Project title: Proteomic identification and therapeutic use of the proteasome machinery targets in human cancer

Cancer remains one of the primary causes of death in western countries. In Poland alone each of the recent years brought over 140.000 new cancer patients, and each year ended with more than 90.000 deaths caused by cancer. In Poland, as in other western countries, the cancers of lung, colon and pancreas will in the near future become primary causes of cancer-related deaths of men and women altogether.

The cellular proteasome machinery is not only a major protein degradation system in human cells but also a strong oncogenic factor. It is highly activated in most human cancer types, including the ones mentioned above, contributing to a degradation of tumor suppressor proteins. Thus, the proteasome is the target of clinically approved inhibitors in human multiple myeloma. However, despite an initial promise, clinical trials have shown a limited effect of proteasome inhibitors in solid tumor types and their metastases.

The main objective of this project is to better understand the oncogenic contribution of the human proteasome machinery to the whole protein content (the proteome) of human cancer cells and to use this knowledge to improve the anti-cancer therapeutic approaches targeting the proteasome and its downstream effectors in human lung, colon/rectum and pancreatic cancers.

Until now the scientific knowledge of proteasome substrates in cancer has been limited to several tumor suppressor pathways. In the proposed research, up to 15 thousand proteins will be identified in a single cell lysate by a mass spectrometry – achieving a depth of the whole cell proteome, allowing to compare cell proteomes in the control and the proteasome inhibition conditions. The protein lists obtained from such experiments in cell lines of different cancer type origin will be overlapped and analyzed by the bioinformatics to find specific and common proteasome targets. Validation experiments will verify if these targets affect the action of proteasome inhibitors and growth in solid-tumor derived organoids - tissue-like structures grown *in vitro*, which retain the characteristics of the patient's tumor.

The proposed research will greatly extend the knowledge of basic cellular mechanisms controlled by the proteasome, as well as it will uncover novel routes of improving or bypassing the proteasome inhibitor-based therapies and combating the resistance arising to the approved proteasome inhibitors. In cancer types which cause deaths of hundreds of thousands of EU citizens and patients worldwide each year, testing such protocols is critical for the progress of the personalized oncology.