**Project title: Mechanism of regulation glycosaminoglycan levels by resveratrol in a mouse model of a neuronopathic disease from the mucopolysaccharidosis group**

**Project objective:**

Mucopolysaccharidosis (MPS) are a group of rare hereditary diseases. It is caused by a mutation in the enzyme responsible for the breakdown of compounds from the group of mucopolysaccharidoses (glycosaminoglycans, GAGs), as a result GAGs accumulate in the cell. The process of their degradation in a healthy body is a sequential reaction of several enzymes, when one of them does not work properly, the reaction stops, accumulating GAG in the cells. Depending on which enzyme is inactive, 11 types and subtypes of MPS are distinguished. GAG accumulation in lysosomes leads to impairment of the proper functioning of cells, organs and in turn the whole organism. Patients have such symptoms as bone deformation, coarsening of facial features, forehead enhancement, organ enlargement, but also in several MPS mental retardation. Many symptoms are common to individual types and subtypes of MPS, but the most severe are those that also affect the central nervous system.

The most commonly used MPS therapy is enzyme replacement therapy, which involves the use of the active form of the missing enzyme. However, the supply of the missing enzyme is not sufficient for MPS types whose symptoms are expressed in the central nervous system, because the enzyme does not cross the blood-brain barrier (enzyme is too large). Therefore, research into alternative therapeutic approaches for these types of MPS is highly desirable. One such alternative strategy is the induction of the process that degradate GAG directly, it is called autophagy, the organelles in which autophagy takes place are lysosomes, characterized by the ability to digest abnormal or unnecessary macromolecules. Autophagy is a process of lysosomal degradation of macromolecules that become abnormal or unnecessary for cells. One of the latest discoveries is that GAGs can also be such molecules. This process occurs constantly, at a very low level, within the cell, thanks to which macromolecules are broken down into single monomers, which can again be used by the cell to build the necessary structures or for energy purposes.

It seems that one of the polyphenols, resveratrol, can meet the requirements. Grapes, peanuts, mulberries and black currants have particularly high resveratrol content. It is characterized by many biological functions such as anti-inflammatory, antioxidant and neuroprotective effects. It is a compound that has been extensively studied and activates the process of macromolecular degradation through several mechanisms.
Resveratrol, due to the pleiotropic mechanism of induction of autophagy, as well as crossing the blood-brain barrier and its safety, is a real candidate for a drug in the neuronopathic forms of MPS. Preliminary results obtained by the principal investigator (PI) showed that resveratrol actually stimulates the degradation of accumulated GAG on skin cells taken from patients with MPS. Therefore, in this project, the molecular mechanism of resveratrol-stimulated GAG degradation investigated. In addition, by testing in mice, we will examine the behavior of animals, which also changes in children suffering from Mucopolysaccharidosis type IIIB (neuropathic), thanks to which we will test the effect of resveratrol on the symptoms of the disease.

**What research will be carried out in the project?**

The research will be conducted on a mouse model of neuropathic mucopolysaccharidosis, which will be administered resveratrol or water (control group). Behavioral tests will include assessing the behavior of mice in the new environment, motor coordination, anxiety level as well as ability to remember and learn. Biochemical and molecular tests will be performed in order to evaluate effects and mechanism of resveratrol in various organs, particularly the brain and liver, where GAG accumulation is at the highest level.

**Reasons for taking the topic**

Mucopolysaccharidoses are a destructive group of lysosomal storage diseases affecting about 1 in 25,000 people. Despite intensive work on potential treatment methods, none have been registered yet for MPS III. Therefore, testing the mechanisms of action and effects of potential drugs for MPSIIIB is important for acquiring basic knowledge that could be further used to develop an effective drug against this and other diseases of similar etiology.