

## DESCRIPTION FOR THE GENERAL PUBLIC

Pseudorabies virus (PRV) is an alphaherpesvirus closely related to common human pathogens, like herpes simplex virus type 1 and 2 (HSV-1 and 2) and varicella zoster virus (VZV). PRV causes dangerous and incurable Aujeszky's disease (AD), causing neurological, respiratory and reproductive disorders in pigs, its natural hosts. Despite successful vaccination campaigns, pseudorabies outbreaks still occur in swine populations worldwide causing huge economic losses. So far, Poland is not considered free from AD and the PRV eradication program in Poland is ongoing (2015-2017). In addition to infection of its natural host, PRV infects a broad range of domestic and wild vertebrates. Infections of non-native host with a wild-type PRV strain is uniformly lethal.

A hallmark of all herpesvirus infections is the ability of the virus to establish life-long dormant (latent) infection, while virus progeny is not detected, and infected swine show no symptoms. Herpesviruses pass from latent to acute infection from time to time. Molecular mechanism of this transition has not been explained so far.

MicroRNA (miRNA) are small RNA molecules that serve as regulators of gene expression. They have been shown to regulate many cellular processes, including cell division, differentiation and oncogenesis. For the past several years a number of reports on the identification of miRNAs encoded within the genomes of herpesviruses, including PRV, has been steadily increasing. Viral miRNAs can regulate the expression of both cell and viral genes, thereby enriching the repertoire of virus-host interaction during infection. Presumably they may act as a molecular "switch" between the latent and acute infection.

So far, the research on the role of PRV-encoded miRNAs has been carried out only by bioinformatics analyses. Therefore, the objective of this project is to experimentally explore the role of PRV miRNAs. We plan to analyze the ability of PRV miRNAs to inhibit the expression of PRV genes which control virus life cycle and virus-host interactions. We also intend to study the impact of PRV miRNAs on productive viral infection.

The effect of viral miRNAs will be controlled via synthetic, selective RNA inhibitors affecting particular miRNA. Obtaining of a pool of inhibitors and the analysis of their activity, as well as a study of control of miRNA production in the cell culture system will constitute an integral part of this project.

PRV has been shown to be a useful model organism for the studies on the pathogenesis and molecular biology of herpesviruses, thus, exploration of the mechanisms of its gene regulation is a significant issue for the further development of programs to combat herpesvirus infections. PRV vaccine strains currently in use do not deter field strains from entering latent infection in vaccinated swine, so the analysis of the role of PRV miRNAs may facilitate the establishment of the effective eradication programs. In addition, studies on the utilization of PRV as a vaccine vector and as an oncolytic vector in human therapy are being conducted worldwide. Therefore, deeper studies on the regulation of viral gene expression seem to be necessary to ensure that these vectors will be safe.

This project takes into account a current trend of miRNA biogenesis regulation *in vivo* and in the cell culture systems in order to study the functions of these miRNAs. Our research may also contribute to the development of new methods of miRNA silencing as a novel antiviral therapy.