Melanoma is a malignant tumor of the skin, mucous membranes and uvea. It derives from the pigment producing cells - melanocytes. The incidence of melanoma is rising in both sexes -over three decades the incidence has increased almost 3-fold. In Poland, in 2010, the number of deaths due to melanoma amounted to nearly 1,200 [National Cancer Registry]. Melanoma is a tumor extremely resistant to chemotherapy and radiation therapy.

For many years, researchers efforts are focused not only on the elimination of tumor cells but also on the observation of the properties of the cells supporting the structure and metabolism of tumors - tumor microenvironment. The tumor microenvironment comprises immune cells, vascular endothelial cells, fibroblasts, and others. Immune cells present in the tumor microenvironment undergo specific "reprogramming". The tumor immune cells do not recognize cancer cells as foreign, lose the ability of tumor antigens presentation to effector cells, able to eliminate cancer cells. The presence of blood vessels formed in the tumor in a process called angiogenesis, is a feature promoting proliferation and invasiveness of the tumor. The vessels enable cancer cells to exchange metabolites. The vessels are often non-functional and leaky and cause the occurrence of a transitional areas of hypoxia, which accelerates the cancer progression.

Therapeutic activities aimed at eliminating tumor blood vessels and stimulating immune system cells are comprehensive solutions, effectively limiting the tumor growth.

In recent years, mesenchymal stromal cells (MSC) have become the subject of interest of researchers worldwide. The availability of MSC cells, their proliferative potential and their ability to migrate specifically towards cancer cells make them an ideal tool for anticancer therapy. MSC *in vivo* are an important functional element of hematopoietic stem cells niche and an integral part of blood vessel walls. MSC secrete pro-angiogenic, cell proliferation stimulating factors and immunostimulants. MSC isolated from bone marrow exhibit taxis towards tumor cells. MSC cells given into the bloodstream of animals bearing tumors localize primarily around the tumor. The specific tropism of MSC cells to tumors has been confirmed in the models of melanoma, ovarian cancer, breast cancer, glioblastoma and liver cancer.

IL-12 cytokine, produced by the cells of the immune system, has a broad spectrum of action. IL-12 exerts both immunostimulatory and anti-angiogenic properties. The problem appears to provide therapeutic protein to hard to reach areas of the tumor. The local release of IL-12 in tumors leads to the stimulation of the immune system and destroying of tumor cells. DMXAA is antivascular factor, effective in the elimination of tumor vessels. DMXAA initiates the release of factors damaging tumor blood vessels (TNF-α, nitrogen monoxide (NO)) from macrophages and induces the secretion by dendritic cells and macrophages chemokines that stimulate the migration of T lymphocytes. DMXAA polarizes the macrophages from anti-inflammatory phenotype (M2) to the proinflammatory one (M1).

The project is a continuation of our research on the use in antitumor therapy anti-angiogenic drug in combination with immunostimulants. This combination proved to be effective in the treatment of mice with melanoma tumors B16-F10. *Novum* of the project involves the use in the treatment genetically-modified MSC cells as carriers of therapeutic IL-12, specifically providing immunostimulatory and anti-angiogenic protein in hard to reach areas of the tumor. The cytokine IL-12 secreted by the MSC cells might activate cells of the immune system in the nearest vicinity of the tumor cells. In addition, the administration of DMXAA results in the destruction and elimination of blood vessels in the tumor.

We hope that therapeutic approach we proposed: the destruction of vessels by DMXAA and stimulation of the immune response with the participation of IL-12, specifically provided by MSC cells, proves to be effective in eliminating cancer cells. The combination of DMXAA with IL-12 should: (1) reduce the number of tumor blood vessels, (2) increase the level of effector cells, and (3) reduce levels of immunosuppressive cells. If successful, the solution we proposed may be the subject of clinical trials.