STIM1 and STIM2 are the "sensors" of the calcium ions (Ca^{2+}) level in the membrane of the endoplasmic reticulum (ER), that participate in the so-called Capacitive calcium entry to this organellum, i.e. store-operated calcium entry (SOCE), when their level decreases in ER storage. This process involves the influx of extracellular calcium through closely regulated channels in the plasma membrane (PM) and then refilling the ER with these ions. ER depletion results in the oligomerization of STIM proteins and translocation of their oligomers towards PM, where they interact with the ion channel protein - ORAI1.

Because neurons produce a much wider spectrum of calcium channels than non-excitable cells and the regulation of intracellular calcium concentration plays a particularly important role, it is possible that in neurons STIM proteins will bind to calcium channels specific for these cells. Indeed, in neurons the STIM protein interact not only with ORAI, but also with L- and T-type Voltage Gated Calcium Channels (VGCC) and with AMPA receptors (AMPAR). STIM proteins appear to be more complex than originally thought, and many aspects of their activity are unexplained. There are a number of evidence, including our published data and preliminary data presented in this project, that STIM proteins can play a role in the transport regulation of different ion channels through which neurons transmit signals between themselves. It is already known that the regulation of AMPAR trafficking by STIM2 increases the level of AMPAR subunit (GluA1) on PM by stimulating exocytosis and by inhibiting GluA1 endocytosis. In turn, STIM1 not only activates ORAI but also inhibits $Ca_V1.2$ and $Ca_V3.1$ VGCC activity leading to their internalization what results in total loss of function of these channels. **The main purpose** of the proposed project is to determine whether and how STIM proteins regulate the NMDA receptors (NMDAR) trafficking in neurons. NMDAR is an ionotropic receptors that is permeable to Na^+, K^+ and Ca^{2+} ions. Functional NMDARs are a combination of two subunits of NR1 and two subunits of NR2 (NR2A, NR2B) or NR3, where glutamine binds to NR1 and glutamate to NR2, which is required to activate this receptor. NMDARs are usually synthesized in the ER, then directed to the Golgi apparatus and further, as mature receptors, along the dendrites to the stimulating synapse. There, they undergo alternating exocytosis to PM and endocytosis to early endosomes and after that directed to late endosomes and lysosomes for degradation, or to recycling endosomes returning to the PM. The number and composition of receptor subunits in synapses are closely regulated by endocytosis, which contributes to the development of synapses and plastic lesions in the brain.

The proposed project will be a continuation of the earlier pioneering research in our laboratory. Experiments will be performed using neuronal cells. We will use modern methods of cellular and molecular biology and a variety of experimental approaches. On the beginning, we plan to evaluate the impact of STIM proteins on the level and subcellular localization of NMDAR and to see if there is direct interaction between these proteins. Next, we will examine the effect of STIM proteins on the various stages of NMDAR transport.

The results obtained during this project will explain phenomena that have not been previously examined and will provide a comprehensive understanding of the regulatory mechanism of NMDAR trafficking by STIM proteins. Moreover, these studies will broaden the basic scientific knowledge about the molecular mechanisms of NMDAR transport itself and the role of STIM1 and STIM2 proteins in neuronal function. In addition, they may contribute in the future to a better understanding of the molecular aspects underlying some brain pathologies, including Alzheimer's disease.