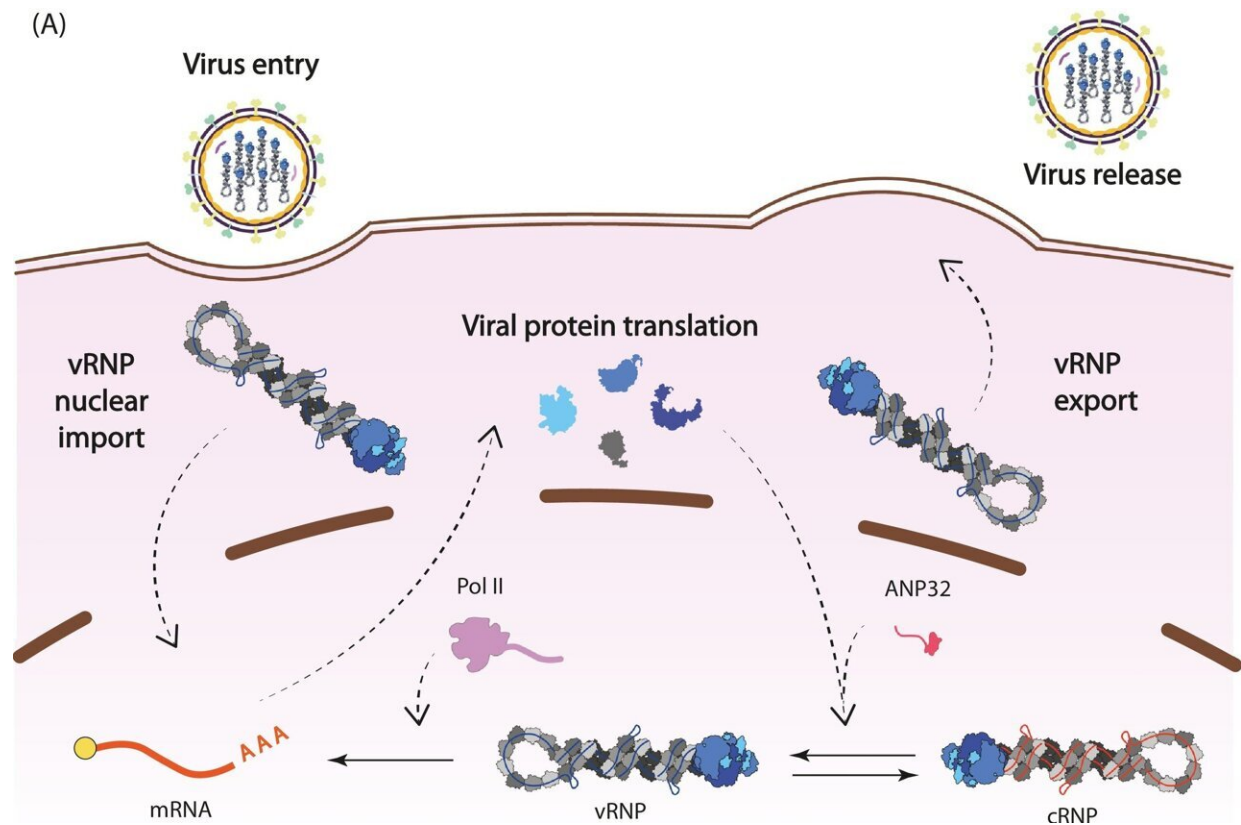


# Gaining structural insight into the influenza virus

November 4 2022



Influenza virus life cycle and structure of the influenza virus RNA polymerase.

(A) Life cycle of the influenza virus with processes involving the viral polymerase highlighted. (B) Cartoon diagram showing the influenza C virus RNA polymerase in complex with vRNA promoter in a replicating conformation, derived from an acidic nuclear phosphoprotein 32A (ANP32A)-bound structure (PDB ID 6XZR). Subunits and domains of interest are shown in different colors. (C) Schematic of the polymerase subunits. Major domains are highlighted in the same colors as in (B). The PB1 catalytic

aspartates, residues 446 and 447, are highlighted in red. Arrows beneath the schematic indicate key interaction sites with viral polymerase and host ANP32A. Blue, residues on a replicating polymerase that interact with an encapsidating polymerase; green, residues on an encapsidating polymerase that interact with a replicating polymerase; pink, residues on a polymerase that interact with host ANP32A. Abbreviations: cRNP, complementary ribonucleoprotein; vRNP, viral ribonucleoprotein. Credit: *Trends in Microbiology* (2022). DOI: 10.1016/j.tim.2022.09.015

A team of scientists at University of Oxford have worked with multiple techniques at Diamond Light Source, to solve the structure of the influenza replication machinery and to determine how it interacts with cellular proteins. This research furthers our understanding of influenza replication and how the virus adapts to different hosts.

