One of the problems in cancer chemotherapy is drug resistance. Resistance is a process, when the drugs which generally kill cancer cells, are by the cells, on different routes neutralized. The problem of resistance also concerns anthracyclines, antitumor antibiotics, commonly used in therapy. The main representative of this group of drugs is doxorubicin.

Resistance to doxorubicin relies on increasing amounts of transporters on the cell membrane - the so-called ABC carriers, particularly ABCB1. Their activity cause that the doxorubicin molecules are actively removed from cell – the site of drug action. Thus, the effectiveness of drug therapy is decreased.

However, other mechanisms of resistance have also been described. One of them is the intracellular reduction of doxorubicin, catalyzed the enzyme carbonyl reductase 1 (CBR1). Reduction of doxorubicin causes that from drug molecule, its metabolite is made - doxorubicinol, which is less active against cancer cells. It has been also described that doxorubicinol may be in the cytosol converted to doxorubicin again. Literature data indicate that the metabolite - doxorubicinol is also more susceptible to efflux mediated by the ABCB1.

The above data indicate that, successive mechanisms of resistance - metabolism and efflux–may intensify their action. Metabolism produces a substrate which is susceptible for efflux from the cell. While efflux, prevents the cytosol conversion of doxorubicinol to doxorubicin. The project will verify if such relationship exists, if it is important for the resistance of tumor cells to doxorubicin, and would indicate why doxorubicinol is more susceptible to efflux than doxorubicin.

Research will be conducted on cancer cell lines in which, after transfection with appropriate genes, increased levels of proteins will be observed. It would allow to determine the relationship between the activity of the proteins and the activity of doxorubicin. It is planned to test how CBR1 and ABCB1 affect cytotoxic, cytostatic, proapoptotic, antimetastatic properties of doxorubicn, as well as how it influence cell cycle distribution, and the intracellular concentration of doxorubicin and its metabolites. In addition, the effect of CBR1 on tumor-sensitizing effects on doxorubicin, the inhibitor of the ABCB1 transporter, will be determined. Finally, it would be indicated activity of ABCB1 protein against doxorubicin and doxorubicinol. In addition, molecular modeling studies will be performed to show the differences in the way of interactions between doxorubicin and its metabolite with the ABCB1 transporter.

Taken study subjects is very significant because it would allow to verify basic mechanism of resistance, which so far were considered as the most important in cancer resistance. Based on them number of compounds, inhibitors of ABC carriers, have been development; which despite chemosensitizing activity in preclinical studies, haven’t been introduced to treatment. Experiments conducted in project will verify the current concept of chemo-sensitizing drugs development and will let establish a new strategy for resistance-reversing drugs.