Glaucoma belongs to a group of chronic diseases of the eye. During the long course of the disease of the optic nerve is gradually damaged and cells are dying. This is most commonly due to an increase in pressure inside the eye. The basic treatment for glaucoma is to reduce the intraocular pressure. However, the current approach to the treatment of glaucoma does not take into account the molecular processes occurring in the tissues of the eye.

The aim of the present project is to examine of the endoplasmic reticulum stress (ER) influence on the development of glaucoma and assess the use of small molecule inhibitors of PERK kinase for its reduction. The authors believe that the PERK dependent UPR response pathway is an important factor leading to the development of glaucoma. Observed increase for ER stress in the eye tissues, namely the trabecular meshwork (TM) in the angle glaucoma that may lead to increased intraocular pressure, whereas ER stress reduction can slow down the development of glaucoma by lowering the intraocular pressure. In addition, high levels of stress are described in ER ocular tissues extracted from patients with glaucoma. There has also been significantly increased levels of protein CHOP (marker of ER stress). This indicates that ER stress in the ocular tissue of glaucoma is maintained at a constant high level. Although the exact mechanisms associated with the development of glaucoma are poorly understood, increased eye pressure, is a major risk factor and remains the primary goal of treatment.

Therefore, the project will make attempts to use small molecular substances that inhibit the PERK kinase to counteract the process of cell death in the angle glaucoma and optic nerve head protecting patients from losing vision. In order to accurately assess the impact of reducing the ER stress on the development of glaucoma, we will investigate the effect of 5 inhibitors selected in the preliminary tests. In the first stage we use two cells of cell lines derived from angle glaucoma (HTM) and optic nerve head (HA-r) being the two regions involved in glaucoma development. In the second stage we will proceed to testing on animals. We will be able to show how the complete removal of PERK gene affects the development of glaucoma. If we confirm that in the absence of activity PERK development of glaucoma will be slowed or stopped providing it will be about the legitimacy of the use of inhibitors tested for a possible therapy. Their therapeutic potential check by the administration to animals who will have glaucoma induced. In parallel we will work towards raising the effectiveness of inhibitors in the body by changing certain chemical groups in the molecule, and then test them in our cell and animal models.

We believe that the implementation of the proposed project significantly broaden knowledge about the causes and course of primary open-angle glaucoma. In addition, results of the project can greatly contribute to the development of new therapies for the treatment of glaucoma taking into account ER stress and PERK signaling pathway.