

## Public/Lay Abstract

Although the diagnosis of metastatic breast cancer often comes with a dire prognosis, many patients with only one or a handful of metastases should probably be considered curable. Some patients with so-called oligometastatic cancer enjoy long-term survival after ablative radiotherapy of their metastases while others experience very slow progression of their tumors and little or no spread to new sites. Current understanding ascribes some of the benefit of metastasis-directed therapy to reducing the suppression of T-cell mediated anti-tumor immune response, allowing the patient to "reject" any remaining cancer cells. However, mechanisms remain unclear and it is not yet possible to predict which patients will benefit or how best to treat them. Our goals for this METAvivor Research Award are to study combinations of ablative radiation and checkpoint blockade to identify optimal treatment for metastatic cancer in mouse models. We hope to gain a better understanding of how best to apply checkpoint blockade immunotherapy to improve outcomes in oligometastatic disease. During this two year funding period, we intend to build on our recent progress to discover mechanisms underlying synergy between metastasis-directed therapy and checkpoint blockade and then leverage these insights to obtain a systemic anti-tumor immune response. Briefly, we will examine conditions that maximize anti-tumor response to both primary tumors and lung metastases from the mammary carcinoma model 4T1 in BALB/c mice. Here, we will take advantage of image-guided radiotherapy, serial needle core biopsy, three dimensional imaging cytometry and flow cytometry to determine how best to enhance local anti-tumor immune response and promote immune destruction of distant metastases. We will thereby be able to determine features of irradiated tumors that predict response to immunotherapy, yielding new candidate biomarkers. These results can be rapidly translated to treating patients, building on ongoing clinical trials combining radiation and checkpoint blockade in metastatic cancer already ongoing at The University of Chicago. Looking forward, we can then use lessons learned from treating oligometastatic cancer to address the much greater challenge of treating and curing polymetastatic cancer.