The aim of the project is the evaluation of the tumor microenvironment changes occurring as a result of cell therapy. Cell therapy will use cytotoxic M1 macrophages derived from mouse bone marrow and from human peripheral blood, which, during *ex vivo* culture, will be modified with genes encoding Interleukin 12 and Green Fluorescent Protein (GFP) (M1/IL-12/GFP macrophages). Migration of modified macrophages will be tracked in the tumor microenvironment. We expect that such a cell therapy transforms the tumor microenvironment from an immunosuppressive and pro-angiogenic microenvironment - promoting tumor growth to an anti-angiogenic and immunostimulatory - inhibiting tumor growth. These changes in the tumor microenvironment should also increase the effectiveness of radiotherapy. A measurable effect of our proposed cell therapy, may be the use of lower radiation doses in radiotherapy, which may contribute to the reduction of negative side effects of radiotherapy and improve the comfort of life of cancer patients.

In the healthy tissue there are two kinds of macrophages, so called macrophages M1 and M2. M1 are cytotoxic, pro--inflammatory macrophages, which task is to destroy microorganisms, microbes, dying cells, as well as abnormal cells, e.g. cancerous cells. They also possess an ability to migrate to the tumor. M2 are the anti-inflammatory macrophages, which main function is creating new blood vessels, healing wounds and repairing damaged tissues. In the tumor microenvironment there is specific macrophages population - Tumour-Associated Macrophages (TAM) with characteristic similar to M2 macrophages. TAM may constitute even 50% of all cells in a tumour. TAM are responsible for tumor growth, tumor blood vessels formation, immunosuppression and metastasis.

In the proposed cell therapy the M1/IL-12/GFP macrophages will be responsible for: (1) destruction of the cancer cells, (2) secreting interleukin 12 (“bioreactor”) into tumor microenvironment (3) reduction of oxygen deficiency in the tumor due to the process of " tumor blood vessels normalization". Interleukin 12 is a cytokine, which activates the immune system and inhibits new blood vessels formation. Administered systemically it shows high toxicity, which limits its usage only to a precise, local administration, e.g. directly into the tumour. IL-12 secreted by macrophages should transform TAMs into M1 macrophages, activate the cells of the immunological system, as well as inhibit the formation of new tumor blood vessels.

Such modified cells of M1/IL-12/GFP macrophages administered into the tumor, where they will start the process of tumor microenvironment changing. As a consequence, activation of the immunological system, the improvement of the oxidation of the tumour, as well as increase of the sensitivity of the cancer cells to radiotherapy should be observed. In the specific moment of the cell therapy the tumours will be irradiated with a single dose of 5Gy.

The project is novel and original. Our research may provide new information about macrophages as carriers of genes encoding therapeutic proteins and the possibility of using them to transforming the tumor microenvironment. The effect of our cell therapy will be the reduction of radiation doses during treatment, which will decrease the negative side effects of the radiotherapy and improve the quality of life of cancer patients. Such a therapeutic solution may become the subject of future clinical trials.