**Lay Description of Important Outcomes**

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. 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.

In the two-year funding period, we completed the following two major research milestones.

1) Demonstrated that targeting specific tumor-associated periostin isoforms by a monocloncal blocking antibody could synergize with chemotherapy to reduce tumor recurrence in TNBC tumor xenografts.

2) Uncover the mechanism of action of periostin in chemoresistance in TNBC: periostin is specifically required for proliferation and invasion, but not for anti-apoptosis function of mesenchymal tumor cells in response to chemotherapy.

Clinical relevance: 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. Our 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. We tested 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. 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.