Stop the biting: tracking the insecticide-mediated allosteric changes in voltage-gated sodium channels and design of selective, photoactivated acyl sulfonamides. Towards understanding the molecular basis of the fast inactivation process.

The most dangerous animals in the world are mosquitoes. These insects spread diseases such as malaria, encephalitis, yellow fever, dengue fever, West Nile fever or Zika virus disease. The main way to reduce transmission is the usage of chemicals that repel or kill insects. Unfortunately, the resistance to many classes of commonly used repellents and insecticides appeared in mosquitoes and other insects around the world. The firsts step to find new chemicals that could stop disease transmission is to understand the molecular mechanisms of insecticides' action and resistance.

Many insecticides act by blocking the voltage-gated sodium channels. These are membrane proteins responsible for sodium ions' conductance and the depolarizing phase of action potentials in nerve and muscle. Insecticides bind to the channel to disrupt its' function leading to the paralysis and death of an insect. However, neither the detailed characteristics of this process, nor the molecular mechanism of channels' fast inactivation is known.

In this project, we are looking for binding sites of insecticides on mosquito, cockroach and human channels (molecular docking). By running computational molecular dynamics simulation of insecticide-channel complexes, we are looking for conformational changes that lead to the channels' prolonged activation and also inactivation. In the next step, we will design selective towards insects, photoswitchable sulfonamide insecticides with light-sensitive azobenzene functional group. Compounds that will give the best results in computational simulations, will be investigated experimentally on the cockroach neurons. Measurements of sodium ions' conductance using the patch-clamp technique will enable us to test how the light-induced conformational change in design compounds affects insect sodium channels.

The project will provide a better understanding of the fast inactivation process of sodium channels. It may be the very first step in the development of a new class of light-controlled insecticides that will act selectively on insects without causing side effects in humans.