

Herpesviruses are among the most widespread pathogens, in addition to the eight species that infect humans (such as alphaherpesviruses: HSV-1 and HSV-2 and chickenpox and hemiparesis virus VZV), this family of viruses (Herpesviridae) also includes numerous species that cause disease in livestock and wildlife. Often these diseases are epidemic in nature, posing a serious economic problem. The best way to prevent the spread of herpesviruses is through prophylactic vaccines. However, due to the developing resistance of herpesviruses to currently used vaccines and drugs, another solution is to develop new antiviral therapeutics. Currently available drugs are mainly nucleotide analogs (acyclovir, ganciclovir, idoxuridine, valacyclovir). The development of effective drugs is possible due to a thorough understanding of the molecular mechanisms of action of herpesviruses, which in the course of evolution have developed a variety of mechanisms to inhibit or evade the innate and acquired immune response of the affected organism. Among the most characteristic features of herpesviruses affecting the course of disease are the ability to reside in the host in a latent state, known as latency, and the ability to modulate the immune response. Cellular immunity, mediated by CD8+ T lymphocytes, is the primary defense mechanism against many viral infections. This immunity depends on the efficient recognition of viral peptides presented by MHC class I molecules on the cell surface. Herpesviruses have developed various strategies to interfere with MHC I processing and antigen presentation, resulting in reduced expression of MHC I molecules on the cell surface. One mechanism for evading the immune response is inhibition of the transporter associated with antigen processing TAP. The physiological role of TAP is to transport antigenic peptides from the cytoplasm to the endoplasmic reticulum for binding to MHC I proteins. Products of the UL49.5 protein orthologs of members of the Varicellovirus genus, including BHV-1, PRV, EHV-1 and EHV4 have been identified as a new class of inhibitors. TAP inhibitors also include proteins of human herpesviruses i.e. EBV and HCMV. In response to the threat of human and animal herpesvirus infections planned research aims to understand what are the key structural factors of these proteins, affecting their biological activity.

The main objective of the presented project is to determine the 3D structure of immunomodulatory viral proteins (TAP inhibitors) of selected herpesviruses and to study their interaction with lipid bilayer models. To achieve the adopted research goal, the spatial structures of TAP protein inhibitors will be determined using circular dichroism (CD), nuclear magnetic resonance (NMR) and molecular modeling techniques. In addition, the affinity of these proteins and their strength of interaction with the lipid membrane will be determined using fluorescent spectral shift assay (SPP) and quartz crystal microbalance with dissipation mode (QCM-D) technique. As part of the project, we plan to conduct studies for the following proteins: protein UL49.5 of bovine herpesvirus type 5 (BHV-5), protein UL49.5 of equine herpesvirus types 1 and 4 (EHV-1, EHV-4), protein UL49. Five of pseudorabies virus (PRV), US6 protein of human cytomegalovirus (HCMV), BNLF2a protein of Epstein-Barr virus (EBV), and CPXV012 protein of cowpox virus (CPX). The proposed research is part of the modern trend of viral protein research. This project may contribute to the development of herpesvirus research, and the determination of the 3D structures of these proteins may help in understanding the pathogenesis and course of the immune response. The results obtained will provide a better understanding of what happens in the human body during disease, but also may allow the development of new therapeutics in the future.