Hypoxia-ischemia in the perinatal period is a serious condition affecting infants, which can result in cerebral palsy, associated disabilities or even death. Significant progress in hypoxic-ischemic encephalopathy research has been made in the last two decades. Although many new molecular mechanisms of hypoxia-ischemia have been identified, the possibilities of therapeutic interventions in hypoxic-ischemic injury are very limited. The recent discovery of the phenomenon of neurogenesis in the adult brain has increased the interest of researchers in the possibilities of replacing irreversibly damaged nerve cells by pharmacological boosting of neurogenesis. Although there is no doubt that neurogenesis occurs after hypoxic-ischemic injury, the number of new cells differentiating into mature neurons is insufficient to replace the damaged cells. Therefore, it seems extremely interesting to undertake research on the pharmacological enhancement of the endogenous repair process, which by increasing the amount of newly formed nerve cells, will enable the regeneration of the damaged brain.

In the early 1990s, it was discovered that the human body produces endocannabinoids that activate the complex endocannabinoid system. This system is one of the most important systems throughout the body, which play a crucial role in maintaining homeostasis and also takes an active part in a previously unknown system of communication between neurons. Furthermore, signaling through this system is involved in the formation, differentiation, survival or death of brain cells, the processes implicated as really important for neuronal development and brain repair. Unfortunately, cannabinoids are available in biological systems for a very short time, and the endocannabinoid system itself is an "on-demand" system, meaning the body does not store cannabinoids „in reserve”. Interestingly, many of phytocannabinoids can stimulate the activity of the endocannabinoid system. Therefore, the use of natural cannabinoids that modulate the activity of the endocannabinoid system give opportunities in therapies supporting the process of neurogenesis after hypoxic ischemic injuries. Cannabidiol (CBD) is one of the natural cannabinoids showing no psychoactive action. However, it exhibits antioxidant, anti-apoptotic, neuroleptic, and anti-inflammatory effects. The interaction of CBD with the endocannabinoid system are extremely complex. CBD binds to its receptors and affects many signaling pathways. While a growing body of evidence suggests that CBD is significantly associated with the enhancement of repair processes in the developing brain following hypoxia episode, it is not possible to accurately identify the mechanism of this beneficial effect. Therefore, the main goal of the proposed project is to find out whether CBD is involved in enhancement of endogenous mechanisms of brain repair (including the increase of neurotrophins level) and to explain the mechanisms responsible for this phenomenon. We suppose that CBD may directly or indirectly affect the activation of serotonin receptors, leading to increase of the brain derived neurotrophic factor level. As the consequence the metabolic changes in nerve cells may be induced, leading to the formation of new connections between cells and "remodeling" of dendrites. Additionally, we predict that CBD may promote neurogenesis through cannabinoid receptors, namely we predict that CBD administration will increase the level of endogenous agonists of endocannabinoid receptors, i.e. 2-arachidonoylglycerol and anandamide.

A crucial aspect of this project is the inclusion of sex-specific analysis, which aims to address the differences in susceptibility to hypoxic-ischemic brain injury and the potential variability in CBD’s therapeutic effects between males and females. Research suggests that sex hormones, genetic differences, and brain development dynamics may influence both the extent of hypoxic damage and the efficacy of neuroprotective interventions. By including both sexes in all experiments (ex vivo and in vivo), we aim to uncover potential sex-specific molecular and behavioral responses to CBD treatment. This analysis will provide crucial insights into whether males and females respond differently to CBD-induced modulation of the endocannabinoid and serotonin systems, as well as to neurogenesis and brain repair mechanisms. The findings will contribute to the development of optimized therapeutic approaches tailored to the specific needs of both sexes, ultimately enhancing the translational potential of CBD for treating neonatal hypoxic-ischemic encephalopathy.