

Public Abstract

Grant Title: Overcoming therapy resistance in TNBC metastases through targeted inhibition of Periostin.

Rationale:

Despite having a relatively good initial response to chemotherapy, triple-negative breast cancer (TNBC) patients present significant higher rates of metastasis relapse and a worse prognosis than those presenting with non-TNBC. Studies show that the metastatic niche, especially the extracellular matrix niche (or tumor associated “soil”) surrounding metastasis-initiating cells, play an important role in the regrowth of metastasis lesions upon chemotherapy. However, no therapies targeting such tumor-associated “soil” have been developed to overcome chemoresistance in TNBC metastases. The proposed research aims to test a therapeutic approach to specifically target the tumor-associated “soil” to overcome chemoresistance.

Research goals:

Our proposed research aims to test the hypothesis that tumor-associated “soil” in TNBC tumors promote chemoresistance and to determine whether therapeutic targeting of one critical protein named periostin in tumor-associated “soil” could enhance chemotherapy responses and improve survival in stage IV metastatic TNBC patients. Furthermore, we plan to understand how this protein exerts its role in promoting metastasis regrowth upon chemotherapy.

To achieve this goal, we plan to first use TNBC tumors generated from human cell lines and human patient-derived xenografts to test whether inhibiting periostin could improve chemoresponses in both primary TNBC tumors and distant metastases in mice. Our next aim is to study how periostin promotes chemoresistance in metastatic TNBC.

Potential benefits for stage IV metastatic breast cancer patients:

The proposed research aims to address a critical issue in treating stage IV metastatic TNBC patients, who mostly have undergone multiple rounds of chemotherapies and developed resistance to most standard regimens. This is particularly relevant to triple-negative breast cancer, for which chemotherapy is the only available treatment option. Most previous efforts in overcoming chemoresistance have been focused on proteins inside tumor cells that regulating cell death and drug transport. The proposed research tests the novel concept that unique changes in tumor associated “soil” upon chemotherapy contribute to chemoresistance by supporting the expansion of tumor-initiating cells upon chemotherapy treatment. Our preliminary studies have identified one such unique protein that is specifically upregulated upon chemotherapy and promotes chemoresistance in TNBC xenografts. Therefore, our study could demonstrate the immediate clinical use of periostin as a predictive marker for chemoresponsiveness in TNBCs. This could aid in identifying TNBC patients who will become chemoresistant and may benefit from the use of novel therapies in addition to standard chemotherapy at diagnosis.

Therapeutic targeting of molecules in tumor-associated “soil” has been challenging partially due to critical roles these proteins play in normal physiology. Our preliminary data indicate that upregulation of a tumor-specific form of the periostin protein upon chemotherapy could provide a therapeutic window to target with minimum toxicity. We will test a novel antibody against this specific isoform of periostin to explore its therapeutic potential in reducing chemoresistance and improve long-term survival in metastatic TNBCs. If the proposed research is successful, the next step is to further develop a humanized version of the periostin antibody and to test in clinical trials the utility of blocking a specific isoform of periostin in reducing chemoresistance in stage IV metastatic TNBC patients. It is our hope that combining periostin blockade with chemotherapy could improve long-term survival and life quality in stage IV TNBC patients with existing metastases.