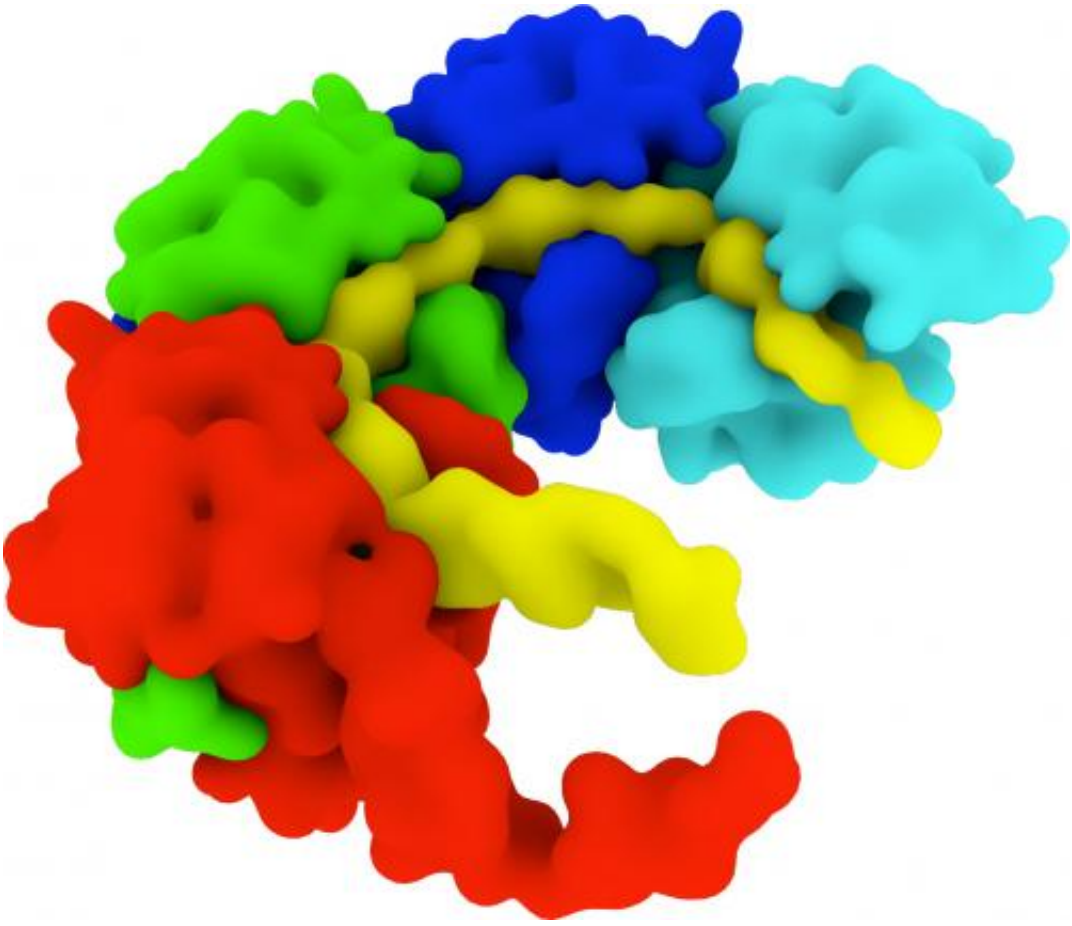

Phlebovirus: The RNA genome is in yellow and each of the "N" protein molecules (N = nucleocapsid protein) is in a contrasting color.

(Medical Xpress)—Researchers in the Life Sciences Institute at the University of Michigan have discovered how a particular type of virus

hides and protects its genetic information from the immune system, a design that allows it to replicate inside cells of an infected person or animal.

The discovery, detailed Nov. 5 in the Proceedings of the National Academy of Sciences, offers the first picture of a potential drug target for phleboviruses, a family of viruses that attacks humans and animals via insect bites.

An increasing number of human cases of different types of phleboviruses have been diagnosed in the last five years, and some have been fatal. There are currently no antiviral medications or immunizations for phleboviruses.

The phleboviruses are part of the bunyavirus family, negative-sense RNA viruses that include about 330 types. Negative-sense viruses have a single strand of RNA, which they must replicate upon entering the cell. Other negative-sense RNA viruses include those that cause flu, rabies and measles.

Researchers in the lab of Janet Smith, a faculty member at the Life Sciences Institute, professor of biological chemistry and the director of the Center for Structural Biology, isolated a protein from the Rift Valley Fever virus, a phlebovirus that typically infects cattle but has also caused fatal outbreaks among human populations in Egypt, Kenya, Saudi Arabia and Yemen.

They found that the Rift Valley Fever virus hides its genome within a protein structure that is "very weird," Smith says. They used X-ray crystallography to diagram the structure of the viral protein and found that it tucks the RNA genome in a narrow groove in the protein, concealing the RNA inside. Unlike other viruses—like flu or measles—that package their RNA genomes in regular, symmetrical

protein shapes, the Rift Valley Fever virus threads its RNA into a seemingly random string of proteins.

Working with Georgios Skiniotis, a faculty member at the Life Sciences Institute and assistant professor of biological chemistry, the researchers used electron microscopy to show that the entire virus uses the same RNA-hiding scheme as the isolated protein.

"We describe it as nature's most 'primitive' packaging scheme," Smith said.

The body's immune system is always on the lookout for odd RNA strands, Smith says, and by keeping its RNA packed into this little slot in the protein, the virus can escape detection.
Aiming a drug molecule at that slot might interrupt the virus's replication mechanism—and stop its spread.

"It's our first picture of a phlebovirus protein in action, the first step in finding a druggable target," Smith said. "X-ray crystallography and electron microscopy techniques capture pictures of the viral proteins in action, pictures that are essential for developing antiviral drugs and vaccines."

Veterinarians first reported Rift Valley Fever virus in cattle in Kenya in the early 1900s. More recently, however, other phleboviruses have been discovered.

In 2009, two Missouri farmers became ill with undiagnosed flu-like symptoms of fever, gastrointestinal distress and low platelet count after being bitten by ticks. Scientists determined that they had been infected with a previously unknown phlebovirus that they dubbed the Heartland virus in a paper published in the New England Journal of Medicine in August 2012.

In 2006, farmers in China began to contract an illness with very similar symptoms; in 2009, researchers pinpointed a new phlebovirus, called SFTS virus (for "severe fever with thrombocytopenia syndrome"), and began tracking patients. Since then, about 170 cases have been diagnosed, with a fatality rate of 12-30 percent.

"This is a little-known part of virology," Smith said. "We really don't know many molecular details about the phleboviruses."

Scientists currently assume that the structure of the Rift Valley Fever virus is very similar to other phleboviruses. Smith says the understanding of how this particular phlebovirus hides its RNA also applies to other viruses in the family.

While the number of reported cases of phleboviruses is rising, Smith says the number is probably rising because scientists are able to isolate and observe viruses and to sequence their genomes.

**More information:** Phleboviruses encapsidate their genomes by sequestering RNA bases. www.pnas.org/content/early/201 … /1213553109.abstract

Provided by University of Michigan