Viruses are a very peculiar form of life that somehow balances on the edge of living. Infectious virions are metabolically inactive and are in a way dead. However these seemingly dead viral particles carry a genetic material that upon entry to a host cell allows them to undergo a transition into the active phase, in which they hijack the cell and use host resources. In other words the infected cell acts as proxy of the virus to fulfill vital goals of the viral life cycle.

Interestingly many types of viruses modify mitochondria, which are indispensable for our cells. Mitochondria are responsible for production of energy, which is necessary not only to fuel our muscles but also to support other crucial functions of our body like vision, hearing and thinking. They are also involved in a process of the programmed cell death that is necessary to support regeneration of our tissues. Moreover mitochondria participate in detection of alien genetic material in the infected cell. There are thus good reasons for the viruses to evolve mechanisms influencing mitochondria e.g. to provide energy for replication or to prevent detection.

Although we recognize the viral influence on our mitochondria we do not fully understand how viruses take control over them. In the case of many viruses the mechanism of this interaction requires that viral proteins enter mitochondria. The goal of our project is to discover molecular mechanisms that allow viral proteins to localize to mitochondria.

Mitochondria have molecular machineries that import proteins because the great majority of over 1000 mitochondrial proteins are synthesized outside mitochondria and require specialized import pathways to reach their final destination. The system of protein import manages different types of proteins that need to find their way to a precise place in the elaborate structure of mitochondria and thus it is far from being simple. Molecular machineries responsible for this process are called translocases and can discriminate between different types of proteins based on targeting signals that are encoded in the amino acid sequence of proteins.

Our interest in the viral proteins targeted to mitochondria stems in part from the apparent lack of known targeting signals in most of them. Even in the case of proteins that possess the targeting signal the precise route of entry has been hardly studied. Moreover we know only a limited number of viral proteins for which mitochondrial localization has been demonstrated. We suspect that such proteins are much more abundant in viral proteins based on a premise that so many viruses interact with mitochondria.

In our project we plan to explore mechanisms of mitochondrial translocation of various viral proteins. We would like to study the proteins that were already found in mitochondria and also these that we will find in the mitochondria infected with selected viruses. However it is impossible to investigate all the viruses in the test tube because there are just too many of them. On the contrary using bioinformatic tools we can analyze thousands of viral proteins. We will screen databases of viral sequences and select those that are similar to mitochondrial proteins or have some kind of a targeting signal. From this list we will choose a small number of proteins encoded in the most relevant viruses with a highest likelihood of mitochondrial translocation and we will analyze them together with candidates selected by other two methods.

These proteins will be expressed in cultured mammalian cells to verify experimentally whether our prediction was correct and they really localize in mitochondria. The proteins that will positively pass this test will undergo more careful scrutiny. We will focus on where exactly in mitochondria they can be found, are they in the membranes or are they soluble and do they form complexes with other proteins. This analysis will lead us to an ultimate goal, which will be to find which translocases bind to viral proteins. This task will be performed by a specific isolation of viral proteins from mitochondria and identifying their partners by mass spectrometry. At the end we will verify our findings by depleting the partner proteins in cells and checking how this influences mitochondrial localization of viral proteins.

We hope that we will discover pathways that enable viruses to hijack our mitochondria. This may include pathways that are already known or completely novel routes of entry to mitochondria. We may also predict important viral interactions with mitochondria in diseases. Ultimately this will lead to better understanding of viral biology yielding new ways to fight infectious diseases.