Beyond causing seasonal flu, [influenza](#) can become pandemic when it jumps from animals to humans. By taking a closer look at the replication cycle of the virus, researchers are piecing together how influenza hijacks human and animal cells for its replication.

A recent review in *Trends in Microbiology* outlines the findings generated using X-ray crystallography and small angle X-ray scattering (SAXS) at the synchrotron and cryo-Electron Microscopy (cryo-EM) at Diamond's electron Bio-Imaging Centre (eBIC).

These structural insights have revealed new potential drug targets for the development of novel antiviral drugs to inhibit influenza virus replication.

The influenza virus stores its genes in RNA and the virus synthesizes its own RNA [polymerase](#) to replicate its genome. This viral polymerase has multiple functions in addition to replication, which [collaborative](#)

[research](#) across Diamond has helped to elucidate.

These studies show that the polymerase regulates the timing of transcription—the first step in [protein synthesis](#)—and replication, which can only begin once [viral proteins](#) have been produced. The findings reveal how the polymerase interacts with a cellular protein, ANP32A, and appropriates it to shelter viral RNA from detection by the immune system.

The currently circulating influenza A viruses are thought to be the evolutionary progeny of the virus that caused the 1918–1919 global pandemic, which was responsible for between 50 and 100 million deaths worldwide. Influenza viruses are normally restricted to infecting one type of animal host, such as birds, and require specific adaptations to jump to a different animal, like humans.

The 1918 influenza virus is thought to have jumped from waterfowl into humans and is considered the 'founder virus' that has contributed viral genome segments for all subsequent epidemic and pandemic strains. In a study published earlier this year, the group determined structures of the polymerase from the 1918 pandemic influenza virus and identified sites on the surface of the polymerase that are sensitive to inhibition<sup>1</sup>. This in turn can help identify and validate targets for drug discovery.

This research is crucial to understanding how ANP32A partly accounts for the host-jumping barrier. ANP32A differs greatly between humans and birds, forcing animal and avian influenza viruses to evolve to become less alike.

Structural biology research at Diamond provides insights into the pandemic potential of different strains of flu. By studying which regions of the viral polymerase interact with ANP32A, the researchers determined that a mutation in avian influenza's polymerase may allow it

to interact with human ANP32A, permitting that strain of bird flu to jump into human hosts<sup>2</sup>.

Structural characterization of large protein complexes is a challenge, and the influenza replication complex was no exception. X-ray crystallography at beamlines I03 and I24 was used to determine the structure of the viral polymerase in near-atomic detail, revealing that the single polymerases pair together to form dimers. To complement the crystal structure of the dimers, a structural technique known as SAXS was performed in solution at beamline B21 to demonstrate the importance of dimer formation to the function of the polymerases.

The researchers proposed that single RNA polymerases carry out transcription early in infection and switch to replication later only when they couple together as dimers, following the production of additional copies of the polymerase<sup>3</sup>.

To expand on this structural work further, the research team performed cryo-EM at eBIC. Professor Jonathan Grimes at University of Oxford explains that "cryo-EM has allowed us to begin to look at very interesting protein complexes that we would find impossible to grow crystals of in the lab."

"Diamond democratizes science. The fact that all of these techniques exist in one place and are available to the scientific community is a hugely valuable resource. These world class cutting-edge facilities are freely available to scientists from universities and institutes across the UK and EU with interesting and important biological questions."

Corresponding author on the *Trends in Microbiology* review, Professor Ervin Fodor, University of Oxford, concludes that "these studies help us to identify and validate targets for drug discovery. We are hoping that the new insights generated into workings of the [influenza virus](#)

transcription machinery using the technologies at Diamond will eventually lead to novel antivirals targeting the influenza polymerase."

**More information:** Zihan Zhu et al, A structural understanding of influenza virus genome replication, *Trends in Microbiology* (2022). [DOI: 10.1016/j.tim.2022.09.015](https://doi.org/10.1016/j.tim.2022.09.015)

Provided by Diamond Light Source

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