

Lay Abstract

Unmet need: The deadliest attribute of breast cancer cells is their ability to leave their initial site of growth and travel to distant secondary sites, a process called metastasis. While survival rates are at an all-time high for breast cancer that is localized or regionally advanced, for patients with advanced or metastatic breast cancer, the 5-year survival rate remains at only 26%. This disparity in survival between early and late-stage breast cancer represents the principal obstacle in breast cancer management.

The tumor immune environment: Cancer cells interact with ‘stromal’ cells in their surroundings and adapt to their environment in the organ at the secondary site. This niche is commonly referred to as the ‘tumor microenvironment’. Interactions between tumor cells and the associated stroma represent a powerful relationship that influences the establishment and outcomes of breast cancer metastasis, and patient prognosis. The stromal cells include endothelial cells (that are the source of blood vessels), lymphatic vessels, fibroblasts, and a variety of immune cells. The immune cells are involved in mounting an immune response against the tumor cells. Cancer immunosurveillance involves an intricate interplay between the ‘first responder (**innate**)’ and ‘effector (**adaptive**)’ immune cells. The innate immune cells are important for programming the adaptive immune system to eliminate the tumor. Tumor cells co-opt the immune system and modulate their own niche to create an immunosuppressive, tumor-promoting environment.

For example: Macrophages are cells of the innate immune system that present the adaptive immune system with signals that can enable the adaptive cells to launch an immune attack to eradicate the tumor. Tumor cells can reprogram macrophages such that the macrophages end up fostering the growth of the tumor rather than pioneering tumor elimination. A similar scenario plays out with T cells that are major players of the adaptive immune system, wherein their killing activity is profoundly reprogrammed by the tumor cells and innate immune cells.

The opportunity: Thus, while the tumor stroma imparts strong influences on disease progression, they also present with a therapeutic opportunity that lies in the pliancy of the tumor stroma. Since the microenvironment is capable of adapting to tumor cells, re-education of immune cells, rather than targeted ablation *per se*, may be an effective strategy for treating cancer.

Our goal for this Metavivor project is to develop novel strategies to treat metastatic breast cancer. Our pre-clinical studies will specifically simulate a patient with metastasis. We will take advantage of immune cell plasticity by re-educating immune cells to treat cancer rather than targeting just tumor cells or stromal cells for ablation.

Our approach: To enable cells to respond and adapt to their environment, they must be able to receive and process information (or ‘signals’) that originate outside of the cell via pathways. We identified that inhibiting a distinct signaling pathway, the Hedgehog (Hh) signaling pathway, re-programs mammary cancer-associated tumor-promoting macrophages to tumor-killing macrophages. We will use two distinct immunocompetent mouse model systems to test approaches to treat metastatic (mammary) breast cancer. We will undertake studies to (i) evaluate if Hedgehog inhibition re-educates the immune system to eliminate breast cancer metastases, (ii) elucidate the mechanism by which Hh/GLI inhibition impacts innate and adaptive immune cells, and (iii) test a chemo-immunotherapy approach to eliminate breast cancer metastases.

Impact on the patient with metastasis: With the prospects of immunotherapy yielding much optimism in breast cancer, our investigations are designed to explore the next frontier of comprehensively re-programming the innate and adaptive immune systems in a breast cancer patient with metastasis. Outcomes from the work will provide evidence that using an approach that targets the tumor and the immune cells is a more effective way to treat metastatic breast cancer.

Projected outcomes, translational potential, and feasibility: The evidence generated will lay the foundation for a knowledge and evidence-based window-of-opportunity (WOO) clinical trial to test an FDA-approved Hh inhibitor in women diagnosed with metastatic breast cancer. The PI already has a great working relationship with the breast oncologists with whom she confers two times a month in a Breast Cancer Working Group. The University of Alabama at Birmingham O’Neal Comprehensive Cancer Center has a state-of-the-art Breast Health Clinic that is fully accredited by the National Accreditation Program for Breast Centers (NAPBC), and provides an excellent research environment. The vibrant interaction between researchers and clinicians enables quick and effective clinical translation of lab-based discoveries. As such, the PI is in a very befitting and competent environment to translate the findings rapidly to metastatic breast cancer patients.