The most numerous group of viruses that cause diseases in humans are viruses encoding their genetic material in the form of ribonucleic acid (RNA). These include, for example, the viruses that cause influenza, SARS, COVID-19, and Zika or Ebola diseases. One subgroup of RNA viruses contains a single strand of RNA that can directly serve as a template for the production of component proteins of new virus particles in an infected cell. These viruses are referred to as (+)ssRNA viruses. In order to produce new copies of the virus, the RNA must be replicated. A special enzyme called replicase first copies the RNA strand into its complementary form (the complementary form is, in a sense, a mirror image of the genetic code sequence, in which within the four letters of the genetic code each letter is exchanged for its equivalent). The complementary RNA is then used to synthesize multiple copies of the RNA strand, identical to its initial form, which can be incorporated into new viruses.

In this project, we will study replicases from two groups of (+)ssRNA viruses. The first is the togaviruses, which include one of the most important new pathogens, the Chikungunya virus that causes epidemics in tropical countries. Symptoms of infection include fever and joint pain that may persist for months. The mortality rate is about 1 in 1000 cases. The second group is the matonaviruses, which include the rubella virus, a fairly common infection with relatively mild symptoms. Rubella, however, can cause congenital problems, if a pregnant woman is infected.

The atomic three-dimensional structures of the replicases from toga- and matonaviruses and their mechanism of action remain unknown. These replicases contain several elements (enzymes) and come in two forms. The first one is present in the early stages of virus replication and its elements are linked together in one long chain. Its role is to synthesize the complementary form of RNA. The second form appears later during infection of the cell. Its individual elements are separated from each other but remain bound to each other. The role of this form is to synthesize the initial RNA form based on the complementary form. It is not known what exactly the differences in the structure of the two forms are and why they have different properties. Our goal is to determine the exact structure of replicases at the level of individual atoms. We plan to use, among other approaches, electron microscopy, which provides magnifications that enable us to visualize individual molecules of large enzymes such as replicases. This will allow us to understand how they work.

At each stage of synthesis, the replicase must find special regions of the genome from which to start synthesis. These regions have been identified, but it is not known how the replicase recognizes them. We will perform biochemical experiments and structural studies to answer this question.

Currently, no drugs are available to combat toga- and matonaviral infections. One of the goals of this project is to identify substances that can inhibit the replicases from these viruses and thus the multiplication of the virus itself. These substances could be used as antiviral drugs.

In summary, this project will provide fundamental knowledge of the mechanisms of replication of viruses that cause, among others, Chikungunya disease and rubella. Learning about these mechanisms will allow us to propose new ways to inhibit the replication of these viruses.