

Stopping Metastasis is Stopping Breast Cancer

People die from breast cancer when it metastasizes and spreads throughout the body. Clinicians and scientists do not fully grasp how metastatic disease spreads and forms. In order to develop better treatments for people with Stage IV metastatic breast cancer (MBC), we need better research tools. Specifically, we need better experimental models that will enable us to capture how metastatic cells move throughout the body and dynamically interact with the immune system.

T cells are a closely studied part of the immune system and scientists have a better understanding of how T cells control many metastatic cancers. T cell directed immunotherapies have revolutionized the care of metastatic disease across multiple cancer types. But for people with MBC, current immunotherapies provide limited benefit. A second type of immune cell, the natural killer (NK) cell, is also a key immune cell that has strong anti-metastatic properties. However, we know a lot less about natural killer cells and how metastatic breast cancer cells and NK cells interact. We created innovative cell culture models that enable us to examine how NK cells and metastasizing breast cancer organoids interact during metastasis. These models have led to key discoveries about NK cells:

- (1) NK cells target metastatic breast cancer cells; they limit metastasis in multiple breast cancer subtypes.
- (2) Tumor cells can reprogram NK cells from tumor killers into cells that promote metastasis;
- (3) Reprogramming of NK cells can be reversed therapeutically;
- (4) Undoing this reprogramming could lead to new ways to treat metastatic breast cancer.

Understanding NK cell biology could lead to new metastatic breast cancer treatments.

We seek to identify novel means of treating MBC. Our research hypothesis is that, if we can return a patient's NK cells to their native tumor killing state, those NK cells will stop breast cancer metastases. I seek a METAvivor Early Career Investigator Award to achieve the following goals:

- (1) to restore human NK cells to their killing state;
- (2) determine the specific mechanisms behind NK cell reprogramming; and
- (3) determine if NK cell reprogramming is similar across subtypes of breast cancer.

In Aim 1, we will validate potential targets that can reverse reprogrammed NK cells to eliminate breast cancer metastases. This aim requires a human version of the co-culture model, which we will achieve using primary human NK cells and patient derived organoids. With this model we will experiment with cell surface binders that may reverse NK cell reprogramming. Next, we will validate targets in mouse models of MBC that have intact immune systems. Time to clinical translation is 3-4 years from target identification.

In Aim 2, we will determine the mechanisms behind NK cell reprogramming. KLRG1 is a cell surface receptor that is highly expressed by reprogrammed metastasis-promoting NK cells. The main ligands for KLRG1 are cadherins. Cadherins are known to be critical in tumor metastasis. Using cutting edge genetic tools and our new models, we will disrupt KLRG1-cadherin interactions to determine the effect on tumor reprogramming of NK cells. Since reprogramming of NK cells can be achieved epigenetically, without altering the DNA sequence, we will determine how KLRG1 is epigenetically controlled. An interim outcome for clinical translation is identifying biomarkers related to this mechanism that classifies which patient will develop metastatic disease.

In Aim 3, we will determine whether reprogramming of NK cells is similar across breast cancer subtypes. This step is critical to judging the therapeutic breadth of NK cell reprogramming. We will assess similarities among reprogrammed NK cells by assessing the distribution, phenotype, and function of NK cells from different metastatic breast cancer mouse models. Interim outcomes for clinical translation are the identification of novel targets of reprogrammed NK cells that are similar across multiple breast cancer subtypes.

Translation and Impact

Therapeutic reactivation of a patient's own NK cells to kill metastatic disease is an exciting new source of immunotherapies for treating MBC. Our work is a critical first step in the MBC immunotherapy discovery pipeline. Additionally, results from our proposal can lead to rational clinical trial designs. For example, applying anti-TIGIT antibody therapies for people that have NK cell enriched MBC. Our approach to restoring human NK cells to their natural killing state uses novel models I pioneered. A key goal of this work is to understand how metastatic tumor cells reprogram NK cells. If reprogrammed NK cells are similar across different subtypes of breast cancer, our NK directed treatment strategy could be used broadly to treat more patients. Such drugs have the potential to completely change the disease trajectory of people with metastatic breast cancer.