# Development of Immune-based Strategies to Enhance Therapeutic Targeting of Metastatic Breast Cancer

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Metastasis is the primary cause of breast cancer-related morbidity and mortality and there is an urgent clinical need to eradicate established metastases and prevent future metastatic growth. During the transition from growth in the primary tumor site to the metastatic tumor site, cancer cells adapt to different environments through interacting with non-tumor cells within the organ site, which establishes the formation of a “tumor microenvironment”. The tumor microenvironment is essentially the soil in which the tumor grows and consists of non-tumor cells and blood vessels that surround the tumor. When systemic therapies are given to target the tumor cells, it is important to realize that these therapies are also acting on the non-tumor cells within the microenvironment. Understanding how therapies affect non-tumor cells within the microenvironment is a key focus of our research lab.

While targeted therapies are examined extensively in pre-clinical studies for their effects on the tumor cells, little is known regarding the potential effects of these therapies on non-tumor cells that reside within the tumor microenvironment. One of the prominent non-tumor cell types within the microenvironment of metastatic lesions is the macrophages, which is normally involved in the immune response to fight infections. Macrophages are capable of communicating with other cells in the immune system, specifically those that are able to eradicate tumor cells and establish a “memory” of the tumor, leading to both eradication of the existing metastasis and inhibition of future occurrences. The studies in this proposal aim to target the macrophages that exist within the metastatic site using pharmacological approaches and enhance their ability to induce antitumor immune responses.

There has been intense focus on the development and use of immunotherapy for cancer treatment. The primary goal of immunotherapy-based approaches is to enhance the tumor killing activity of T cells, which can ultimately lead to the generation of memory and lifelong protection against further metastatic tumor growth. However, a key challenge of this type is immunotherapy is that for it to work effectively, T cells need to be present within the tumor. Although relatively little is known regarding the presence of T cells in metastatic lesions compared with primary tumors, early evidence suggests that there are less T cells in metastatic lesions compared with matched primary tumors. Therefore, there is a need to develop strategies to enhance T cell infiltration into the metastatic site in order to enhance the effectiveness of immune based therapies.

Using a mouse model with a fully competent immune system, we believe that we have identified an approach to instruct macrophages within tumors to produce potent factors, called chemokines that will promote T cell recruitment into the metastatic site. However, these macrophages also express proteins that will inhibit T cell activity. Therefore, we propose to develop a combination therapy that will 1) enhance T cell recruitment into metastatic tumors and 2) promote the tumor cell killing activity of T cells. Studies are proposed in this application to test this combination therapy using an immune competent model of mammary tumor metastasis to the lung. The ultimate goal of these studies is to develop strategies that use the immune system to eradicate established metastases lesions and inhibit the formation of future metastatic lesions.

**Expected outcomes:** We expect to develop a combination therapy using clinically relevant inhibitors that will eradicate established metastases. The Masonic Cancer Center at the University of Minnesota has a number of programs and mechanisms focused on helping their researchers translate their basic discoveries into clinical utility, thus we will have access to resources that will facilitate the clinical next steps of these studies. The data generated from these studies will provide key pieces of preliminary data that will be used for a new R01 application.

**Clinical benefits and Impact:** These studies will provide proof-of-principle that combining clinically relevant inhibitors with immune based therapies will lead to enhanced targeting of metastatic breast cancer. As described in the Pathway to R01 statement, we have been spending time generating additional models of metastasis, including a bone metastasis model. Thus, we plan to expand our studies of the immune system into additional metastatic sites, thus we anticipate broad impact of these studies for patients with metastatic breast cancer.