Multiple myeloma (MM) is a lymphatic neoplasm characterized by uncontrolled clonal proliferation of plasmatic cells, mainly in the bone marrow. MM accounts for 1% of all tumors, 10% of hematological malignancies and is still an incurable onco-hematological disease. Adhesion of myeloma cells to bone marrow cells leads to increased secretion of proangiogenic and proinflammatory cytokines, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), tumor necrosis factor (TNF) and interleukin-6 (IL-6). Pro-angiogenic and anti-angiogenic factors are produced by both myeloma cells and cells in the bone marrow microenvironment, including endothelial cells. In myeloma, the balance between these factors is disturbed, with a large predominance of production of pro-angiogenic factors. The clinical correlation between these cytokines and the disease progression indicates an important role of angiogenesis in pathogenesis of myeloma and its progression. An increased number of proangiogenic factors also provides the shorter survival of myeloma patients, which also correlates with density of microvessels in myeloma. As a result, neoangiogenesis plays a key role in tumorigenesis and is a typical pathomorphological feature of MM. It is believed that antiangiogenic therapy may contribute to improving the outcomes of MM treatment and the survival of patients. The main proangiogenic factor is a family of VEGF cyutokines (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PlGF), which stimulates endothelial cell proliferation and survival and increases the permeability of vessels. The group of factors stimulating cell proliferation within the vascular buds during angiogenesis also includes proteins such as Angiopoietin and Angiogenin. Additionally, the migration of endothelial cells to the sites of active angiogenesis is also stimulated by VEGF. Since the development of myeloma depends on neoangiogenesis and indirectly on endothelial cell proliferation, pharmacological inhibition of VEGF may prevent the development of MM tumor and induce the positive therapeutic effect. However, the use of drugs specifically lowering VEGF concentration in monotherapy in MM patients did not result in a quite good response to this treatment. Therefore, other possibilities of blocking neoangiogenesis are still being sought, including attempts to use specific angiogenesis inhibitors. Endostatin belongs to the group of factors inhibiting endothelial cell proliferation. In contrast, Angiostatin inhibits especially endothelial cells migration. Unfortunately, there is lack of reliable results of preclinical and clinical studies that would evaluate the effects of these two proteins in the neoangiogenesis inhibiotion and the development of MM in different research models. Undoubtly, understanding their role in the induction of antiangiogenic mechanisms in neoangiogenesis would contribute to the establishment of more effective therapeutic strategies of MM and could bring significant benefits to the MM treatment. However, effective delivery of therapeutic substances to cancer tissue is limited for many reasons, including the short half-life of biological substances in the cancer microenvironment, which requires repeated administration of the drug. Innovative modifications that increase the stability of therapeutic substances and extend their release through the use of nanocapsules may be an important step in creating a novel and effective therapy that will inhibit the development of MM neoangiogenesis.

The aim of this research project is to determine the biological effects at the cellular and systemic levels of biodegradable nanostructures developed independently by our team, characterized by the slow/permament release of two angiogenesis-inhibiting proteins, i.e. angiostatin and endostatin, embedded on a core consisting of human albumin modified with hyaluronic acid. The planned *in vitro* studies in myeloma cells and human endothelial cells will allow for the assessment of the level of activity of individual regulatory mechanisms of neoangiogenesis and the influence of the tested proteins on them, released separately and in a complex form. Additionally, the potential synergistic effect in the case of combined classic antiangiogenic therapy using an anti-VEGF antibody and the tested nanocapsules will be determined. Next, the research hypothesis will be verified *in vivo* to determine the potential biological effect of innovative nanocapsules in the complex organism in an animal model. For this purpose, comprehensive studies of neoangiogenesis activity in a mouse xenotransplantation model of human MM are planned.

The proposed research project is an original attempt to determine the real effectiveness of selected antiangiogenic protein factors, persistently released in tumor tissue, in blocking the development of neoangiogenesis as a key phenomenon for the development and progression of myeloma. A comprehensive analysis will be performed using the modern molecular and epigenetic methods, including methylation analysis, global miRNA/RNA expression microarrays, and angiogenic and inflammatory secretome from MM cells. According to the available literature, this will be the first such comprehensive basic study that would determine the mechanisms of action of angiostatin and endostatin combination in inhibiting myeloma neoangiogenesis and could lead to the development of new optimal antiangiogenic treatment strategies. The implementation of the project will also allow to assess to what extent inhibition of neoangiogenesis with angiostatin and endostatin can be proposed as a safe and synergistic adjuvant strategy towards increasing the efficacy of current anti-MM therapies.