

Public Abstract: Using B Cells to Eliminate Triple Negative Breast Cancer Liver Metastases

Metastasis is the leading cause of death for patients diagnosed with breast cancer (BC). The complexity of metastasis has unfortunately resulted in a delay of researchers' abilities to deliver safe and effective therapeutic options for patients. There is an immediate need to provide therapies that work for patients with liver metastasis (BC-LM), where survival is 4-8 months if untreated. Currently, the "best" treatment options for triple negative breast cancer liver metastasis (TNBC-LM) consists of surgical removal and a treatment regimen that only 10-20% of patients benefit from.

The worse overall survival observed in TNBC-LM is due to cancerous cells being able to persist as undetected by a patient's immune system. We do not yet know exactly how tumor cells avoid the immune system in metastatic disease. These immune evasion mechanisms ultimately establish fatal metastatic disease. This incomplete understanding translates to inappropriate therapeutic approaches, which fail to address the unique molecular environments of metastasis.

Our immune system is our greatest defense against cancer. Immune therapy is often used to stimulate an immune response against cancer. The B cell is an important immune cell type that can be activated by immune therapy. Stimulated B cells can recognize cancer cells and produce an antitumor response by secreting antibodies. Fortunately, patients who have B cell recognition of their metastases have the longest survival and we discovered how to activate B cell responses therapeutically in primary tumors. This treatment ultimately activates necessary B cells resulting in a powerful antitumor immune response in mice.

Metastasis presents significant differences in tumor and tissue microenvironments that stunts an effective immune response. We need to learn how to conduct this same restoration of B cell recognition in metastatic lesions to then be able to increase the survival of those living with metastatic disease. Not only do we aim to increase survival, but our goal is to optimize treatment regimens with the findings made possible by this funding to eventually make BC-LM non-lethal with lasting remission.

We hypothesize that tumor metastases are established, progress and resistant to ICI therapy by suppression and avoidance of the T/B cell response. The goal of this proposal will be to find what is causing suppression of the necessary B cell response in metastasis. To identify these mechanisms, we will collect data and test the activities of B cells during progression and treatment of metastatic lesions. This will then allow us to provide new druggable targets and guide the discovery of effective treatment for metastatic disease. Given the clinical data indicating that B cell activity leads to better survival, we propose to examine our current innovation to combinatorial immunotherapy that activates B cells. Our lab has representative mouse models of BC-LM and state-of-the-art equipment to conduct the necessary experiments and analysis. Together, when this work is complete, we will identify the necessary molecular interventions to overcome metastatic disease and develop effective therapies that can greatly reduce the mortality and improve the quality of life (QOL) in patients with TNBC-LM.

The work in this proposal will increase the likelihood of translating our *in vivo* findings to the clinic. In providing preclinical effective treatment options accompanied by mechanistic rationale to our clinical collaborators, we can initiate phase I studies and patients that are battling metastatic cancer will then have the well-deserved opportunity to enroll in a clinical trial using these proposed regimens. Moreover, the results of this study would assist future research in which we can expand our findings to not only cure metastatic disease but also be able to prevent metastasis in patients with premetastatic stages of cancer.