Acquired drug resistance is the major challenge for modern anticancer therapy. Cancer cells develop the resistance to chemotherapeutics despite their strong initial activity. Due to random mutations in their genetic material, cancer cells gain features that help them to survive and divide under different conditions. Chemotherapy leads to selection of cells able to live in such harsh environment. These cells continue to divide and we observe this phenomenon as a disease recurrence. This is why, similarly as in case of developing the new generation antibiotics against, there is a strong need for search of new therapeutic strategies that would target cells survived after previous treatment.

Multiple myeloma is a malignancy originated from bone marrow cells– called plasmocytes – which are responsible for production of antibodies. Multiple myeloma cells retain some features of plasmocytes but produce in excess a fragment of immunoglobulins. It overwhelms the machinery involved in protein synthesis located in endoplasmic reticulum (ER). Therefore, multiple myeloma cells are characterized by high basic ER stress level. Normally, permanent ER stress leads to cell death, but cancer cells cope with this condition by initiating the special signalling pathways. Chemotherapeutics used in multiple myeloma treatment intensify the ER stress in cells. But despite of their high initial efficiency, the selection of cells able to cope with such conditions occurs.

Glutamine is an amino acid necessary for survival of cancer cells, including multiple myeloma cells. It serves as a source of energy and is a substrate for compounds pivotal for cell viability such as lipids and nucleotides. Recent studies show that changes in glutamine metabolism play role in response to agents with ER stress intensifying activity. Stress enhanced in breast cancer cells by such therapeutics decreased their glutamine uptake and as a consequence – caused their death. Moreover, scientists proved the anticancer potential of agents with ER stress intensifying activity in combination with glutamine metabolism inhibitors. Though there is no data on the effects of such therapy on cells resistant to such chemotherapy.

In our project we aim to improve the understanding of the role of glutamine metabolism in multiple myeloma cells resistant to chemotherapy and to evaluate the anticancer potential of therapeutic strategy combining agents inducing ER stress and inhibitors of glutamine metabolism. We hypothesise, that modulation of glutamine metabolism would sensitize resistant multiple myeloma cells to the activity of ER stress inducing chemotherapy. We believe that such a “double impact” would become a promising strategy in battle against multiple myeloma resistant to chemotherapy.