

Project is addressing an important and still unresolved problem of BCa metastasis. The metastatic spread of BCa accounts for the vast majority of cancer-related deaths. The disease remains incurable for patients with distant metastases. Unfortunately no significant improvement in treatment of metastatic BCa has been observed over last 30 years. Despite intensive research, our understanding of metastatic spread is still insufficient to effectively control and treat metastatic disease. Therefore project focuses on deciphering the interplay between breast cancer cells and their surrounding microenvironment in metastasis formation process.

Stroma cells are considered to play key role in the carcinogenesis, tumor dissemination and metastasis formation. Among many other processes, they contribute to phenotypic plasticity of cancer cells, defined as ability to undergo phenotypic changes between epithelial and mesenchymal states. Tumor cell plasticity has been recently postulated to be essential for successful completion of metastatic cascade and has been linked with most aggressive subpopulation of cancer cells, providing them the highest possibility of adaptation to different conditions. The direct mediators of metastasis are circulating tumor cells (CTCs) present in blood of cancer patients. Their presence constitutes the switch from localized to systemic disease. However, it is still a matter of debate which population of CTCs is really the bad one that contributes the most to successful metastasis formation. According to our previous results, CTCs with mesenchymal phenotype seem to be particularly aggressive.

Although the key role of tumor stroma in cancer development is commonly agreed, its influence on phenotypic plasticity of tumor cells in different compartments (primary tumors vs lymph nodes) is scarcely known. Within the project, tumor microenvironment cells in primary tumors and lymph node metastasis will be analyzed in order to find molecular markers correlating with mesenchymal CTCs phenotype. Identified molecular markers will be further clinically and functionally validated. Clinical significance will be examined in the independent group of breast cancer patients, while functional validation will include analysis of identified factors influence on phenotype and aggressiveness of cancer cells *in vitro* and their dissemination and distant metastasis formation potential *in vivo* in mice model.

With the comprehensive design integrating *in vitro*, *in vivo* and clinical samples-based research, the current project has potential to broaden our knowledge about influence of microenvironment on the route of dissemination (lymphatic or hematogeneous) and the phenotype of disseminated cancer cells. Analysis of the cellular processes responsible for cancer spread, particularly cancer and stroma cells cross-talk in different niches, can contribute to improved understanding of the metastasis formation mechanism. It can also lead to the emergence of novel biomarkers associated with invasion and dissemination, which can be used for diagnosis and better prediction of disease progression. In further perspective more efficient treatments could be designed if we had deeper knowledge about the stages of metastasis formation.