The objective of the project and the reasons for choosing the research topic:
The aim of this project is to acquire scientific knowledge regarding the molecular background of patients resistance present with renal cell carcinoma to the newest type of therapy - to targeted therapy, in this particular example - anti-angiogenic therapy. It is not chemotherapy, which kills cancer cells. Targeted therapy - in this case employing sorafenib, a tyrosine kinase inhibitor - focuses on impairing specific signaling pathways, which in turn is done to inhibit excessive angiogenesis around the tumor, which colloqially speaking means to "starve" the tumor. Regardless of primary successes in treatment (which last until today as targeted therapy is still more effective in treating renal cancer patients than chemo- or radiotherapy) in a significant amount of patients the sickness progresses within 3 months. Some of them become resistant to TKIs as a result of their long-term usage and this phenomenon is called aquired drug resistance - its molecular background is partially known in renal cell carcinoma (publications of *inter alia* Gotink et al. 2011, 2012; Buczek et al. 2013, Bielecka et al. 2014). However, some patients do not react to targeted therapy from the very beginning of the treatment - there is a known phenomenon of a so-called multidrug resistance, but it does not explain mechanisms of primary resistance well enough to effectively conquer it. Therefore, a real need exists to identify molecular pathways, which may be activated/switched off/avoided in the course of primary resistance to TKI in renal cancer. This project focuses on sorafenib - preliminary results showed the primary resistance of human kidney cancer stem-like cells (judged by many researchers as tumor-initiating cells) to sorafenib in hypoxia - in conditions present inside the tumor, *in vivo*. It is crucial to know that the impact of anti-angiogenic agents on renal cancer cells *in vitro* has been documented in many experimental publications (Gotink et al, Bussolati et al, Bruno et al. etc.). The results of the research planned to be conducted in this project will further in terms of primary drug resistance to TKIs - the next step would be, after finishing this project, to acquire knowledge on actual changes on the gene and protein level (posttranslational modifications, mutations etc.) which are responsible for drug resistance, and the next step after that would be to invent the "repairing" molecules (the last in applied scientific project).

Basic research to be carried out in the project:
The research will be conducted in order to acquire new knowledge in the field of medical biotechnology, molecular medicine, with the use of inter alia proteomics, the studies of single protein and gene expression. Those studies will be performed with the use of life sciences research field and basic research. The project is to include only the original experimental research work and has been written to broaden actual state of the art concerning primary resistance to sorafenib. Proteomic analysis with the use of mass spectometry will be used for initial identification of altered expression of several proteins, and those results will be confirmed by Western Blot. Subsequently, the expression of genes encoding those proteins will be checked, which would allow for the better reliability of the research. For the purposes of acquiring the material for analysis, 3D cell cultures will be performed *in vitro*, which would better mimic tumor biology *in vivo*, rather than standard 2D cultures. Taking everything into consideration, all studies carried out in this project comprise original research work which all meet the criteria of basic research and do not relate to applied research.