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PUBLIC ABSTRACT

One in six women with breast cancer have triple negative breast cancer (TNBC) – an aggressive subtype of the disease that lacks the estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor targets for some of our most effective breast cancer treatments. In the U.S. alone, approximately 69,000 women are diagnosed with TNBC every year and nearly 12,000 lose their lives to this disease. The vast majority of these deaths are due to the spread and growth of breast tumors in organs other than the breast, termed stage IV metastasis. Once tumor cells leave the breast and take up residence in foreign organs, TNBC is incurable. The long-term goal of this research is to improve targeting strategies for TNBC metastases growing in secondary organs to improve the long-term management of metastatic TNBC.

While the most common metastatic site of ER+ breast cancer is the bones, TNBCs most frequently metastasize to the lung, brain, and liver. The majority of metastatic TNBC patients have metastases in greater than one organ site, so therapies to effectively treat stage IV disease must target vulnerabilities of tumor cells that are shared between distinct secondary organs. The major goal of my proposed research is to identify properties of tumor cells that are shared between the most common organs of TNBC metastasis – the lung, brain, and liver. I will then use this knowledge to kill tumor cells that are growing in those three metastatic sites. Molecules needed for survival of metastatic tumor cells that have established in foreign organs will be excellent therapeutic targets for future preclinical and clinical therapeutic studies.

 The proposed studies will be accomplished using a type of mouse model whereby primary breast tumor cells, obtained directly from primary tumor biopsies of patients with TNBC, are grown in the mammary glands of mice that have been "humanized" with normal human breast cells. We have demonstrated that TNBC grows in these "humanized" mammary glands and metastasizes to the lungs, brains, livers, and bones of mice. Furthermore, we have demonstrated that these models faithfully maintain the molecular features of the patient's breast tumor biopsy from which they were derived.

Using two of these models, I conducted a study in which I tagged each individual primary tumor cell with a unique DNA 'barcode', allowing me to monitor each cell, and its progeny 'daughter cells' which also carried the same DNA barcode of the parent cell, as they grew in the mouse's mammary gland and metastasized to foreign organs. I discovered that the same subpopulations of primary tumor cells, which were present as a very low-abundance population in the primary tumor, made up the bulk of the metastatic tumor cell population in the lungs, livers, and brains of mice. Because the same groups of tumor cells are able to survive in diverse types of organs, the tumor cells may have targetable properties that enable them to do this. The goal of my proposal is to identify these properties, then disrupt them to kill established metastases.

In the first aim of my proposed research, I will collect primary tumors and lung, liver, and brain metastases from mouse models established from breast tumor biopsies of TNBC patients. I have labeled the tumor cells in these mouse models with a color, enabling me to use a technology called "bioluminescence imaging" to see and dissect metastatic tumor cells in secondary organ sites. I will then collaborate with a world expert, Dr. Nicholas Navin, to analyze these samples using an emerging revolutionary technology called single-cell sequencing. This technology enables measurement of all genes that are turned on in each individual cell, allowing me to observe whether any genes are congruently turned on in cells found in metastases of multiple organs. Genes turned on in multi-organ metastases may play a role in allowing the tumor cells to survive in those distinct organs, and thus will be prioritized for in-depth studies. In the second aim of my proposed research, I will use gene-targeting technologies to turn off the expression of these genes. In order to focus my work on treatment of metastatic tumor cells that have already started to thrive in the metastatic site (thus modeling stage IV disease), I will use the above mouse models to allow metastatic lesions to establish in secondary organs, then I will activate the gene-disruption technology. I expect that turning these genes off will lead to killing of metastatic tumor cells in multiple foreign organs.

Genes required for the survival of already established multi-organ metastases will serve as excellent therapeutic targets for follow-up therapeutic treatment studies. My long-term goal is to extend these findings to clinical trials in patients to kill tumors growing in lungs, livers, and brains of TNBC patients with stage IV metastatic disease. The knowledge gained by studying how breast cancer cells survive in multiple foreign organs is expected to stimulate the development of novel therapeutic strategies for treating stage IV metastatic disease and for identifying novel prognostic markers for TNBC metastasis.