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Molecular 3D structure of viral "copying machine" deciphered

Researchers at the University Medical Center Göttingen (UMG) and the Max Planck Institute (MPI) for Multidisciplinary Sciences have shown, for the first time, how the genetic material of the Nipah virus replicates in infected cells. The virus can cause fatal encephalitis in humans. Using cryo-electron microscopy, the team led by Prof. Dr. Hauke Hillen was able to visualize the three-dimensional structure of the viral "copying machine". These findings could contribute to the future development of antiviral drugs for the treatment of Nipah virus infections. The results of the study have now been published in the journal Nature Communications.

Disease outbreaks and regional epidemics caused by viruses transmitted from animals to humans continue to occur around the world. Many pandemics that spread across national borders also originate from this mode of transmission. Early research into pathogens is essential to ensure that effective drugs and vaccines are available in the event of an epidemic or pandemic.

The World Health Organization (WHO) classifies Nipah virus as a potentially very dangerous virus for humans. It has caused several outbreaks in Asia in recent years. The virus can be transmitted from bats to humans, causing severe disease that can be fatal in up to 70 percent of cases. It can also be transmitted from person to person, spreading very quickly. There are currently no targeted drugs or vaccines available to treat Nipah virus infection.

Approach for drug development

Researchers led by Prof. Dr. Hauke Hillen, head of the "Structure and Function of Molecular Machines" research group at the Department of Cellular Biochemistry at the University Medical Center Göttingen (UMG) and research group leader at the MPI for Multidisciplinary Sciences, have succeeded in visualizing the three-dimensional structure of the Nipah virus copy machine, also known as RNA polymerase, at molecular resolution for the first time. The RNA polymerase is responsible for the replication of viral genetic material and the activation of viral genes, and is essential for the replication of the virus in cells. It is therefore a promising target for drug development. The scientists used cryo-electron microscopy to decipher the three-dimensional (3D) structure of the RNA polymerase. They shock-froze the RNA polymerase in two different states, free and bound to viral RNA, and then took thousands of individual images of the molecule in a state-of-the-art electron microscope. High-performance computers were then used to calculate a 3D structure with almost atomic resolution.

"This is an important milestone because until now it was not known exactly what the RNA polymerase of the Nipah virus looks like and how it interacts with the viral RNA. Our data show that it is similar to the RNA polymerases of other related RNA viruses, such as Ebola, but has some special features," says Prof. Hillen. The data also reveals how such a viral RNA polymerase uses the genomic viral RNA as a template for the copying process, and how it binds the newly produced product RNA and nucleotide building blocks. "These results are particularly exciting because a molecular snapshot of the RNA polymerase in its active state has never been visualized before, even for related viruses such as Ebola," says Dr Fernanda Sala, postdoctoral researcher in the research group "Structure and Function of Molecular

Machines" and first author of the study. "By comparing the snapshots of free and RNA-bound RNA polymerase, we were not only able to decipher its structure, but also to gain new insights into its dynamics. Such data can be useful in the targeted development of drugs that could inhibit the RNA polymerase," she continues.

The results have been published in the journal Nature Communications.

Original publication:
Sala F, Ditter K, Dybkov O, Urlaub H, Hillen HS. Structural basis of Nipah virus RNA synthesis. Nature Communications (2025). DOI: https://doi.org/10.1038/s41467-025-57219-5

The study in detail

The RNA polymerase works like a molecular copying machine, reading the genetic information of the virus and using it as a template to make an exact copy of the viral genome. Many antiviral drugs, such as acyclovir for herpes infections or remdesivir for COVID-19, act as inhibitors of viral RNA polymerase. In the case of Nipah virus, however, the exact three-dimensional structure and function of the RNA polymerase was unknown, making the development of specific inhibitors difficult.

Elucidation of the structure of the RNA polymerase

In Nipah virus, the RNA polymerase consists of two distinct subunits, the L and P proteins. The researchers were able to purify these proteins and study their structure using cryo-electron microscopy (cryo-EM). The RNA polymerase molecules were shock-frozen in solution and then examined in an electron microscope at minus 196 degrees Celsius. The researchers used the microscope to take thousands of individual images of the molecule and then used high-performance computers to calculate a 3D structure with near-atomic resolution. These high-resolution snapshots allowed the scientists to see for the first time how the L and P proteins interact to form the polymerase complex.

