ABC (ATP-binding cassette) transporters are responsible for multidrug resistance in many cancer cell lines. Multidrug resistance appears in subsequent cycles of chemotherapy and leads to a decrease in its effectiveness, which is an extremely important problem during intensive therapy. It is associated with increased expression of genes encoding ABC (ATP-binding cassette) transporters, which remove cytostatics outside the cell.

In my studies, I have been able to demonstrate that serine-dependent ADP-ribosylation is responsible for the overexpression of some of ABC family proteins in the doxorubicin-resistant triple-negative breast cancer cell line MDA-MB-231. ADP-ribosylation is a process that is catalyzed by poly(ADP-ribose)1 polymerase (PARP1).

To this time, the formation and activity of the PARP1/HPF1 complex and ADP-ribosylation of serine residues have been primarily attributed to DNA damage repair because the C4orf27/HPF1 protein regulates PARP1/PARP2 activity during the early DNA damage response and leads to chromatin relaxation at damage sites. HPF1 is responsible for identifying damage sites and binding to the catalytic domain of PARP to initiate ADP-ribosylation.

My research demonstrated that the functional interaction between HPF1 and PARP1 in a doxorubicin-resistant line occurs without induction of DNA damage, and that ABC transporter gene expression is controlled by the PARP1/HPF1 complex.

The aim of this project is therefore to identify functional regions on chromatin that lead to the formation of the PARP1/HPF1 complex and to identify transcription factors and/or transcription cofactors that will allow the discovery of proteins responsible for complex-dependent overexpression of ABC transporters in doxorubicin-resistant breast cancer cells.

The project research will be conducted on doxorubicin-resistant triple-negative breast cancer (TNBC/MDA-MB-231). The planned project includes the following steps: application of the ChIP-Seq method to locate the coding site of PARP1 and HPF1 on the genome, identification of transcription factors or chromatin remodeling enzymes that are responsible for the constitution of the PARP-1/HPF1 complex. Only one that may play a key role in binding the complex to chromatin regulatory sites will be selected. Next, DNA motifs typical for PARP1/HPF1 complex formation in the MDA-MB-231 cell line and (co)transcription factors at the molecular level that may play a key role in regulating ABC transporter expression and become pharmacological targets will be selected. From the complete list of factors, one will be selected and its role in maintaining the PARP1/HPF1 complex on chromatin in a doxorubicin-resistant line will be verified. In addition, the hypothesis of ADP-ribosylation of HPF1-dependent selected "factor", which may affect overexpression of ABC transporters, will be verified.

So far, the battle against multidrug resistance in cancer has not been fully successful. This problem has motivated me to undertake a study that will further our understanding of the regulation of ABC transporter expression and identify a potential pharmacological target while fighting cancer.