

PUBLIC/LAY ABSTRACT

The majority of breast cancer deaths are due to metastatic disease. More than 150,000 patients in the US live with metastatic breast cancer (MBC). Approximately 6% of MBC patients present with metastatic disease upon initial diagnosis. The high incidence and mortality associated with MBC, coupled with an overwhelming lack of effective therapies, warrant the exploration of novel treatments capable of impacting MBC patient survival.

Immunotherapy, wherein the patient's immune system is activated to eliminate cancer cells, has led to impressive clinical benefits in cancers such as melanoma and non-small cell lung cancer (NSCLC). Strategies include: 1) immune checkpoint blockade (ICB), relying on inhibitors to checkpoints, such as programmed cell death protein 1 (PD-1), that regulate antitumor immunity; and 2) adoptive cell transfer (ACT), wherein the patient's T cells are activated and expanded *ex vivo* and re-introduced into the patient. Both approaches aim to increase the number of CD8+ T cells that can engage and eliminate cancer cells. Immunotherapy has been applied to MBC, but responses have proven modest, especially in clinical trials involving ICB. A major obstacle to immunotherapy is immunosuppression and T cell exhaustion upon tumor entry. The tumor microenvironment leads to mitochondrial defects and a loss of mitochondrial content in T cells, contributing to metabolic dysfunction. This ultimately limits the cancer cell killing potential of T cells.

Our objective is to metabolically-prime T cells to bolster their antitumor immunity in ACT. Nuclear respiratory factor-1 (NRF-1) activates mitochondrial transcription factor A (TFAM), which drives mitochondrial biogenesis. Increased mitochondrial mass ultimately improves mitochondrial respiration and ATP production. We hypothesize that NRF-1 mRNA treatment of isolated T cells will increase mitochondrial biogenesis and boost their bioenergetic fitness, protecting T cells against mitochondrial dysfunction and metabolic stress, ultimately enhancing their antitumor immunity in ACT. To test this hypothesis, we will first examine whether NRF-1 mRNA-induced mitochondrial biogenesis in T cells can improve CD8+ T cell immune function in mouse models of MBC. We will then evaluate whether metabolically-reinforced T cells can improve antitumor efficacy in a synergistic fashion with PD-1 inhibitors in mouse models of MBC.

This work will demonstrate that increasing mitochondria will reinforce favorable T cell bioenergetics needed for effective immunotherapy against metastatic breast cancer, improving patient outcomes. Enhancing mitochondrial respiration in T cells as a strategy to potentiate immunotherapy, as well as organelle (mitochondria) biogenesis as an approach for energization of potentially metabolically-compromised cells, represent innovative aspects of the proposed work. Of note, the approach relies on clinical strategies, pharmacotherapies, and antibodies currently in clinical use. This makes the findings from this work highly relevant and impactful for patients with established MBC because there is a clear potential for expeditious clinical translation.

We will evaluate mitochondrial biogenesis in T cells, with the aim of bioenergetically priming them towards a metabolic phenotype capable of enhancing their persistence and antitumor immunity in ACT. Successful completion will highlight a strategy that can improve immunotherapy in metastatic breast cancer patients.