Various forms of synaptic plasticity are the primary substrate of learning and memory. The process of memory traces encoding largely relies on plastic changes within synapses. These changes usually manifest as a synaptic long-term potentiation (LTP) or long-term depression (LTD). So far, the molecular mechanisms underlying LTP and LTD induction in excitatory synapses have been relatively well understood. However, about 20% of adult brain neurons are responsible for synaptic inhibition and secrete GABA as a neurotransmitter. The plasticity of these inhibitory synapses is relatively poorly understood. Thus, our knowledge about the neuronal plasticity of over 20% synapses in the brain is disturbingly limited. Therefore, **the main goal of this project is to investigate the molecular mechanisms of plasticity at inhibitory synapses**

The excitatory synapse is not built solely from the presynaptic and postsynaptic compartments. At the subcellular level, also the interactions of the extracellular matrix and membrane adhesion proteins constitute synaptic architecture. In addition, the astrocytic fine processes located in the vicinity of the synapse also modify its structure and function. Therefore, in addition to presynapse and postsynapse, the architecture of the extracellular matrix and the perisynaptic astrocytic processes form an integral part of the excitatory synapse and influence its plasticity. In this context, it should be emphasized that the function of extracellular matrix and astrocytes in the plasticity of inhibitory synapses is practically unexplored. In excitatory synapses, membrane proteins as well as extracellular matrix and perisynaptic astrocytes co-create synaptic architecture, and extracellular proteolytic activity allows for its functional and morphological remodeling during the plasticity and learning. By analogy, the main purpose of this project is to investigate the role of extracellular matrix, adhesion proteins, extracellular proteases and factors released by nearby astrocytes in the mechanisms of plasticity at inhibitory synapses in the hippocampus.

This research project concerns basic science. It touches one of the most important topics in modern neuroscience – the molecular mechanisms of memory trace formation at the cellular and network level. It is worth emphasizing that inhibitory synapses, besides their physiological plasticity, are known to play also a crucial role in various neuronal pathologies. Impaired excitatory/inhibitory balance in neuronal networks underlies the pathomechanisms of epilepsy or schizophrenia. Thus, unraveling the new mechanisms of plasticity at inhibitory synapses may open promising avenues into therapeutic interventions.

Research plan proposed here concerns a fundamental problem of contemporary neuroscience - molecular bases of cognition. Specific aims of this project are related to key problems of neuroplasticity: the function of perineuronal nets; the mobility of membrane receptors; the synaptic adhesome; the perisynaptic astrocytes - but in the novel context of GABAergic plasticity. We believe that our research will significantly expand our knowledge on the local molecular interplay between excitatory and inhibitory synapses, and in a broader perspective will advance our understanding of cognitive processes.