Deciphering and Targeting Signaling Nodes that Drive Metastatic Breast Cancer

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Breast cancer is the most common cancer and the second leading cause of cancer death in women in the United States. Distant metastatic disease is overwhelmingly the cause of breast cancer deaths. Women with Stage IV metastatic breast cancer have a 5-year overall survival rate of 22%, according to the American Cancer Society. Therapies against metastatic breast cancer (MBC), and especially against the triple negative subtype, are severely limited. Furthermore, acquired resistance to therapies remains a major hurdle. Tumor heterogeneity is believed to be a major cause of therapy failures. Identifying and targeting key signaling pathways that drive metastatic progression and outgrowth is critical for developing effective therapies for treating patients with Stage IV breast cancer.

FRA-1 has been identified as an important driver of metastasis and tumor heterogeneity in cancer, including breast cancer. In breast cancer patients, FRA-1 expression is inversely correlated with metastasis-free survival. FRA-1 is a transcription factor that regulates the expression of many genes involved in multiple aspects of metastatic progression. Developing drugs that directly target transcription factors remains challenging. However, we have identified a protein kinase, MLK3, which controls the production of FRA-1 in triple negative breast cancer cells. We have used a technology called CRISPR to remove the MLK3 gene from triple negative breast cancer cells and find that these MLK3-deleted cancer cells have reduced FRA-1 levels. A small molecule inhibitor of MLK3 also controls FRA-1 levels in triple negative breast cancer cells.

The goal of this METAvivor project is to demonstrate the importance of MLK3 in an *in vivo* model of triple negative metastasis by testing the ability of MLK3-deleted breast cancer cells to form metastases. We will then test the efficacy of a small molecule drug targeting MLK3 on pre-existing metastases in an in vivo model in order to determine if this compound, which has been shown to be non-toxic in previous clinical trials, is a potential therapeutic for patients with metastatic disease. Finally we will bring to our lab newly developed human metastatic triple negative tumorgraft models, which have been shown to better represent patient tumor characteristic and drug responses, and test their response to the MLK inhibitor. These studies provide the opportunity to test an existing, safe drug as an unexploited therapeutic approach against metastatic triple negative breast cancer.