Public/Lay Abstract:

Triple-negative breast cancer (TNBC) is an aggressive and difficult to treat form of breast cancer that frequently spreads to other parts of the body (called metastasis). Among the organs it affects, the lungs are one of the most common sites of metastasis. Once it reaches this advanced stage, treatment options are limited, and survival is often short. Over the past decade, immunotherapies, particularly immune checkpoint inhibitors (ICIs), have transformed treatment for many cancers, including TNBC that has not yet spread to other organs. These therapies work by harnessing the body's own immune system to selectively target and destroy cancer cells and, in some patients, have achieved long-lasting control. Unfortunately, ICIs are far less effective against metastatic TNBC, as these tumor cells have learned to hide from the immune system. They do this by losing MHC-I, a molecule that normally helps the immune system recognize and attack tumor cells. Without MHC-I, cancer cells can turn themselves invisible to immune attack, making them significantly harder to treat.

To address this problem, my research team has engineered AT-EVoids, tiny particles made from activated T cells, which can restore MHC-I on cancer cells. In doing so, these particles are able to reawaken the immune system's ability to fight cancer, even in metastatic TNBC cells that do not respond to standard drugs that are commonly used to boost immune system recognition. These particles are also structurally stable and can be inhaled, rather than injected into the blood,which allows them to travel directly to the site of lung metastases while minimizing unwanted side effects to other body parts.

Focusing on TNBC lung metastases, we will first develop an advanced preclinical model that mimics how lung metastases occur in patients, capturing the aggressive, immune-evading behavior seen in patients with this cancer. Using this model, we will test whether inhaled AT-EVoids, either alone or in combination with ICIs, can help activate the immune system directly at the site of the cancer to slow metastatic spread or even shrink lung metastases.

If successful, this work could pave the way for a new type of immune therapy that helps the immune system recognize and attack 'immune-invisible' metastases – turning previously hidden cancer cells into targets for treatment. This new approach could provide patients with stage IV breast cancer that has spread to the lung a safer, targeted, and more effective way to control their disease, improving both their survival and quality of life.