Bunyaviral strategies to reorganize and exploit cellular translation

Viruses are simply shells of lipids and proteins with genetic material embedded inside. When they enter the host cell, they need to multiply it, package it into new viral particles, and spread out. Different groups of viruses have their own, specialized, multifunctional polymerases, responsible for copying the viral genome and converting it into mRNA, which is then translated into viral proteins. At the same time, viruses are fully dependent on ribosomes - molecular machines of the cell responsible for building proteins. In fact, translation of proteins is one of the main battlefronts between viruses and the host cell. On one hand, viral infection triggers an innate immune response, which launches an antiviral alert in the cell. Most of the cellular translation is then turned off and only selected proteins, used to fight the virus, are produced. On the other hand, viruses use special strategies to seize control of the ribosomes, forcing them to produce their proteins.

I plan to investigate the strategies used by bunyaviruses to reorganize and exploit cellular translation. Bunyaviruses are a large and diverse group of neglected RNA viruses. Three of them are listed by the WHO among eight infectious RNA viruses that can cause future pandemics. Worryingly, in light of global warming, some of these mosquito-transmitted pathogens emerge in new regions of the world, like Central Europe. In humans, bunyaviruses cause either fatal haemorrhagic fevers or nervous system inflammations. Given that we do not have specific countermeasures against them, it is highly important to broaden our knowledge of their molecular repertoire.

Bunyaviral polymerase initiates transcription of the viral genome into mRNA by stealing the 5′ cap feature from the host mRNA. This guarantees that the 5′ end of the viral mRNA will not be considered foreign. Another smart bunyaviral strategy, ensuring efficient translation of the viral mRNA, is the coupling of the viral polymerase with the ribosome, unique in the eukaryotic system. Despite substantial advancements in the bunyaviral field during the last decade, molecular details of these two important mechanisms remain unclear.

With my SonataBis project, I will fill these gaps in our knowledge. I plan to perform experiments on human cell lines and use only those elements of the virus which are necessary for its transcription and translation. In other words, complete viruses will not be used, which will simplify all the experimental procedures. I will identify host proteins abused by bunyaviruses during both these processes. I will also monitor how the translation of bunyaviral proteins affects the overall production of cellular proteins. Finally, I will use cryo-electron microscopy to determine the structures of the protein complexes involved in the bunyaviral transcription and translation. Results of my studies will define new research avenues in the RNA virus field and will allow to design innovative therapies and broad-spectrum antivirals, thus raising our preparedness against future pandemics.