Poxviruses belong to the family of large animal viruses that cause infections in humans and various animal species. The largest representative of poxviruses is the smallpox virus (VARV), responsible for highly infectious and debilitating disease in humans, with high mortality rates (up to 30%). In 1980, the World Health Organization (WHO) announced the complete elimination of smallpox from our globe, thanks to the successful vaccination campaign against smallpox. So far, this is the only unprecedented eradication of human infectious disease.

The eradication of smallpox has led to the cessation of routine preventive vaccinations. Currently, decreasing antipoxvirus immunity in human population has two major consequences. Firstly, there is a risk of intentional or accidental introduction of VARV into the environment, since the virus has not been destroyed and is held and examined at two research institutes closely cooperating with WHO [i.e. Center for Disease Control and Prevention (CDC) in Atlanta, USA and the VECTOR State Research Center for Virology and Biotechnology in Kolcovo, Russia]. In addition, using advanced synthetic biology techniques, it is possible to re-emerge the virus only from viral DNA obtained as a result of chemical synthesis. Therefore, CDC considers VARV as a category A bioterrorism agent, what means that this virus is the highest priority factor that pose the greatest threat to the entire society in the world. The second consequence of vaccination discontinuation is undoubtedly the increasing incidence of zoonotic infections caused by other orthopoxiruses, not only in humans, but also in animals accompanying humans. This applies to infections caused by vaccinia virus (VACV), cowpox virus (CPXV) and monkeypox virus (MPXV). The latter virus starts to acquire adaptability to human as its "new" host, and it is suggested that in the future it will be able to maintain itself independently in the human population, especially in immunocompromised individuals.

Because of obvious reasons, experiments using VARV cannot be conducted (except the aforementioned laboratories), meanwhile new antipoxvirus drugs still should be developed. Therefore, to study pathogenesis of VARV, a surrogate model of ectromelia virus (ECTV) infection in mouse is used, which is currently the best small animal model to study interactions of the poxvirus with its natural host. Similarly to VARV, ECTV has a very narrow range of its natural hosts (human and mouse, respectively), therefore it is possible to determine a wide spectrum of sophisticated strategies acquired by the virus to control functions of immune cells, including dendritic cells (DCs). DCs are key cells involved in stimulation of specific immune response aimed at eliminating invading infectious agents and conditioning recovery. Our previous study has shown that ECTV, in contrast to VACV and CPXV, can productively replicate in DCs. Moreover, ECTV reduces the expression of cysteine cathepsins, i.e. cathepsin B, L and S, to improve the efficiency of its replication cycle in DCs. Meanwhile, cysteine cathepsins are important group of proteases that regulate numerous physiological processes and usually occur in high concentrations in endosomes and lysosomes, where they are crucial for protein breakdown and regulation of immune response involving major histocompatibility complex (MHC) class II proteins. Cathepsins may also promote development, expansion and metastasis of tumors, and can be associated with other pathological conditions such as chronic inflammation, autoimmune disorders and cardiovascular diseases.

The aim of this project is to investigate the role of cysteine cathepsins, such as cathepsins B, L and S in regulation of the course of orthopoxvirus infection. In particular, the project will concern 1) determining the regulation and activity of individual cathepsins and cystatins (cathepsin inhibitors) during infection with ECTV (virus-natural host system) and VACV (virus-non-natural host system) in susceptible and resistant mice, especially in DCs; 2) determining if and how cathepsin deficiency influences disease progression and regulates DC functions during the course of poxvirus infection. Obtained results will allow to learn about the role of cathepsins in promoting/limiting viral infection and stimulation of a specific antiviral immune response. A better understanding of poxvirus interaction with host immune cells can contribute to the improvement of poxviral vectors used to combat infectious and cancer diseases (e.g. VACV is used as a replication vector in cancer therapy).