METAvivor Early Career Investigator Award Public Abstract

There is an unmet need to develop treatments for metastatic breast cancers, especially aggressive triple negative breast cancers, that have durable responses and significantly improve overall survival. While immunotherapies such as immune checkpoint blockade have led to 'cures' for some other metastatic cancers such as melanoma, responses in breast cancer have been more modest especially in metastatic disease and even more so with liver metastases. One reason for this impairment is deficiencies in antigen-presenting dendritic cells (DCs), which are essential for initiating and sustaining an immune response against tumors. In breast cancer, these cells become dysfunctional, particularly in advanced stages and in metastatic sites like the liver.

Our research aims to overcome this problem by testing a new treatment strategy that combines three approaches to enhance dendritic cell function and improve immune responses against cancer. The treatment includes a CD40 agonist, a molecule designed to activate DCs, thereby improving their ability to stimulate the immune system; Flt3 ligand, a growth factor that increases the number of DCs including cDC1 cells, which are particularly effective in presenting cancer antigens; and anthracycline chemotherapy (Doxil) that not only helps release cancer cell antigens but also induces a type of cell death that promotes an immune response. In preclinical studies using mouse models, this combination treatment has shown promising results, significantly reducing tumor growth and improving survival rates compared to standard chemotherapy alone. We are now extending this approach to human trials, specifically for patients with metastatic breast cancer with a focus on metastatic triple negative breast cancer. Our findings indicate that this combination therapy successfully enhances the activity of DCs and increases the infiltration of cancer-fighting immune cells into tumors. However, the presence of suppressive regulatory CD4 T cells may still limit the treatment's effectiveness. We have observed that eliminating these CD4 T cells can lead to more effective tumor eradication and create long-lasting immune memory.

While we've made progress, we still don't fully understand how immune-based treatments interact with cancer that has spread to different organs. In this proposal, we will investigate these interactions in primary breast and metastatic models and at various sites of metastasis (lung and liver). Distant metastases, especially in the liver, often show compromised DC function, and emerging evidence highlights the role of Tregs in their limited anti-tumor immunity, contributing to their resistance to current treatments. However, these sites may be more responsive to our proposed therapeutic approach.

To advance our research, we have outlined two specific aims. The first aim is to investigate how our treatment performs across various tumor sites, including primary breast tumors, lung metastases, and liver metastases, using mouse models. By comparing the clinical effects and changes in immune cell dynamics at these different sites, we aim to gain insights into how the treatment impacts tumor control and immune responses. We will also validate these findings using patient samples from an ongoing clinical trial with this combination. The second aim is to explore the role of T regulatory cells in hindering the effectiveness of our treatment across these metastatic sites. We will use multiple methods to deplete these suppressive cells and assess how this affects the treatment's success. Additionally, we will analyze changes in immune cell populations within tumors to understand the mechanisms driving both positive responses and resistance by site of disease site.

This research aims to refine our treatment strategy, develop more targeted immunotherapies, and ultimately improve the outcomes for patients with metastatic breast cancer and other solid tumors. By addressing the specific challenges posed by different tumor sites and immune cell interactions, we hope to advance more effective and personalized treatment options. The results of this study will lay the foundation for NIH level independent grant funding and also future investigator-initiated clinical trials.