Description for the general public

Neurodegenerative disorders, like Alzheimer's or Parkinson's disease, are extremely serious public health problem affecting increasing number of people. Although they are distinct nosological entities with complex aetiology it is believed that neuroinflammatory processes and genetic/epigenetic phenomena may be critically important in the pathomechanisms of these diseases. In the brain, immune system is represented by microglial cells. High diversity of microglia is caused by its high versatility in reacting to changes in microenvironment. Microglial cells adopt different phenotypes in response to different stimuli (phenotype polarization). Neuroinflammation and activation of microglia are commonly considered as detrimental processes leading to neuronal dysfunction and neurodegeneration, however, simple anti-inflammatory pharmacotherapy is often not effective. To develop novel therapeutic strategies for neuroinflammation-related disorders one needs to understand deeply molecular mechanisms of these processes. Acetylation-deacetylation of DNA-bound proteins is a crucial epigenetic mechanism controlling the structure of chromatin and genes activity. Bromodomain and extra-terminal domain (BET) proteins use their bromodomain to recognize acetylated lysine groups in histone H4 and other acetylated proteins and initiate formation of multi-protein complex involved in controlling activation or suppression of gene transcription.

In mouse (similar to human) there are three proteins of this family, Brd2, Brd3, Brd4. Potent and specific inhibitors of BET proteins, which were recently developed, stimulated researchers to study the function of BET proteins in cancer, as BET proteins control expression of oncogenes and anti-apoptotic proteins. Recent studies showed that pharmacologic inhibition of BET proteins may affect the progression of inflammation. The review of the scientific literature suggests that pharmacological modulation of BET proteins, via epigenetic mechanisms, may affect activity of microglia. This effect would not be simply inhibition, but rather shift of phenotype. The study will not be limited to analysing the role of BET proteins in microglia, but it will also examine the impact of BET-dependent shift of microglial phenotype on its cytotoxic or cytoprotective action.

The aim of this project is gaining new knowledge on the role of BET proteins in microglia-dependent neurodegeneration. It is planned to use *in vitro* and *in vivo* experimental models. *In vitro* studies will enable analysing both direct and indirect (via released mediators) effect of microglia on neurons.

Activation of microglia (immortalized murine microglia cell line BV2) will be induced by amyloid beta (Aβ) which plays an important role in the pathomechanism of Alzheimer's disease. Activated microglial cells or conditioned medium will be transferred to neuronal cells (immortalized murine neuronal cell line HT22) to study various aspects of interaction between microglia and neurons. It is planned to analyse the function of BET proteins in controlling activity of microglia, and to analyse the effect of BET inhibitors on activity of microglia and neuronal damage evoked directly (phagoptosis) and indirectly (mediators) by microglia. It is proposed to examine expression and post-translational modifications of BET proteins, expression of phenotype markers, release of free radicals, lipid mediators, cytokines, chemokines, trophic factors, complement components, activity of transcription factors, poly(ADP-ribosyl)ation processes, phagocytic activity, changes of neuronal synaptic proteins and trophic factors, neuronal viability, apoptosis and phagoptosis. By using genetic and pharmacologic methods of inhibition, the involvement of BET proteins will be analysed. Analogical studies will be performed *in vitro*, on animal model of chronic neuroinflammation which recapitulates pathological alterations typical for AD.

The project will provide new knowledge concerning pathomechanisms of neurodegenerative disorders and may potentially lead to developing new therapies in the future. Additionally, the results may also be important for improving understanding of the role of BET proteins in the regulation of the immune system. Due to the ongoing clinical trials on use BET inhibitors, the results of this project may be useful also beyond the field of neurodegenerative diseases.