In search for molecular targets to overcome doxorubicin resistance in triple-negative breast cancer with the use of innovative drug carriers and combination therapy

Breast cancer is the cancer of highest morbidity and mortality among women. Triple-negative breast cancer (TNBC) is characterized by an aggressive clinical course and, consequently, a poor prognosis for patients. The main problem in the therapy of this type of breast cancer is the lack of expression of known receptors, molecular targets against which therapy could be applied. Therefore, this type of breast cancer is still treated with systemic chemotherapy with doxorubicin (DOX), the use of which is limited. Resistance is often developed against it and it has serious side effects such as cardiotoxicity. It is important to search for new mechanisms to address these limitations. There are modifications of this therapy available on the market, which consist in enclosing doxorubicin in carriers such as lipid envelope - liposomes, and the possibility of combining doxorubicin with other compounds in combination therapy is being investigated.

The aim of the project is to analyze the main issues that may contribute to breaking drug resistance to doxorubicin in triple-negative breast cancer. In the project, we will use a combination of doxorubicin with a naturally derived compound, sulforaphane (SFN) encapsulated in a novel vehicle.

We will investigate the Nrf2 signaling pathway responsible for drug metabolism and protection of cells from harmful agents such as reactive oxygen species. In addition, we will investigate the involvement of breast cancer stem cells (CSCs), which play a role in tumor recurrence and reduced effectiveness of therapy. The third and most important point of the project will be the identification of new potential molecular targets for doxorubicin, proteins, or molecules that play a role in preventing chemo-resistance, which could be modified by the addition of other compounds in combination therapy. The project will use advanced models and novel research methods, shown in Fig.1.

The project will be carried out in cooperation with specialists in related disciplines, which will allow for comprehensive analysis of the problem and will allow proposing new combinations of doxorubicin encapsulated in carriers, increasing the effectiveness of anticancer therapy. The outcome of the project will be a significant knowledge of the effect of sulforaphane on the mechanism of doxorubicin chemoresistance and the identification of cellular targets that doxorubicin attacks. If such a protein or molecule is identified, it may become the basis for the development of a new, effective and safe targeted therapy or a new treatment strategy for triple-negative breast cancer.

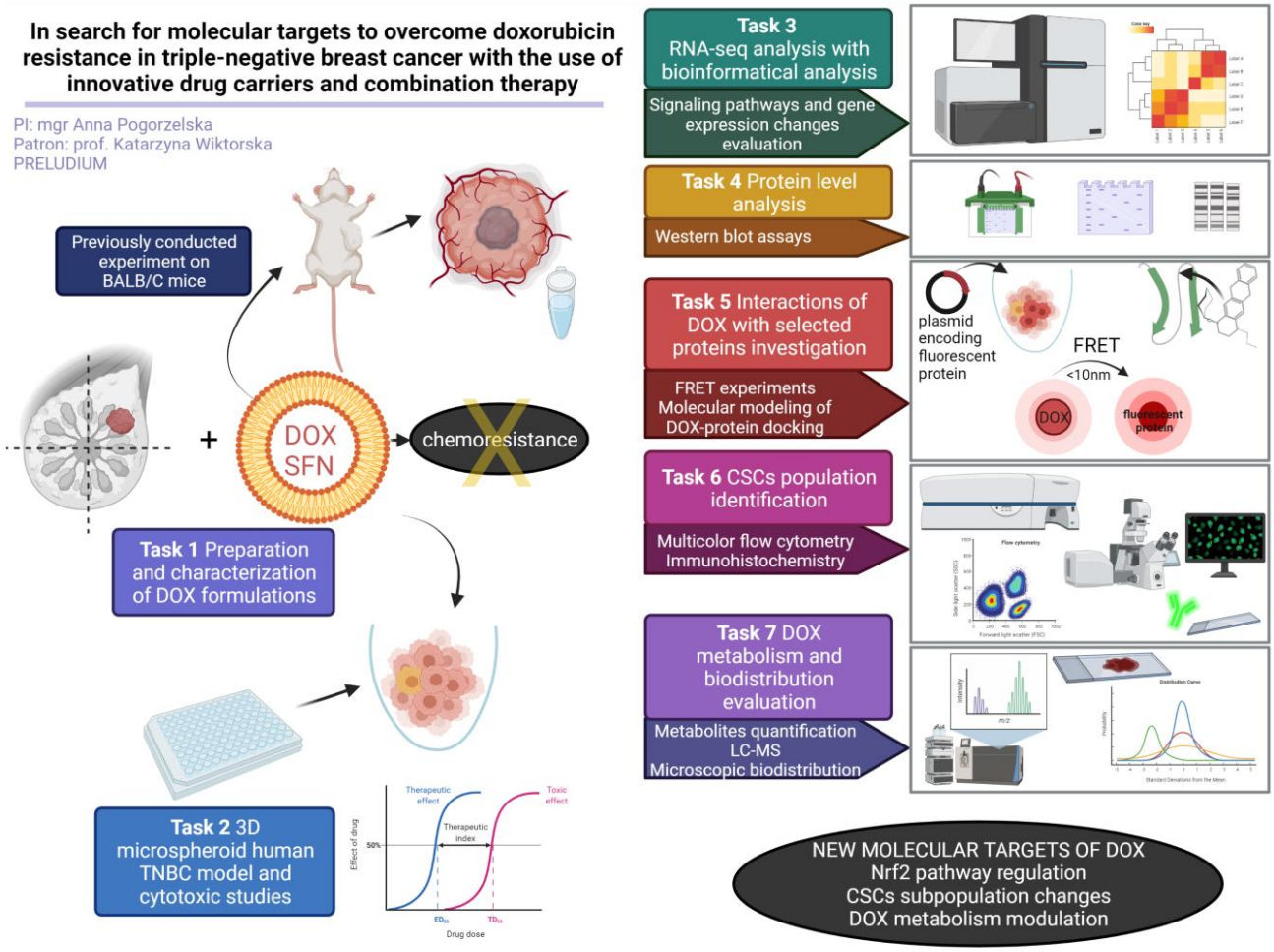

Fig. 1 A graphical abstract of the project. Created with BioRender.com