More than 500 thousands people currently suffer from malignancies in Poland only and ca. 160 thousands new cases are diagnosed each year. Pancreatic adenocarcinoma has one of the worst clinical prognoses, as only 6% of patients will survive beyond 5 years post diagnosis. Similarly, brain glioma tumors are highly lethal in human. A combination of surgery, radiation, and chemotherapy is the standard first-line therapy. However, even such aggressive multimodal approach have not significantly improved patient survival; median overall survival rate in glioma is only about 18 months. Every year more than 1 million people will develop colorectal cancer worldwide. Despite substantial improvement in treatment and diagnostics, disease-specific mortality rate is nearly 33% in the developed world. Expression of GPR55 and β_2-arenergic receptors is a common feature of pancreatic, glial and colon cancers cells. It is well established that these receptors control the growth, motility and metabolic activity of the cancer cells. The molecular mechanism exploited by the receptors exploit to control the physiology of cancer cells remains unknown. Thus, the aim of this project is to gather new knowledge on the intracellular mechanism of action of GPR55 and β_2-arenergic receptor to facilitate new drugs discovery.

We have modified a structure of fenoterol, a clinically used drug, to develop a set of unique compounds that act on the GPR55, β2-adrenergic receptor or both receptors simulationously. With these compounds, we plan to determine to what extent these receptors affect the growth, motility and metabolic activity of tumor cells of pancreatic, glial and colon origin. Then, we will examine how the GPR55 and β_2-adrenrgic receptors control these different aspects of cancer cell physiology by looking at the biochemical signals generated by the receptors inside the cells. We are particularly interested in *phosphorylation* – type of signaling that functions as a biological on/off switch. For instance, phosphorylation (i.e. switching on) of enzymes that induce production of new proteins will help the cells to grow. Thus, our objective is to reveal which cellular proteins are being switched on and off by phosphorylation in response to drugs acting on GPR55 and β_2-adrenrgic receptors.

Sir James Black, laureate of the 1988 Nobel Prize in Physiology or Medicine, famously stated that “the most fruitful basis for the discovery of a new drug is to start with an old drug”. We are convinced that our test compounds that derive from an “old drug” (i.e. fenoterol) can be forged into “new” anti-cancer agents. In this project, we will use our molecules to gain new knowledge about the action of GPR55 and β_2-adrenergic receptors. This new knowledge will form a rationale for applying our compounds as adjuvant agents for standard chemotherapy or as standalone anti-cancer drugs.