The role of circular RNA – *MALAT1* in breast-to-brain cancer metastasis.

Breast cancer was the most commonly diagnosed cancer in 2020 worldwide (over 2.2 million cases; 11,7% of total cancer cases). At the same time, 380,000 deaths were recorded as a result of breast cancer, and it is estimated to reach 550,000 by 2030. Thus, breast cancer is a first-tier healthcare problem and the increasing number of cases as well as high mortality underlines the urgent need to develop new therapeutic approaches.

Breast cancer can be classified according to various criteria. A useful tool in the assessment of prognosis and selection of the appropriate therapy is to check whether tumor cells respond to hormonal signals through the special receptors located at the cell membrane. The combination of hormone receptors status with specialized microscopic examinations allowed the development of the molecular classification of breast cancer and selection of the appropriate therapy. One of the subtypes is basal-like breast cancer. This particular subtype has the poorest prognosis as 70%-80% of patients do not express hormone receptors (estrogen, progesterone, and HER2). Importantly, basal-like breast cancer frequently metastasizes to distant locations, including the brain, resulting in high mortality in this group of patients. Therefore, the search for new therapeutic targets in breast-to-brain metastatic (BTB met) cancer is crucial.

As the research on protein-coding genes brought about only incremental progress in the development of anti-BTB met therapy, much attention is devoted to understanding the role of non-coding RNAs, including microRNAs, and most recently, circular RNAs in BTB met cancer. As the name suggests, non-coding RNAs are molecules that do not serve as a matrix for protein synthesis. However, due to their ability to regulate many protein-coding genes, they have been recognized as key gatekeepers of cell fate decisions and differentiation. The microRNAome - all microRNAs being expressed in a cell at any given time - is an important indicator of cellular balance, and its formulation is mainly regulated by the DICER enzyme. A growing body of evidence suggests that a novel class of non-coding RNA - circular RNAs is also engaged in microRNAome output. The loss of tumor-suppressive microRNAs leads to dysregulation of the tumor cell microRNAome composition, promoting cancer progression, metastasis and inducing treatment resistance.

Our team's pioneering studies showed that the circular RNA (a circular form of *MALAT1)* participates in the loss of the microRNAome through DICER relocation, preventing the proper processing of microRNA maturation in glioblastoma stem cells, boosting their carcinogenic potential. Additionally, in the preliminary data, we demonstrated high expression of this circular RNA in patient-derived BTB met cells and confirmed concurrent deregulation of their microRNAome. **Taking into account the preliminary data and previous publications, we hypothesize that circular *MALAT1* participate in molding the molecular landscape of BTB met cells.**

These studies will be conducted using a unique collection of the BTB met cells isolated from metastatic disease patients that have been identified as the most clinically relevant basal-like breast cancer subtype. The most important element for developing new treatment strategies is to know your enemy. Therefore, initially, we aim to characterize these patient-derived cells, which is essential for understanding their nature, molecular characteristics, and susceptibility to treatment. Additionally, we will evaluate the microRNAome profile and determine the role of circular *MALAT1* in shaping microRNAome composition. Finally, we will evaluate the effect of circular *MALAT1* downregulation on BTB met cells' molecular traits and the response to standard-of-care chemotherapy.

The achievement of the scientific goals of the proposed project will help to understand the role of a new group of non-coding RNAs, circular RNAs, in shaping BTB met cells phenotype, an important scientific problem. In addition, this project would help identify new clinically relevant therapeutic targets and determine whether the inhibition of the circular form of *MALAT1* can be considered as a sensitizer to therapy in BTB met cancer.