1. THE OBJECTIVE OF THE PROJECT

The World Health Organization has established that 15 million people experience stroke worldwide each year. Of these, 5 million die and another 5 million are permanently disabled. All therapies except for anti-thrombolytics and hypothermia, have failed to reduce neuronal injury, neurological deficits, and mortality rates following cerebral ischemia, which shows that novel therapies against cerebral hypoxia/ischemia are urgently needed. An increasing body of evidence supports that targeting ligand-activated transcription factors, such as aryl hydrocarbon receptor (AhR) and peroxisome proliferator activated receptor γ (PPARγ), could be a promising therapeutic approach for the nervous system disorders, including Alzheimer's disease and stroke. In the present project, we intend to identify neuroprotective mechanisms of actions of new AhR and PPARγ ligands in experimental models of stroke, i.e., hypoxia, oxygen and glucose deprivation (OGD), perinatal asphyxia, and photothrombotic stroke. Particular attention will be paid to achieve a synergistic neuroprotective effect of GNF351 and L312. The basic research hypothesis assumes that the new ligands possess neuroprotective potential and cause a synergistic neuroprotective effect in experimental models of stroke *in vitro* and *in vivo*. The mechanism of neuroprotection would be associated with an impairment of AhR and an increase in PPARγ signaling, that is accompanied by normalization of epigenetic statuses of the neuronal cells undergoing hypoxia/ischemia.

2. THE RESEARCH TO BE CARRIED OUT

The proposed research is original and adequate to the challenges of modern biology and medicine. To address translational and developmental aspects, we plan to carry out the experiments both *in vitro* - on primary cultures of embryonic mouse neuronal cells, and *in vivo* - on 7-day-old rodent pups and adult mice. Neuroprotective capacities of the AhR and PPARγ ligands will be estimated in respect to the hypoxia-, OGD-, perinatal asphyxia-, and photothrombotic stroke-evoked effects i.e., necrosis/neurotoxicity, apoptosis, and autophagy. To take into account clinical aspects, the compounds will be given till 12 h after initial hypoxic/ischemic insult. qPCR, ELISAs, western blots, relevant microarrays as well as immunofluorescence labeling and a confocal microscope will be used.

3. REASONS FOR CHOOSING THE RESEARCH TOPIC

According to the World Health Organization, stroke is the second leading cause of death and a frequent cause of disability, which proves that it is a serious social problem. High mortality and a low percentage of cures among stroke patients are due to the lack of drugs with a wide therapeutic window. Due to the diverse etiology and course of stroke, effective therapy should aim to achieve a synergistic neuroprotective effect. Stroke is accompanied by an increase in the expression and activity of AhR and dysregulation of PPARγ signaling. Despite this knowledge, little is known about the neuroprotective potential of AhR antagonists during hypoxic/ischemic insult. No attempts have been made to combine the neuroprotective properties of AhR antagonists and PPARγ agonists to protect nerve cells and the entire brain from hypoxic/ischemic damage. In this context, the breakthrough would be to show that combining the neuroprotective potential of the AhR ligands, i.e., GNF351 or DIM, with the neuroprotective potential of the PPARγ ligands, i.e., L312 or amorfrutin B, is the basis for the design of new drugs that will effectively treat strokes.