Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS). It is most commonly diagnosed in people aged 20-40. The disease reduces the natural survival time by an average of 6-7 years, which is the result of neurological symptoms, limited activity and immobilisation. It is estimated that the incidence of multiple sclerosis in Poland ranges from 45 to 92 per 100,000 inhabitants, and about 2,000 new cases are reported each year.

Despite many studies, the etiology of MS is not fully understood. Currently, it is assumed that the causes of the disease are multifactorial. The epidemiological data have indicated that immune, genetic and environmental factors are important. Multiple sclerosis is characterized not only by inflammatory demyelination but also by neurodegenerative processes. Some evidence has indicated that axonal injury might appear before myelin loss, suggesting that neurodegeneration could be independent of demyelination and may occur prior to or in parallel with demyelination. Many studies have indicated that deficiency of neuroprotective factors, including neurotrophins, sirtuins, and heat shock proteins may play an important role in the pathogenesis of neurodegenerative disease, including MS. HSPs have been shown to play a neuroprotective role by preventing aggregation of misfolding proteins acting as chaperone and by inducing anti-apoptotic mechanisms. SIRTs stimulate expression of genes responsible for energy metabolism and pro-survival mechanisms. Additionally, SIRT1 selectively suppresses genes involved in apoptosis, and inflammation. Therefore, sirtuins play a role in multifaceted mechanisms that lead to increased cell viability. In the CNS, neurotrophins play a protective role towards specific neuronal populations. They also facilitate synaptic transmission and plasticity that are crucial for memory and regeneration processes. In MS patients failure to produce the adequate neurotrophins concentrations might result in decreased protection of the CNS, consequently leading to increased atrophy, which is the main determinant of MS patients' end-point disability.

In recent years, many research has focused on the role of microRNA (miRNA) in the pathogenesis of many diseases, including neurodegenerative diseases. MicroRNA are a class of endogenous, short non-coding RNAs. In the CNS they regulate gene expression in physiological conditions as well as disease, during development, immune system activation, neurogenesis, and myelin formation. In multiple sclerosis, it has been observed miRNAs profile changes within the CNS and the immune system, which results in the levels of gene expression in many cell types involved in the disease. However, there is no data about role of microRNAs in regulation of expression level of neuroprotective protein, including neurotrophins, heat shock proteins and sirtuins in multiple sclerosis development. Moreover, no research has considered changes in distribution of miRNA processing pathway.

In proposed project we would like to investigate microRNA processing pathway as a molecular mechanism potentially involved in multiple sclerosis development. We postulate that disturbances in miRNA processing pathway cause up- or downregulation of miRNA expression and that may conduct to changes in expression of genes encoding proteins involved in neuroprotection in MS.

The detailed aims of the presented project are:

- The analysis of the polymorphic variants occurrence of genes that are involved in miRNA processing pathway.
- Evaluation of the miRNA expression level and its effect on expression (mRNA and protein level) of selected neurotrophins (BDNF, NGF, NT-3), heat shock protein (HSP70, HSP27) and sirtuin SIRT1 in MS patients group and control group.
- Assessment of matured miRNAs level by Pre-miR miRNA transfection in PBMCs of multiple sclerosis patients and healthy donors
- Assessment of matured miRNAs level by Pre-miR miRNA transfection in multiple sclerosis non-isogenic cell line (ESi051-A) and human induced pluripotent stem (IPS) cell line (ATCC® ACS- 1019TM)
- Perform a network of interactions between investigating molecules.

Analysis of miRNAs dysregulation and the resulting changes in mRNA and neuroprotective proteins expression level may contribute to a better understanding of the multiple sclerosis etiology as well as new alternative methods for the diagnosis and treatment of the disease.