Neurodegenerative diseases (NDs) are associated with the dysregulation of physiological functioning of neurons in the human brain. These diseases are incurable and increasingly common. They mostly affect people over 60 years of age, and still, despite intense research efforts, no drugs have been found to either effectively inhibit or treat them. NDs are deadly conditions, which development and course are influenced by many factors. Various neurotransmitters acting through their respective receptors have been shown to play an important role in ND pathophysiology. Such receptors include serotonin 5-HT_6 receptors (5-HT_6R), which are found mainly in the central nervous system where they are involved in memory processes and cognitive functions. Also crucial in ND pathology are kinases, that is the proteins which stimulation activates multiple signaling pathways in the body. Key to the induction of necroptosis, i.e. genetically programmed cell death, is kinase RIPK1. Increased incidence of necroptosis is observed in NDs, especially in Alzheimer's disease. Research shows that inhibition of 5-HT_6R may have a beneficial effect on ND therapy, including AD, as does the blockade of RIPK1 kinase.

Our project is searching for so-called dual 5-HT_6R/RIPK1 inhibitors and that is an entirely novel concept, since there are no compounds yet described in the literature that act on both therapeutic targets simultaneously. Our preliminary studies discovered compound KCH-1, the first dual inhibitor, which was selected in this project as the lead structure for further modifications. In addition, we proposed the second leading structure WH-18, designed as a hybrid of the potent RIPK1 inhibitor (PN-10) described in the literature and the hydantoin 5-HT_6R agent (KMP-10) with significant memory-protective action in rats, which opens the route for additional modifications to obtain dual RIPK1/5-HT_6R agents with improved therapeutic potency. As part of this multidisciplinary project, we plan to use computer-aided design of new compounds, organic synthesis of selected structures (including synthesis of compounds with, among others, sulphur or selenium) and numerous pharmacological studies both *in vitro* and *in vivo*. For *in vitro* studies, we plan to assess the compounds affinity to 5-HT_6R, determine their activity profile at these receptors (agonist/antagonist), estimate the ability to inhibit necroptosis together with the testing of affinity towards RIPK1 using microscale thermophoresis and determine the effect of selected compounds on neuroprotection. Furthermore, additional (bio)chemical studies and analysis of parameters affecting absorption, distribution, metabolism or toxicity will be performed. The best selected compounds will be studied *in vivo* to evaluate their ability to reverse memory impairment and improve cognitive function in behavioral tests. For the most promising structures, experiments will also be performed to assess their pharmacokinetic parameters *in vivo*. The project will be carried out in collaboration with the Saarland University in Saarbruecken, Germany and University of Niteroi, Brazil (synthesis of some compounds especially with selenium) as well as with the Sapienza University of Rome, Italy (research on extended neuroprotection mechanisms).

The results of these studies will be used to perform structure-activity relationship analysis and will be described in publications and presented at national and international scientific conferences. We hope that they will make a significant contribution to global efforts to find new effective drugs against neurodegenerative diseases, with a particular focus on Alzheimer's disease.