Herpesviruses are one of the largest and the most widespread family of viruses in the world, represented by roughly 200 species. The scientists say that every organism may have at least one herpesvirus invader. The most common representatives infecting humans are herpes simplex virus type 1 and 2 (HSV-1, HSV-2) and varicella-zoster virus (VZV). Many herpesvirus infections are relatively mild in symptoms, however, due to the virus ability to establish a so-called latent infection once infected individuals will carry the virus for the entire life. The frequency of reactivation from the latency, and subsequent outcome of the infection depends on the condition of the immune system of a host. When we suffer from immunosuppression, recurrent infections happen more often and can cause serious complications.

The success of herpesviral long-life survival was achieved thanks to their remarkable immunomodulatory properties. During co-evolution with their host, herpesviruses have developed distinct mechanisms to evade the immune response. An important strategy aims to escape cytotoxic T cells patrolling our body. Our cells present to cytotoxic T cells probes of their content, called antigenic peptides, on molecular platforms formed by MHC I (major histocompatibility complex class I) molecules. Inside a cell, the peptides must be transported by a dedicated transporter – TAP, which can be blocked by a viral protein. Mechanisms of TAP inhibition vary among viruses, and one of them – bovine herpesvirus 1 (BoHV-1) exhibits a unique ability to cause not only inhibition but also degradation of the transporter by proteasomes. Despite very intensive research on a protein responsible for this action – UL49.5 – the exact mechanism of TAP removal remains unknown.

Proteins targeted for degradation are tagged by a small molecule called ubiquitin. The cellular ubiquitin-proteasome system utilizes a specific group of enzymes – E3 ubiquitin ligases – for protein degradation. Our hypothesis is that virus UL49.5 protein could hijack the host ubiquitin-proteasome system to induce TAP degradation. In this project, we propose a novel approach that aims to analyze changes in the cellular protein degradation machinery in the presence of UL49.5. The preliminary study with the use of gene silencing technology combined with high throughput fluorescent microscopy has led to an identification of 20 potential candidates out of 2000 tested. This project aims to validate and confirm the role of these proteins in viral immune evasion.

Infections with bovine herpesvirus 1 are of a big economic importance among cattle breeders. Although BoHV-1, as a species-specific pathogen, is not capable of replicating in normal human cells, it may infect a number of human cancer cells. This observation made BoHV-1 a potential candidate for oncolytic anti-cancer therapy. The advantage of oncolytic viral vectors over traditional anti-cancer therapies is the selectiveness of viruses to kill tumor cells. However the clinical application of BoHV-1 in oncolytic therapy requires a better understanding of the basic principles of viral immunomodulation, which is the aim of this project. What is more, elucidating the basic molecular mechanisms of virus-host interaction on a veterinary model can be helpful in the research on closely relates human-infecting herpesviruses.