The metabolic syndrome (MetS), also called syndrome X, includes several other clinical conditions that increase the risk of developing atherosclerosis, type 2 diabetes, and cardiovascular complications. It should be emphasized that the main factors contributing to the development of MS are genetic predisposition and environmental factors, such as a sedentary lifestyle, low physical activity, and poor diet. The basis of the syndrome is visceral obesity, followed by insulin resistance, hyperinsulinism, hyperglycemia, hypertension, and dyslipidemia. Currently, obesity affects more than 1 billion adults and it is estimated that the number of obese people will double by 2030. In contrast, according to the report of the International Diabetes Federation, about 537 million adults suffer from diabetes, and this number is expected to rise to 643 million by 2030 and 783 million in 2045. Thus MetS is a very serious problem for public health requiring the implementation of pharmacological treatment aimed at various components related to insulin resistance, diabetes, hypertension, hyperlipidemia, and progressive inflammation. Nowadays, there are no new monotherapies with greater efficacy and fewer side effects.

TSPO, previously defined as peripheral benzodiazepine receptor (PBR), is primarily localized in the outer mitochondrial membrane and is implicated in several vital mitochondrial processes including binding to the voltage-dependent anion channel (VDAC) and adenine nucleotide translocase (ANT) as part of the mitochondrial permeability transition pore (mPTP); regulation of reactive oxygen species (ROS) formation and apoptosis; regulation of cellular respiration and energy production. TSPO is mainly produced in steroidogenic tissues, and it is considered that the most important function is translocating cholesterol from the cytoplasm into mitochondria, which is the rate-limiting step in the synthesis of neurosteroids and other steroids.

TSPO is considered as a unique mitochondrial protein that is involved in a variety of cellular processes.

Dysregulation of TSPO expression was found in pathologies involving changes in tissue energy demands such as cancer, and obesity, also is up-regulated in activated macrophages during the inflammatory response.

Our preliminary studies showed a promising therapeutic effect of the TSPO ligand on metabolic disorders. In the hyperglycemic zebrafish model, we demonstrated the effectiveness of one of the prototypical TSPO ligands, Ro5-4864, as a potential glucose-lowering agent. Literature reports state that stimulation of TSPO modulates a broad spectrum of activity regulating metabolism which together with our results point out targeting TSPO as a new approach in the treatment of the metabolic syndrome.

Thus the proposed project aims to explain the therapeutic effects of TSPO modulation in MS. We will use the zebrafish model of metabolic syndrome, characterized by e.g. obesity, hyperglycemia, and atherogenic dyslipidemia. The experiment was planned to decipher the role of steroidogenesis and to identify pathways at genetic level in the therapeutic effects of TSPO stimulation.
So far, no effective MetS therapy has been developed, thus our pioneering studies will be helpful in the future modeling of new candidate molecules of drugs acting on the metabolic components of this disease.

The planned analytical and genetic studies are focused on elucidating the post-receptor mechanism of TSPO's action.