Prostate cancer is one of the most frequently diagnosed cancers and the second leading cause of cancer-related death in European and American men. It is characterized by a presumed long latency period and a moderate (but compared only to most aggressive cancers!) propensity to metastasize. On the other hand, the risk of prostate cancer increases with age, which means that its therapy should be shaped to consider relatively bad physical condition of the affected patients. Palliative treatment of advanced prostate cancer is predominantly based on surgical intervention and androgen ablation. This method only transiently decreases the risk of metastasis formation. It is most probably due to the proceeding androgen-independence of cancer cells after castration. A range of cytostatic drugs interfering with cancer cell proliferation and/or induction of apoptosis have been elaborated. These drugs, for instance, docetaxel (DCX) and mitoxantrone (MTX) , while providing some symptom relief, are incapable of changing the natural history of hormone-refractory prostate cancer. DCX/MTX-based therapies are also burdened by a number of adverse effects, which limit their long-term application and increase the morbidity and mortality rates of the patients. Therefore, they should be applied with care and tailored to individual patients, especially in the case of palliative treatment of progressed prostate cancers. On the other hand, the cessation of chemotherapy; its potential pre-selecting effect of cytostatic drugs together with the general bad condition of the affected organism, leads to abrupt and lethal cancer relapses.

The way out of this "vicious circle" is the introduction of the approaches that would employ the combinations of cytostatic drugs, such as DCX and MTX, with other "non-aggressive" pharmaceuticals that would act in a manner complementary to the basic drugs. They should not evoke any adverse effects, instead they should be expected to augment the effect of cytostatics on invasive populations of prostate cancer cells, which in general tend to be drug-resistant. Fibrates, among them fenofibrate, represent the group that seems to met these requirements. Notably, fenofibrate is FDA-approved drug which limits the costs of its possible introduction into prostate cancer treatment. It is widely used in clinical practice to lower plasma levels of triglycerides and cholesterol, to improve LDL:HDL ratio, and to prevent atherosclerosis. In parallel, the vasoprotective activity of fenofibrate, independent of its lipid-lowering activity, has been reported, including its activity in improving physiological neovascularization. Several reports indicate that fenofibrate may suppress endothelial cell proliferation and migration leading to the attenuation of tumor vascularisation. Because the penetration of endothelium by circulating cancer cells is crucial for cancer progression and fenofibrate is commonly prescribed to old people, the question arises about possible fenofibrate application in cancer therapy. Our previous studies demonstrated that fenofibrate inhibits proliferation, induces apoptosis and attenuates the invasive potential of cancer cells in vitro, while other studies showed a corresponding activity of fenofibrate in vivo. In particular, we have shown that fenofibrate reduces the efficiency of prostate cancer cell diapedesis, a key process in the metastatic cascade of this cancer.

Collectively, these data prompted us to speculate that fenofibrate can multidirectionally affect the cancer development in general and prostate tumor development in particular. This idea is especially attractive in the light of relatively unidirectional activities of the drugs commonly used in cancer therapy. Development of cancer, including their progression and metastasis, is determined by genetic and epigenetic changes, undergone by the tumor cells. These changes are especially crucial for the development of invasive cancer cell lineages, capable of local invasion and distant metastasis. During the metastatic cascade, this development is stimulated by preselection/expansion cycles, related to the penetration of tissue barriers by the cells. Therefore, only the progeny of single cells is capable of spreading throughout the organism and of tissue colonization. Chemotherapeutics undoubtedly belong to the factors inducing and directing the microevolution of invasive prostate cancer cell lineages. In the case of the acquisition of drug-tolerance by such cells (which is a pretty common phenomenon!), there is no further way to attenuate their invasiveness. Multidrug resistance is an adaptative trait of cancer cells related to the increase in the efficiency of drug metabolism and/or their expulsion outside the cell. It is commonly correlated with the invasive behavior of cancer cells. Conceivably, cytostatic drugs can affect the development of invasive cancer cell sub-populations through the preselection of drug-resistant cancer cells, leading to their expansion after the cessation of chemotherapy. Considering these facts, the results of our own experiments and literature data on anticancer activities of fenofibrate, we hypothesized that fenofibrate can prevent the abrupt and lethal relapses of prostate cancer after the cessation of chemotherapy.

To achieve the basic aim of the project, i.e. to estimate the suitability of fenofibrate for the palliative treatment of prostate cancer, we intend to use the whole spectrum of prostate cancer cellular models and comprehensively analyze their properties. For this purpose, we will employ the techniques of cell proliferation, apoptosis and motility assessment (cell counters, flow cytometry, videomicroscopy). They will be assisted by the analyses of gene expression (with RT-qPCR, immunoblotting, immunofluorescence, and the models of metastatic niche in vitro and in vivo metastasis. We want to focus on the effect of fenofibrate on the effective doses of MTX and DCX. Further, we will concentrate on the changes (evolution) of the invasive potential of cancer cells induced by the cytostatic drugs commonly used in prostate cancer chemotherapy, and estimate the effect of fenofibrate on this process. Finally, we want to estimate the interrelations between the pathways regulated by fenofibrat (PPARalpha- and ROS-dependent) and by local inflammation a(including Cx43/SMAD/Snail-1 axis) and their role during the drug-induced expansion of invasive prostate cancer cell sub-populations.

The research concept is based on the new look on prostate cancer cell lines in vitro, as the biological system at least partly shaped by the microevolution processes active in vivo. Till now, the research on the influence of cytostatic drugs on cancer cell physiology were predominantly limited to the analyses of cell proliferation and apoptosis, sometimes accompanied by the estimations of their invasive behavior in vitro and in vivo. They did not consider the direct effect of cytostatics on the expansion (microevolution) of drug-resistant cell lineages, and their invasive potential was interpreted separately from other traits crucial for cancer invasion. Establishment of the model that would relate the activity of cytostatic drugs commonly used in prostate tumor therapy with the expansion of invasive lineages of prostate cancer cells and their permanent reprogramming should help to better understand the mechanisms of prostate cancer progression. On the other hand, analyses of the role of pro-inflammatory factors and Cx43 function in invasion and diapedesis of prostate cancer cells will help to clarify the controversies on this topic. Most importantly, the proposed experiments will answer the question whether fenofibrate can be introduced into prostate cancer therapy as an agent that interferes with cancer relapse after the cessation of chemotherapy. Taking into account the importance of this problem, the outcomes of this project may be of utmost importance for the development of new palliative strategies of prostate cancer treatment.