Cancer is a leading cause of death worldwide standing behind 8.2 million deaths annually, according to World Health Organization. Approximately 14 million cases of cancer are newly diagnosed every year. According to the latest report from the International Agency for Research on Cancer (IARC), it is expected that annual cancer cases will rise from 14 million in 2012 to 22 million within the next 2 decades.

In Poland, cancer is the second most frequent cause of death following cardiovascular diseases. However, while mortality due to cardiovascular diseases significantly declined in recent years, mortality as a result of cancer has substantially increased. Indeed, in Poland the cancer mortality in 2008 was still higher than in 1980, accounting for 25.8% of all deaths. An important fact is that both incidence of and mortality from cancer in Poland are one of the highest among all EU countries.

Standard therapeutic modalities, such as surgery, chemotherapy and radiotherapy, are at the moment only partially successful in the fight against cancer. Despite numerous advances in fields of genetics and molecular biology, virology, chemistry, pharmacology, malignancies continue to evade treatments. However, the pace of innovation, scientific discovery and technological advances continues to grow and, as a result, the picture of cancer is being profoundly redrawn. While still in the early stages, personalized medicine is steadily emerging as the new healthcare paradigm for cancer.

A part of this novel paradigm is understanding cancer as a systemic disease, where an intense interplay takes place between the tumor and the host, especially the host's immune system. It must be pointed out, that by current understanding the capability of the specific recognition of cancer-related molecules by the human immune system makes it an extremely precise and highly suitable tool for personalization of the anti-cancer treatments. That especially holds true for cancers related to the infection by such viral pathogens as HCV, HBV or HPV, The Science Magazine has named Cancer Immunotherapy a 'Breakthrough of the Year 2013'. Without any exaggeration, Immuno-Oncology is undoubtedly one of the most vigorous and promising areas in cancer research and raising great hopes for finding cure for this devastating illness.

It is being foreseen that over the next decade, immunotherapies will be the backbone of cancer treatments in 60% of cancer types. Yet, before the immune system can be successfully used in the fight against cancer, several main challenges must be addressed. These challenges can be grouped in two main areas: 1. Understanding the mechanisms of tumor evasion from the immune system; 2. Identification of the most successful immune-based anticancer effectors.

Multiple lines of evidence suggest that malignancies use at least several different mechanisms of avoiding the control by the immune system. One of these mechanisms relies on the exaggerated conditions of oxidative stress and high levels of reactive oxygen species (ROS), such as hydrogen peroxide, present within the tumor mass. Another important element present in the tumor environment is low oxygen concentration, known as hypoxia. Such conditions tend to switch off numerous antitumor capabilities of the immune system cells. Thus, it is important to understand how the immune cells can adapt to function under in such hostile environment. This is one of the objectives of the current proposal.

Natural killer (NK) cells are components of a human immune system and their proper functions play an important role in the fight against viral infections and cancer. Therefore, intensive studies are currently conducted to successfully use these cells as therapeutic tools against cancer. Yet, the anticancer activity of NK cells can be suppressed by high levels of oxidative stress and hypoxia, which can severely hamper their applicability in oncology. Here, we aim to understand in details the mechanisms which are regulated in NK cells under oxidative stress and hypoxia. On this basis, we are going to select the mechanisms that can potentially protect NK cells against inhibitory effects of oxidative stress and hypoxia. In the final stage of the project are going to generate NK cells that will be able to overcome the inhibitory effect of the tumor environment and thus efficiently kill tumor cells.

In this proposal, we plan to utilize a range of modern biomedical techniques, including RNA sequencing, to identify changes occurring in NK cells under oxidative stress and hypoxia. Performed studies will provide us with a wide-range of information about changes in the gene expression in NK cells under conditions which are associated with tumor environment On the basis of the acquired knowledge, we are going to modify NK cells to allow them for efficient recognizing and killing of tumor cells under hostile oxidative stress and hypoxia conditions.

Deciding on this ambitious project we want to contribute to identify and understand the molecular mechanisms that regulate the activity of NK cells in the tumor environment, and then use this knowledge to generate NK cells resistant to the suppressive effect of the cancer environment. In the future, this knowledge will prospectively lead to fine-tuning of the novel NK-based therapeutic approaches to anticancer treatment. Moreover, this therapy could be also applied in other human diseases.