

## **PUBLIC ABSTRACT.**

Metastasis is the primary cause of death in breast cancer patients and claims the lives of over 44,000 people in the United States each year. The relative 5-year survival rate for people with breast cancer contained to the breast is ~90%. However, once breast cancer metastasizes to distant organs, the 5-year relative survival rate drops to just 29%. Metastatic triple-negative breast cancer (mTNBC) is a highly aggressive subtype with a tendency for visceral organs and brain and overall survival of approximately 18 months. There is a critical need to develop improved, molecular targeted therapies for patients with mTNBC that have enhanced efficacy, less toxicity, and improve survival, ultimately aiding to reduce the morbidity and mortality associated with mTNBC.

We believe the development of MUC1-theranostic approach would lead to a more effective strategy to treat mTNBC. Mucin-1 (MUC1) is a transmembrane mucin family protein, highly overexpressed in over 90% of breast cancers and 94% of the triple-negative subtype. MUC1 expression correlates with aggressive, metastatic disease, and poor survival. Underglycosylation of MUC1 in BC reveals core peptides of the extracellular domain that are masked in normal tissue and represent promising and highly selective targets for anti-cancer therapy. We will optimize, test, and develop a novel theranostic peptide targeting MUC1 for imaging and treatment of mTNBC. This agent will have dual functionality for both diagnostic imaging using positron emission tomography (PET) and targeted radionuclide therapy (TRT) using  $\beta$ -emitting isotopes. The diagnostic component enables identification and selection of patients who would benefit from targeted treatment and subsequent treatment monitoring. The therapeutic component results in specific targeting of cancer cells throughout the body and induces the cytotoxic effects of ionizing radiation with minimal effects on normal tissues. This peptide will be optimized, prepared, and evaluated for imaging and treatment of mTNBC in mouse models.

Given the mortality associated with mTNBC and the critical need for targeted treatments, this MUC1 theranostic strategy will have high impact for the treatment and management of mTNBC. Our strategy is designed with clinical translation in mind, specifically we will utilize short, peptide sequences. These have the benefit of rapid production, low cost, appropriate clearance properties for radionuclide therapy, and can be readily translated. We intend for our results to lay the foundation for the subsequent development of controlled clinical trials that assess this promising treatment in patients with mTNBC. In addition, we plan to apply this strategy to other subtypes of MBC as MUC1 is found in over 90% of breast cancer. The knowledge gained from these studies could have a far-reaching and beneficial impact on patients diagnosed with MBC of all molecular subtypes.