Breast cancer is one of the most common illnesses diagnosed among women, accounting for over 25% of all cancer cases. According to 2018-WHO data, it is estimated that almost 2.1 million new breast cancer cases were noted around the world. Annually in the European Union more than 562,500 women are diagnosed with breast cancer and about 98,700 die because of this disease. In Poland, 20,200 cases appear each year, of which almost 6,400 result in the death of the patient. Therefore, breast cancer poses a serious health and socio-economic problem worldwide. Drug resistance is a major problem, particularly in patients with advanced cancer, underlying the need for new targeted therapies. Different mechanisms of drug resistance are responsible for tumor treatment failure, including decreased intracellular drug concentrations due to drug transporters and metabolic enzymes.

The surfaces of cells are characterized by the presence of many carbohydrate chains carried by membrane components called glycoconjugates (glycoproteins, proteoglycans, glycosphingolipids), which are responsible for proper membrane organization and function. Numerous studies on cell surface glycoconjugates of normal and cancer cells have revealed characteristic changes in their expression associated with physiological (e.g. differentiation, embryogenesis) and pathological (e.g. neoplastic transformation) conditions. It is especially true for their carbohydrate moiety synthesized by glycosyltransferase enzymes. In cancer, such carbohydrate structures, called tumor-associated carbohydrate antigens (TACA), are used as tumor markers and targets for anti-tumor therapies.

Enzyme - ceramide galactosyltransferase (UGT8) is responsible for synthesis of simple glycosphingolipd - galactosylceramide (GalCer), widely known as cerebroside. We found that UGT8 is a significant index of tumor aggressiveness and a potential marker for prognostic evaluation of lung metastases in breast cancer. Significantly higher expression of UGT8 was observed in: (1) metastatic lung tumors than in primary tumors, (2) tumors of malignancy grades G3 than in G2 as well as in G3 than in G1, and (3) node-positive primary tumors than in node-negative primary tumors. We also showed that accumulation of GalCer in breast cancer cells has profound effects on their apoptosis, tumorigenicity, and metastatic potential. Our results suggest that the presence of GalCer in tumor cells is associated with their increased resistance to hostile molecular stressors associated with a tumor's microenvironment. We also found that increased expression of UGT8 and GalCer increases the resistance of breast cancer cells to apoptosis induced by doxorubicin and other chemotherapeutic agents such as paclitaxel and etoposide, suggesting that GalCer can be involved in intrinsic drug-resistance of breast cancer cells. Furthermore, we found that accumulation of GalCer was correlated with highly increased expression of the anti-apoptotic BCL-2 gene and highly decreased expression of two pro-apoptotic genes: *TNFR2/CD120b* and *TNFR9/CD137*.

Based on the above results, the primary goals of this project are as follows: 1) elucidation of the molecular mechanisms responsible for the anti-apoptotic activity of GalCer and drug-resistance of breast cancer cells, 2) molecular targeted therapy directed against breast cancer tumors expressing GalCer based on conventional chemotherapy and supported by the specific inhibition of UGT8, and 3) regulation of *UGT8* gene expression in breast cancer cells. Therefore, we propose the use of UGT8 inhibitors as drug resistance (DR) modulators, which are not *per se* chemotherapeutic drugs.

We believe that the results of our studies can open new possibilities in treating subsets of breast tumors overexpressing the *UGT8* gene by improving the efficacy of conventional chemotherapy as the result of increased sensitivity to anti-cancer drugs.