**Functional genomic analysis of *Staphylococcus aureus Kayvirus* genus phages in a search for molecular basis of wide-host range and strategies of survival with a host population**

***Staphylococcus aureus* is one of the dominant bacteria pathogenic to humans.** It is included in the so-called **ESKAPE** group - pathogens that are the leading causes of nosocomial infections due to their fast acquisition of resistance to antibiotics. The range of infections caused by *S. aureus* varies from minor skin lesions, through severe and complicated skin and soft tissue infections, to life threatening invasive diseases such as septicemia, endocarditis or toxic shock syndrome. **The increasing problem of antibiotic resistance of *S. aureus* strains has resulted in the growing interest in the methods of fight with this bacterium, alternative to antibiotics. Among them are bacteriophages - naturally occurring bacterial viruses that are harmless to humans, animals and plants. Bacteriophages of *Kayvirus* genus are obligatorily lytic phages that infect and kill cells of the majority of *S. aureus* strains isolated from patients, including antibiotic resistant strains.** They were proven to be effective antistaphylococcal agents in experimental therapies of staphylococcal infections in humans and animals. The problem is insufficient knowledge of their biology and properties responsible for their high infectivity, which are necessary for the understanding of kayviruses interactions with bacteria and for the assessment of the safety of kayviruses use. Functions of over half of ~200 genes of these bacteriophages are unknown. It is also unknown why rare strains of *S. aureus* are not successfully infected. **The aim of this project is the functional analysis of unexplored genes of a representative *Kayvirus* genus phage, learning the mechanisms that allow kayviruses to overcome the bacterial systems of defense against bacteriophages, as well as the identification of *S. aureus* genetic traits determining the sensitivity or resistance of certain strains of this bacterium to infections with kayviruses.** Our previous studies led to the determination of complete genomic sequences of seven *Kayvirus* genus bacteriophages, to the determination of specificity of these bacteriophages for various *S. aureus* strains and to the development of a method of phage therapeutic efficacy testing in curing staphylococcal infections with the use of staphylococcal infections of nematode as a model system. In the proposed project we will use a new method of construction of the tested bacteriophage derivatives depleted of single gene functions out of 60 genes selected for the analysis. We will test the properties of the defective phages obtained: their development and adsorption to host cells, their ability to infect cells of various *S. aureus* strains and to destruct the staphylococcal biofilm, and also to cure nematodes infected with a lethal dose of *S. aureus*. Additionally the tested genes will be introduced to *S. aureus* cells, with the aim to test whether and how they change the properties of bacteria. We will use fluorescent and electron microscopy, respectively, to determine the localization of tested bacteriophage proteins in *S. aureus* cells and to determine the influence of the lack of tested genes on the development and properties of the tested bacteriophages. A separate goal of the project is the identification of those proteins of tested phages that allow them to avoid the destruction of their DNA by protective mechanisms of bacteria. In turn, the *S. aureus* genes protecting strains of this bacterium from the infection by some *Kayvirus* genus phages will be identified by comparative genomic analysis of strains sensitive and resistant to the infection by particular phages. **In a view of increasing problem of antibiotic resistance in bacteria, studies on antibacterial agents, whose activity encompasses antibiotic-resistant strains have a key significance for the development of human and animal health protection system. The proposed project will provide groundbreaking data concerning kayviruses - bacteriophages that are the most effective from among others in a fight with staphylococcal infections.** It will allow one to determine the significance of numerous bacteriophages' genes that have not been explored so far e.g., for the efficiency and time of phage propagation, efficacy of staphylococcal cell infection, avoidance of staphylococcal cell mechanisms protecting them from infection with bacteriophages, destruction of staphylococcal biofilm, and therapeutic efficacy in curing staphylococcal infections. An important effect of the project will be the identification in the genomes of *S. aureus* strains, genes that are responsible for the sensitivity to infection with bacteriophages of *Kayvirus* genus, and also genes responsible for the insensitivity of rare strains to particular kayviruses. Our results may help in the future choice of certain bacteriophages of Kayvirus genus for so called personalized therapies, based on the results of fast screening methods of infecting S. aureus DNA analysis. Additionally, our studies on the influence of particular genes of bacteriophages tested on S. aureus cell properties will allow one to verify, whether the products of these genes do not influence the pathogenicity of *S. aureus* - a key question for the evaluation of safety of therapies with kayviruses.