Analyzing RNA polymerase in action

In a second step, the team deciphered how the RNA polymerase interacts with the viral RNA genome during the copying process. To do this, they reproduced this process in a test tube by adding an RNA template and building blocks for the RNA copy, called nucleotides, to the RNA polymerase. Using biochemical analysis methods, they showed that the purified RNA polymerase was active in the test tube and made new RNA from the nucleotides. The researchers then used cryo-EM to visualize the 3D structure of the RNA polymerase in this active, RNA-bound state at molecular resolution.

The study was funded by the Excellence Cluster Multiscale Bioimaging: From Molecular Machines to Networks of Excitable Cells (MBExC), the German Research Foundation and the European Union.

Caption

Artistic depiction of the 3D structure of Nipah virus RNA polymerase in the active state. The structure of the Nipah virus RNA polymerase is shown as a transparent surface representation (L protein in green, P protein in orange). The viral RNA, which serves as a template for the RNA polymerase, is shown in blue, the newly produced product RNA in red. The nucleotide substrate is shown in yellow. Image: umg/fernanda sala

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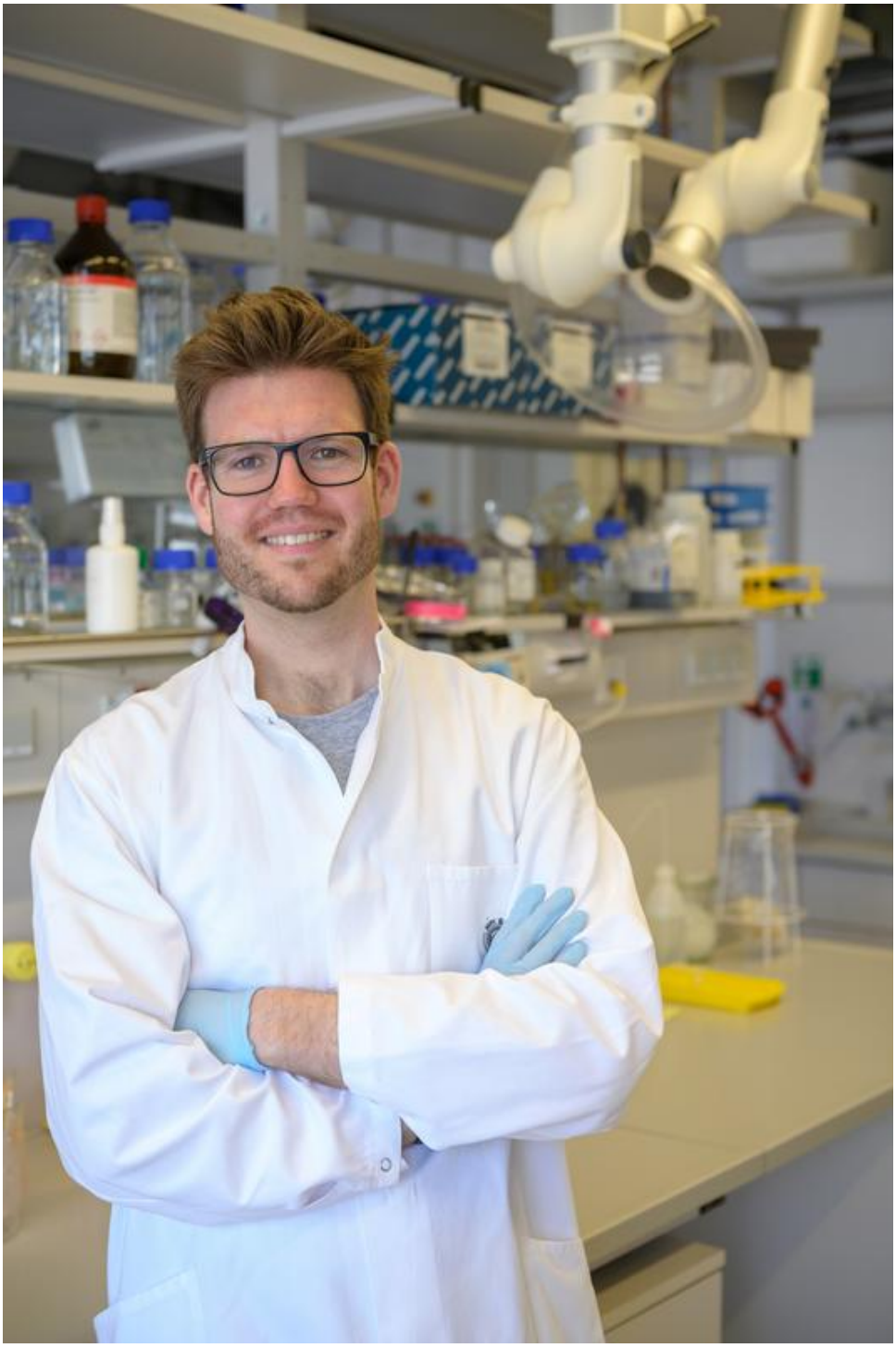
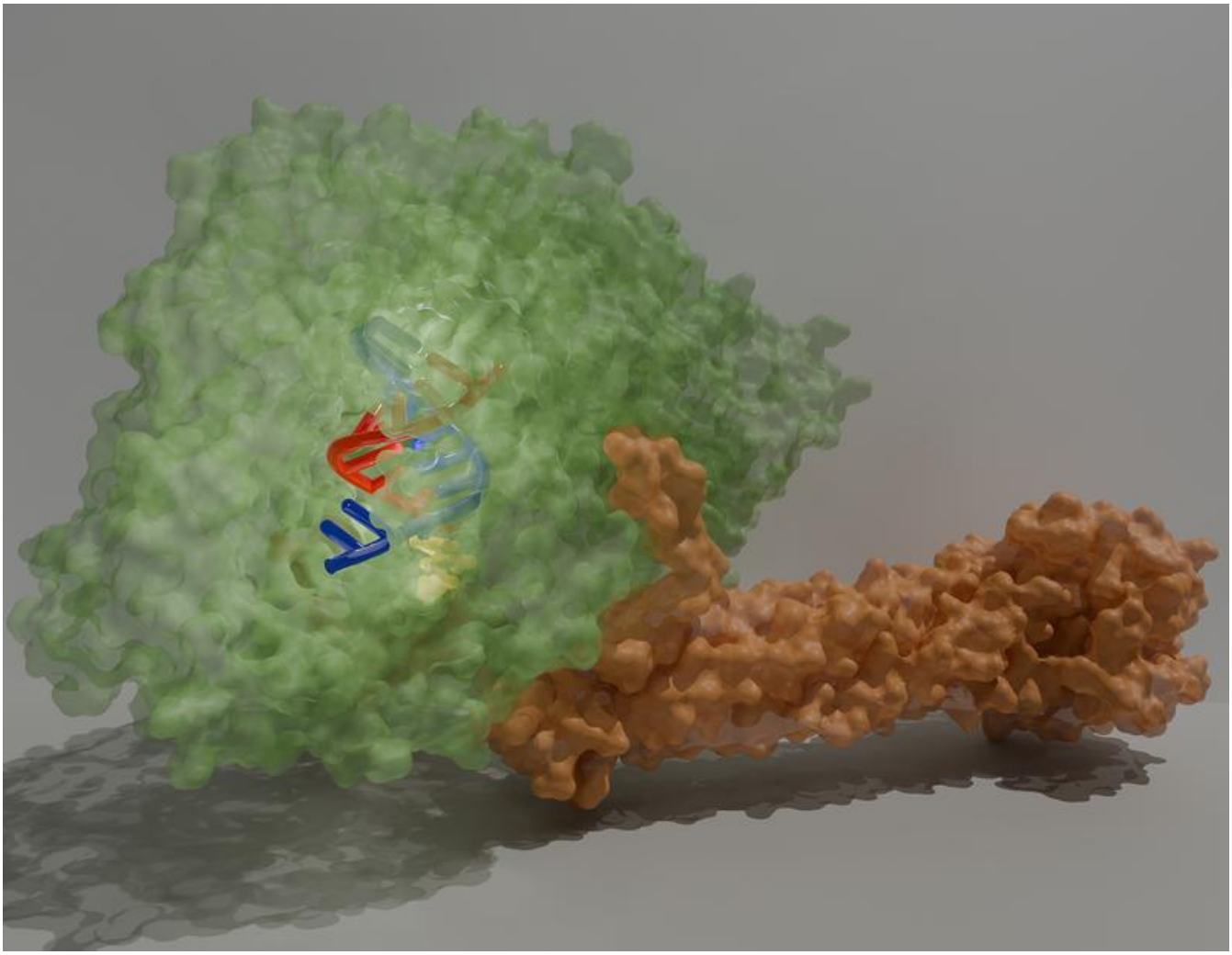


Prof. Dr. Hauke Hillen, head of the "Structure and Function of Molecular Machines" research group at the Department of Cellular Biochemistry at the University Medical Center Göttingen and research group leader at the MPI for Multidisciplinary Sciences.
Irene Böttcher-Gajewski/MPI for Multidisciplinary Sciences



Artistic depiction of the 3D structure of Nipah virus RNA polymerase in the active state. (See full caption at the end of the press release).
umg/fernanda sala