Autism spectrum disorder (ASD) is a developmental disability that can cause significant social, communication and behavioral challenges. Most patients do not achieve full independence in life, or have a full-time job. Moreover, up to 40% of cases suffer from intellectual disability. The number of cases is steadily increasing – currently 1 child in 100 is diagnosed with autism (1 in 68 in the U.S.). The elusive etiology of ASD may include multiple environmental stressors interacting with genetic susceptibility factors. High level of signaling molecule, ATP in the extracellular compartment and subsequent activation of neuronal purinergic receptors may signal such stress leading to mitochondrial dysfunction and bioenergetic disturbances in neuronal endings. Altered energy metabolism is an important pathological feature of ASD. Although the prevalence of classic mitochondrial disease is relatively low in ASD children (ca. 5%), it has been pointed out that 30-50% ASD cases display altered mitochondrial biomarkers, and mitochondria-linked genes are among risk factors. ASD-linked metabolic disturbances have been proposed as targets for intervention, although their incomplete understanding resulted in rather inconclusive outcomes of corrective attempts. We hypothesized that excessive release of ATP from the neuronal or glial cells, its increased level in the extracellular compartment and further interaction with specific neuronal purinergic receptors (P2X or P2Y receptors) is a corner stone of bioenergetic disturbances in synaptic endings that lead to synaptopathy and autism development. Indeed, our very promising preliminary data indicated elevated ATP level in the cerebrospinal fluid of autistic-like rats prenatally exposed to valproic acid (VPA). Moreover, purinergic signaling disturbances are noted in ASD and may constitute its critical element, altering energetic metabolism in synaptic endings and switching it into a less efficient, stress-related mode and in consequence synapses disturbances. To test our hypothesis, we will use a rat model of ASD induced by prenatal exposure to VPA. The project's main goals are:

1) Analysis of the disturbances in extracellular ATP signaling in presynaptic terminals and glial subcellular particles in the VPA model of ASD;

2) Elucidation of the role of purinergic signaling in the dysfunction of synaptic mitochondria evoked by prenatal exposure to VPA;

3) Elucidation of the role of purinergic signaling in the bioenergetic alterations in the neuronal terminals evoked by prenatal exposure to VPA;

4) Investigation of antipurinergic therapy on behavioral alterations in the VPA-induced animal model of ASD;

This project performed in a pre-clinical model of ASD is innovative and elucidating novel mechanisms of metabolic disturbances observed in autistic patients. The role of extracellular ATP acting on specific P2 purinergic receptors in synaptic mitochondria dysfunction and bioenergetic deregulation in neuronal endings have not been investigated so far. Addressing the role of ATP-dependent signal transduction in the deregulation of glycolysis and mitochondrial respiration in VPA-induced rat model of autism holds the promise for better understanding of ASD pathomechanism and the identification of novel therapeutic targets. This may bring a measurable benefit for improving the quality of life of patients and their families, and has a significant economic dimension.