Vascular dysfunction after breast cancer neoadjuvant chemotherapy.
The significance of menopausal status and estrogens.

The increasing number of cardiovascular risk factors has contributed to the development of cardiac events such as coronary artery disease and heart failure in cancer survivors. In particular, the presence of hypertension increased the risk of cardiovascular events. Chemotherapy is the most common therapy used to treat cancer, significantly increasing both 5- and 10-year survival of patients. It has been observed that in this period the main cause of death in people who have recovered from cancer are diseases of the circulatory system, in particular those associated with arterial hypertension and accelerated development of atherosclerosis, coronary artery disease and cardiotoxicity. The effect of chemotherapy on cardiovascular risk may be due to both side effects and may affect signalling pathways that are critical both in tumor development and in the regulation of vascular function.

In our recent research, we have shown how breast cancer chemotherapy may cause vascular damage in postmenopausal women, explaining how survivors of breast cancer most frequently pass away due to cardiovascular diseases. When examining the vascular system of women who have been treated with chemotherapy prior to mastectomy, we observed serious dysfunctions of vascular endothelium in postmenopausal women, which greatly affects the health of the circulatory system. This dysfunction was chiefly caused by one of drugs used to fight breast cancer: **docetaxel**. This drug caused an increase in reactive oxygen species vascular production through the NADPH oxidase subunits NOX2 and NOX4 in human arteries. In particular, up-regulation of NOX4 contributed to the dysfunction.

The main objective of the proposed project is to elucidate the pathophysiological mechanisms by which neoadjuvant therapy with docetaxel precipitates vascular dysfunction, with an emphasis on the influence of menopausal status as a key determinant of increased cardiovascular risk in breast cancer survivors.

Cardiovascular diseases are the leading cause of death in men and women. While premenopausal women are less likely to develop cardiovascular disease than men of the same age, this difference disappears after menopause. Additionally, the incidence of breast cancer has been found to be slightly higher in postmenopausal women than in premenopausal women. However, premenopausal women are more likely to develop more advanced breast cancer than older women. Older age and the risk of cardiovascular disease in women after breast cancer had the greatest impact on mortality from causes other than cancer. While neoadjuvant chemotherapy induced vascular damage in postmenopausal women with breast cancer, premenopausal breast cancer patients may be protected.

In the proposed project, we intend to investigate in detail how estrogens protect against neoadjuvant chemotherapy-induced endothelial dysfunction using human blood vessels and an animal model. Molecular characterization of the preventive effects of estrogens in docetaxel-induced vascular dysfunction can help the identification of new therapeutic targets.