Researchers reveal 3-D structure of bullet-shaped virus with potential to fight cancer, HIV

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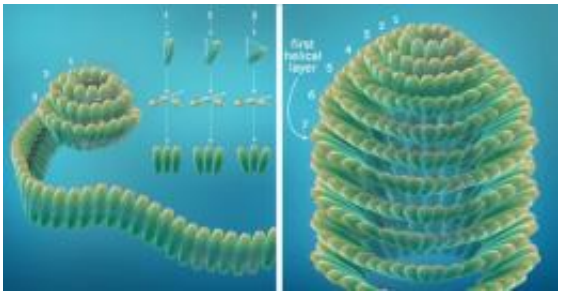

Assembly of bullet-shaped VSV virion.

(PhysOrg.com) -- Using cryo-electron microscopy and advanced image-processing methods, UCLA researchers have developed a model of how the potentially therapeutic vesicular stomatitis virus assembles.

Vesicular stomatitis virus, or VSV, has long been a model system for studying and understanding the life cycle of negative-strand RNA viruses, which include viruses that cause influenza, measles and rabies.

More importantly, research has shown that VSV has the potential to be genetically modified to serve as an anti-cancer agent, exercising high selectivity in killing cancer cells while sparing healthy cells, and as a potent vaccine against HIV.

For such modifications to occur, however, scientists must have an accurate picture of the virus's structure. While three-dimensional structural information of VSV's characteristic bullet shape and its assembly process has been sought for decades, efforts have been hampered by technological and methodological limitations.

Now, researchers at UCLA's California NanoSystems Institute and the UCLA Department of Microbiology, Immunology and Molecular Genetics and colleagues have not only revealed the 3-D structure of the trunk section of VSV but have further deduced the architectural organization of the entire bullet-shaped virion through cryo-electron microscopy and an integrated use of image-processing methods.

Their research findings appear this month in the journal *Science*.

"Structures of individual rhabdovirus proteins have been reported in *Science* and other high-profile journals, but until now, how they are organized into a bullet shape has remained unclear," said study author Z. Hong Zhou, UCLA professor of microbiology, immunology and molecular genetics and a member of the CNSI. "The special shape of VSV — a bullet head with a short, helical trunk — has lent to its evasion from three-dimensional structural studies."

Based on their research into the structure of VSV, the team proposed a model for the assembly of the virus, with its origin at the bullet tip. Their data suggest that VSV assembles through the alternating use of several possible interaction interfaces coded in viral protein sequences to wind its protein and RNA chain into the characteristic bullet shape.

"Our structure provides the first direct visualization of the N and M proteins inside the VSV virion at 10.6-Ĺ resolution. Surprisingly, our data clearly demonstrated that VSV is a highly ordered particle, with the nucleocapsid surrounded by, instead of surrounding, a matrix of M

proteins," said lead study author Peng Ge, a visiting graduate student at UCLA from Baylor College of Medicine. "To our amusement, the sequence in assembling viral protein and RNA molecules into the virus appears to rhyme with the first several measures of Mozart's piano sonata in C-Major, K.545." (This musical correlation is illustrated in the paper's supplementary movie 2.)

The findings could help lead to advances in the development of VSV-based vaccines for HIV and other deadly viruses, according to the researchers.

"Our structure provides some of the first clues for understanding VSV-derived vaccine pseudotypes and for optimizing therapeutic VSV variants," Zhou said. "This work moves our understanding of the biology of this large and medically important class of viruses ahead in a dramatic way. The next stage of research for our team will be to reveal the details of molecular interactions at the atomic scale using advanced imaging instruments now available at CNSI."

The Electron Imaging Center for Nanomachines (EICN) lab at the CNSI has Cryo-EM instrumentation, including the Titan Krios microscope, which makes atomically precise 3-D computer reconstructions of biological samples and produces the highest-resolution images available of viruses, which may lead to better vaccines and new treatments for disease.

More information: The *Science* paper is available at www.sciencemag.org/cgi/content/full/327/5966/689

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