**Polymorphisms of miRNA genes and in the 3'UTR region of the ADME genes in breast cancer patients treated with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) chemotherapy.**

Drug resistance is one of the most serious causes of breast cancer treatment failure but simultaneously the exact mechanisms of this phenomenon are not completely understood. The absorption, distribution, metabolism, and excretion (ADME) of drugs are mediated by drug-metabolizing enzymes and transporters. Expression of ADME genes is tightly regulated at the transcriptional and translational levels, as well as through posttranslational modification, membrane trafficking, subcellular organization and some signal transduction pathways. Variations in the ADME processes of xenobiotics in humans, may lead to a reduced drug efficacy or to an adverse drug reaction in pharmacotherapy. Change of ADME gene expression by miRNA may lead to an altered capacity of drug metabolism and disposition, as well as to different response to xenobiotics. SNPs in miRNA can potentially affect the expression of multiple genes involved in pathways regulating drug absorption, metabolisms, disposition, stem cell function and the cell cycle, and may affect the overall clinical efficacy of a drug or may be the reason of resistance to that drug because miRNAs can potentially regulate expression of multiple genes and pathways. SNPs occurring in the regulatory noncoding sequences of genes (3'UTR) may be the cause of the interindividual variation in treatment response in breast cancer patients. The polymorphisms in the miRNA binding sites could lead to drug-resistance/drug sensitivity.

In this study, we are going to investigate a panel of SNPs in miRNA genes and 3'UTR regions of ADME genes and correlate these results with breast cancer treatment response. This research project will perform a genetic analysis between groups of breast cancer patients who are responders and non-responders to chemotherapy of three drugs in combination (5-fluorouracil, doxorubicin and cyclophosphamide). The study will use genomic DNA isolated from breast cancer patients treated with FAC first-line chemotherapy. The chosen group of patients was composed only from non-carriers of the Silesian most common germline mutations on *BRCA1* and *BRCA2* genes. SNPs in miRNA and 3'UTR fragments of ADME genes will be detected by sequencing, RFLP-PCR method ang TaqMan genotyping. Uni -and multivariate statistical analysis will be conducted using dominant, recessive and additive model.

This project results could bring a significant contribution to existing knowledge of the genetic basis of drug resistance. Simultaneous analysis of many genetic factors, which individually may have very subtle impact on the cellular processes and therefore may be omitted, allows the understanding of their cumulative impact on the response to FAC regime. The approach proposed in this project provides the overall insight into multidrug resistance mechanism, due to the analysis of variation in genes encoding proteins important for drugs intake, biotransformation and also for their therapeutic effect. Insight into the complex molecular mechanisms resulting in drug resistance during breast cancer treatment, may be also potentially relevant for the further research focused on developing drugs tailored to breast cancer patients' genetic profile.