Stroke is a serious, life-threatening medical condition that occurs when the blood supply to part of the brain is cut off. As a result, rapid cell death occur in ischemic core, however, long after the incident, cell death is observed in the ischemic surrounding, called penumbra, making the injury even worse. Similar, delayed neuronal cell death is observed after transient global brain ischemia. It is considered that such delayed neuron death may results from the activation or inhibition of particular signalling pathways in neurons and better understanding of the molecular mechanisms after stroke may result in identifying targets for potential therapy for stroke patients.

According to current knowledge, mitochondria emerge as a key elements determining the cell fate. Mitochondria stands for main, in neurons the only, source of energy, by ATP production. However, in case of oxygen and glucose deprivation during stroke, mitochondria function is impaired in survived neurons and they become a source of a proteins and factors, which activate the signalling pathways leading to the programmed cell death - apoptosis. Therefore, much attention is paid to mitochondria physiology, especially to the selective process of mitochondria clearance, mitophagy, and to the opposite process of mitochondria biogenesis, which leads to the restoration of mitochondria content.

Among variety of proteins involved in these processes, mitofusin 2 (Mfn2) seems to play an unique role. Mfn2 is a protein present at the surface of mitochondria and endoplasmic reticulum (ER), therefore participating in mitochondrial fusion and tethering mitochondria to ER. Studies on Mfn2 role in brain ischemia showed, that Mfn2 protein level varies after the ischemic insult and that Mfn2 over-expression attenuated cell damage.

Considering above, **the aim of this project is to investigate the precise role of mitofusin 2 in cell death and cell survival in different models of transient brain ischemia, especially considering its implication in mitophagy and mitochondria biogenesis.** What we are going to learn is the answer to the question whether different vulnerability of particular neurons towards transient ischemia may result from differences in mitophagy and mitochondria biogenesis course, what is the implication of Mfn2 to cell survival and if Mfn2 role in cell survival depends on mitophagy and mitochondria biogenesis.

To answer these question, research will be divided into three main research tasks. Firstly, Mfn2 co-relation with cell survival, mitophagy and mitochondria biogenesis will be characterized in different regions of the hippocampus in animals after transient brain ischemia followed by reperfusion. It is known, that neurons of particular regions of hippocampus in this transient brain ischemia model reveal different vulnerability towards the insult. Therefore, the same stimuli causes cell death in particular region, while the rest neurons survives. The second task aims to describe the precise role of Mfn2 in mitophagy and mitochondria biogenesis after ischemia and will be performed on cell models regarding primary culture of hippocampus neurons and the neuroblastoma cell line, which will be used to generate Mfn2-deficient cells. Finally, the third task will be performed to verify if transient ischemia alters Mfn2 interaction with Ras proteins, which are known to participates in pro-survival signaling pathways, and to analyze how this interaction may affect cell survival.

Studies will be performed with biochemical methods, electron microscopy and fluorescent techniques.

As a result of this project we expect to better understand the molecular mechanisms that are responsible for neuronal survival after the ischemic insults, what may contribute to the development of new targets for clinical treatment of stroke patients. At the same time we expect to verify whether Mfn2 promotes cell survival through participation in mitophagy and its role in signal transduction in the cell. Presented project will also answer the question, if lack of Mfn2 in neurons will significantly impair mitochondria functions, mitophagy and, secondarily, mitochondria biogenesis.