

EPN BAG report
Cryo-EM structures of full-length Hantaan virus polymerase
21/06/23-23/06/23

Hantaan virus is a dangerous human pathogen whose segmented negative-stranded RNA genome is replicated and transcribed by a virally-encoded multi-functional polymerase. We recently observed that, in the absence of viral RNA, a fraction of Hantaan polymerase sample oligomerizes in different multimers in equilibrium, ranging from dimers to multimers. A krios session was necessary to determine their structure as they are minoritarian, corresponding to 10 % of the particles for the dimers and 2% of the particles for the hexamers, the rest of the polymerase being monomeric (monomeric structure already determined by us).

The data collection of 14.650 movies at 105.000 x magnification performed on the ESRF Krios CM01 equipped with a Gatan K3 allowed to derive the high-resolution structure of symmetric dimers at 3 Å resolution and symmetric hexamers, composed of trimer of dimers, at 3.3 Å resolution. Multimerization of apo polymerases induces the stabilization of every polymerase domain, including the C-terminal region that notably contains a C-terminal domain involved in polymerase multimerization and a lariat region that contributes to the polymerase global steadying. The structure also reveals the location of the cap-binding domain that is essential to transcription initiation. This suggests the potential involvement of the multimers as storage systems that would stabilize the otherwise flexible C-terminal domains. These results significantly advance our understanding of Hantaan polymerase oligomerization and will be key to define antiviral compounds to counteract these life-threatening viruses.

We would like to really thank all the people who are maintaining and operating the ESRF CM01 Krios, in particular Lindsay McGregor who was our local contact for this shift.

We are in the process of writing an article relating these results and thus request this summary to remain confidential.