Efficient treatment of cancerous diseases still remains a great challenge for the modern medicine, especially in the light of the number of diagnosed cases still rising. The most common malignancies in women, and at the same time ones of highest mortality rate, are breast cancers. This disease is particularly heterogeneous and often accompanied by complications such as metastases to distant organs and resistance to the standard therapies. This resistance is particularly associated with drugs like **doxorubicin (DOX),** commonly used in breast cancer treatment. Despite years of research, the biology of breast cancer and the mechanisms driving metastasis and drug resistance, including DOX, remain insufficiently understood.

It is now well established on the basis of numerous studies that high metastatic potential of breast cancer is largely related to the phenomenon called epithelial-to-mesenchymal transition (EMT). This is a process of changes in cancer cell phenotype from regularly shaped, tightly connected to each other (epithelial-like) to spindle-shaped, non-adhesive cells with large nuclei, endowed in high migratory ability (mesenchymal-like). What is quite a new aspect, emerging evidence suggest that EMT-undergoing cells rather than binary states present a **spectrum of transition states** between these phenotypes, known as **epithelial/mesenchymal plasticity (EMP)**, and such ability of cancer cells to switch between various hybrid states, is strictly connected with cancer progression including migration, acquisition of self-renewing stem cell features, metastases formation, and chemoresistance. These transient cells are able to confer therapy resistance and induce metastatic activity even to a greater extent than mesenchymal cells with completed EMT program, previously suspected to be responsible of above complications. This topic is only yet beginning to be studied in various types of cancer, opening an attractive research field, supported by encouraging data published so far.

In the light of rising cancer prevalence, as well as issues related to chemoresistance, there is still a need for new, effective anticancer agents in the field of oncology. Although new drug candidates are being developed, their translation into clinic is a long-standing (approximately between 10 and 15 years) and extremely costly process. Moreover, the majority of newly developed agents fail during clinical trials. Thereby, the concept of **drug repurposing** – application of the already existing therapeutic agents in the treatment of different conditions or diseases, than they have been initially developed to cure – is gaining in significance. In comparison to any brand-new drug, this approach is connected with lower risk, reduced overall costs and duration of the development process. Repurposing strategy seems to be particularly attractive and promising in terms of cancer treatment due to possibilities to overcome growing resistance to currently used chemodrugs and expand therapeutic options, particularly in difficult-to-treat, metastatic or advanced cancers. So far, several antihypertensives and antidiabetics have been identified via repurposing as exhibiting anticancer potency. Attention is being paid also to antidepressants, which show anticancer effect towards various cancer types, including breast cancer, according to a number of in vitro studies. However, except for fluoxetine, their activities and anticancer mechanisms are yet insufficiently evaluated in context of breast cancer, and even more so, there are no studies investigating their influence on the interrelated processes of DOX resistance and EMP.

Thereby, in this project we aim to **evaluate the relationship between doxorubicin resistance, epithelial-mesenchymal plasticity** characterized by occurrence of specific phenotypic states, **and effects of selected antidepressants on breast cancer cells and aforementioned processes** using drug repurposing approach. Studied antidepressant agents will be representatives of three classes: selective serotonin reuptake inhibitors (sertraline), tricyclic antidepressants (imipramine), and tetracyclic antidepressants (mirtazapine). In this order, we plan to induce DOX resistance in two breast cancer cell lines of different characteristics, which will be grown in both classical monolayer and three-dimensional spheroid cultures. Since DOX resistance development is well documented to be associated with the acquisition of cancer stem cell properties, the presence and relative abundance of breast cancer stem cells will also be investigated. Before and after resistance induction, the effects of antidepressant agents in various concentrations, as well as combination of each drug with DOX will be studied, including their influence on cancer cell viability, stem cell population, DOX resistance, and epithelial/ mesenchymal markers expression. As we expect to confirm anticancer activity of the studied antidepressants, further steps would include elucidation of their apoptosis/necrosis induction ability and pathway of apoptosis in cultured cells, and answering the question if the tested compounds attenuate breast cancer resistance to DOX.

Such a collection of data would allow to determine anticancer efficacy of selected antidepressants towards breast cancer cells in context of DOX resistance and EMP, the issue which had not been investigated before, and enable identification of cellular events and pathways responsible for their effects. This work would offer a comprehensive insight into complex interrelation between E/M plasticity and DOX resistance, as well as may uncover new potential therapeutics and/ or drug combinations improving current treatment strategies, including potential sensitization of chemotherapy-resistant breast cancer cells by antidepressants.