Multiple myeloma (MM) is a disease characterized by the proliferation of malignant plasma cells. These cells are able to producing monoclonal, homogeneous immunoglobulins which genes have been mutated. MM accounts for 1% of all malignancies and is the second most common hematological malignancy, with an incidence of 6/100,000 in Europe. MM is disease of unknown, complex etiology and affects primarily older adults which the median age at diagnosis is 65 - 70 years. The course of the disease and survival time of patients is very heterogeneous but over the last decade we have observed evident progress in the treatment of this incurable disease. Understanding of the molecular mechanisms of action of adhesion molecules, cytokines and signaling pathways involving in MM development and progression has led to creation of novel targeted therapies improving the quality of life and significantly prolonging the median survival time of patients. Currently used drugs are substances characterized by immunomodulatory mode of action. They are directed towards various signaling pathways in malignant myeloma cell, interfere in mechanisms of proliferation, apoptosis, angiogenesis, and influence interactions between myeloma cell and bone marrow stromal cells. Therapeutics that have proven to be highly active include immunomodulatory drugs: thalidomide and its newer analogs: lenalidomide and pomalidomide as well as proteasome inhibitors: bortezomib and karfilzomib. Their use in the treatment of multiple myeloma has contributed to more than double the survival time of patients. However, the use of thalidomide and bortezomib is also associated with occurrence of a serious and common problem which is the drug-induced peripheral neuropathy. The mechanism of the development of the peripheral neuropathy is poorly understood.

The main aim of the project is to evaluate the impact of neurotrophins and proangiogenic factors on the occurrence of treatment-induced peripheral neuropathy after regimens involving drugs that among their adverse effects could induce neuropathy (Bortezomib Thalidomide). Assessment of the concentration and expression of the genes for examined factors can provide key information to an in-depth understanding of pathophysiological mechanisms involved in the development of neuropathy.

For the purpose of this project it is planned to recruit patients to analyzed groups including 80 patients: i) patient with diagnosed MM without neuropathy before treatment; ii) patients after treatment with regimen VMP (Bortezomib, Melfalan, Prednizone) or VTD (Bortezomib, Thalidomide, Dexamethasone) with neuropathy grade 3^o or 4^o; iii) patients with diagnosed multiple myeloma with peripheral neuropathy due to disease *per se*; and additionally, 80 healthy age-matched individuals as a control group. Peripheral blood and the bone marrow will be analyzed. The proposed project will include a detailed analysis of neurotrophins and proangiogenic factors using modern molecular methods including Luminex technology and separation of plasmocytes from the bone marrow by immunomagnetic method based on antigen-specific antibodies associated with paramagnetic beads. Then, RNA and protein isolated from plasmocytes will enable: i) precise analysis of gene expression changes of studied factors in the cells; ii) assessment of protein amount; iii) visualization of neurotrophins and proangiogenic factors in obtain plasmocytes. Aditionally, the estimation of percentage of plasmocytes using flow cytometry will be performed and analysis of wide panel of gene expression and miRNA changes using microarray technique will be made. Bioinformatic analysis of microarray data will allow identification of certain miRNAs and genes with changed profile in MM patients.

Therefore, obtained results can be an important contribution to the extension of the knowledge concerning pathogenesis of polyneuropathy and in the future, it may help to reducing the incidence of the complication in patients with multiple myeloma. In addition, the level of neurotrophins and other soluble protein factor with a neuroprotective effects, could also become a new marker for estimation of predictable clinical course of the disease in this aspect and to avoid complications resulting from treatment.