

Predicting future pandemics is an impossible task. However, continuous interactions between human activities and wildlife populations increase the risk that the next epidemic or epizootic will be caused by a virus transmitted from wild animals to humans and domestic animals. Orthoflaviviruses transmitted by mosquitoes are the most likely to spread to new regions because of the increased geographic distribution of the insects. This project will focus on a group of Orthoflaviviruses related to the yellow fever virus (YFV). In addition to YFV, this group is composed of rarely studied, so-called neglected viruses: Wesselsbron virus (WESSV), Sepik virus (SEPV), and Fitzroy River virus (FRV). These four viruses are zoonotic, meaning that infect both humans and animals. The viruses are mainly transmitted by mosquitoes, but we have shown that WESSV can also be transmitted directly. Despite the availability of an effective vaccine against YFV, thousands of people in endemic regions are still infected with YFV, and the severe form of the disease is untreatable and fatal in 50% of cases. For the other viruses, no vaccines or drugs have been developed, highlighting the urgent need to deepen our understanding of their biology and to create new therapies.

A thorough understanding of the functions of these viruses, their replication, and the cellular pathways that they exploit in the host organisms is crucial for understanding the disease mechanisms and for developing effective antiviral strategies. During an infection, the virus machinery (a few enzymes) takes over the host cells to turn them into small factories producing more viruses. Host cell responses are modified by these viral enzymes, which are also essential to for the virus to grow. **The NS2B/NS3 protease is an essential enzyme for Orthoflaviviruses and this project is focused on (1) elucidating the disease-inducing role of this protease in infected host cells; and (2) developing molecular tools for studying the viruses and testing novel inhibitors of the protease that could be used therapeutically (Fig.1).**

In this international collaboration between a Polish group specialized in biological chemistry and a Swiss group expert in virology and immunology, we will address key questions regarding the biology of YFV and the three related neglected viruses. We will combine our interdisciplinary expertise and state-of-the-art infrastructure and technologies to reach our goals. The project will promote the training and development of young scientists, provide interdisciplinary training, foster scientific exchanges, equal opportunity, and excellence in Science. Focusing on neglected zoonotic diseases, this project also enhances pandemic preparedness through basic research with translational potential.

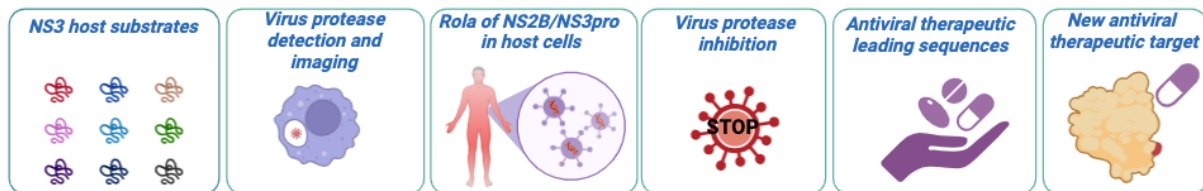


Figure 1. The main objectives and assumptions of the project include investigating the role of viral NS2B/NS3 proteases in susceptible host cells and developing cell-permeable antivirals targeting this protease using state-of-the-art technologies, including the application of macrocyclic chemical compounds and proteomics. Created with Biorender.