The aim of the submitted project is to test the hypothesis whether the neuroprotective/neurogenic effect afforded by Sodium Butyrate (SB) – a histone deacetylase inhibitor, after neonatal hypoxic-ischemic brain injury is associated with an anti-inflammatory action. In addition, we will compare the response of SB with the action of another deacetylase inhibitor-Givinostat (ITF2375). For this purpose we will determine the temporal pattern of expression and co-localization of microglia/macrophage phenotype markers following this insult.

Perinatal hypoxic-ischemic injury (HI) (known as asphyxia) still remains an important issue as it is associated with high rate of infant mortality. It should be also pointed out, that babies surviving HI episode exhibit life-long behavioral abnormalities (such as cerebral palsy, seizures, cognitive and motor deficits). Undoubtedly, brain damage following hypoxic-ischemic insults is a complex process which develops over several hours to days and by this provides an opportunity for therapeutic intervention. However, despite the significant progress in knowledge relating the mechanism(s) underlying evolving brain injury, there are currently no effective therapies to reduce brain damage and its long-term sequel in infants. It was recently reported that the treatment of adult animals with histone deacetylase inhibitors: trichostatin A (TSA), sodium butyrate (SB) and vorinostat (SAHA) administered just before as well as after the onset of stroke, provides neuroprotection. The beneficial effect of these agents has been connected with decreasing the lesion volume, neurobehavioral improvement and reduced expression of various factors engaged in inflammation. The present study was undertaken to examine whether the neuroprotective/neurogenic effect of sodium butyrate in a model of neonatal HI (Ziemka-Nalecz et al. 2017) might be as well associated with an anti-inflammatory action. In addition, we will analyze the effect of another deacetylase inhibitor, Givinostat presenting a different than SB chemical structure. It is generally accepted that one of the most important components of neonatal brain damage is inflammation induced by activated microglia, infiltration of macrophages and production of inflammatory cytokines, NO and free radicals. All these factors may exacerbate neuronal injury and cause neurological disturbances. Activated microglia play an equally important role in the reparative processes. To participate in that diverse range of activities, microglia/macrophages are capable to acquire distinct activation states due to polarized phenotypes M1 and M2. Whereas phenotype M1 favors the production of inflammatory mediators, phenotype M2 displays neuroprotective properties due to release of anti-inflammatory and trophic factors. This dual and opposing role may imply that therapies should be shifted toward adjusting the balance between beneficial and detrimental responses. The interesting preliminary studies performed recently by our group showed that sodium butyrate treatment after HI increased the number of cells presenting M2 phenotype and reduced the expression of pro-inflammatory cytokine IL-1beta. Nevertheless, this limited data indicates an anti-inflammatory action of the applied inhibitor. To confirm the role of microglia reaction to SB further studies are needed. Therefore, the project aims at getting insight into previously unexplored aspects of microglia/macrophage phenotype changes, namely the presence of specific phenotype markers and their temporal expression at different time after HI. In case of the expected beneficial action, SB may be considered as a candidate for future treatment of neonatal asphyxia.