PUBLIC ABSTRACT

Metastasis, which is when cancer spreads to other parts of the body, is responsible for about 75% of deaths from breast cancer. However, there are no existing treatments that specifically target two key aspects of this process: The way existing metastatic tumors manipulate the immune system in the metastatic site, and how tumor cells spread from one metastatic site to another. If we could develop new treatments that make the metastatic site hostile to tumor cells and prevent further spread, it would be a major therapeutic breakthrough for metastatic breast cancer patients.

There are two big challenges to achieving this goal. First, existing methods for screening potential treatments are not good at finding drugs that can reverse the ways that tumors manipulate the immune system in the metastatic site. Second, we don't yet fully understand how existing metastatic tumors spread to new sites – a process called secondary metastasis – largely because we lack proper models to study this process. My research aims to overcome these challenges in two ways.

First, I will invent a new drug screening platform for finding immunotherapies that are maximally effective and minimally toxic. This platform differs from existing methods that use unrepresentative models, such as tumor cell lines, by instead testing drugs on metastatic lung tissue samples grown outside the body that more accurately represent a common breast cancer metastatic site. Further, this platform is distinct because it uses a new type of measurement (i.e., single-cell genomics) that can determine how every individual cell type in the metastatic site responds to each drug, unlike existing methods that use less information-rich measurements. To demonstrate the potential of this technology, I will use it to find drugs that can block an immune response recently found to be linked with breast cancer spreading to the lungs.

Second, I will establish the first mouse model to study secondary metastasis, focusing on how breast cancer lung metastases spread to the bone. While many existing mouse models mimic human breast cancer by spreading to multiple sites, these models are not useful for specifically studying secondary metastasis because it is impossible to disentangle whether tumor cells in a specific metastasis were seeded from the primary tumor or an existing metastasis in another part of the body. I will use a technique called 'in vivo passaging' to create a new mouse tumor model spreads in a specific order: first from the breast to the lung, and then from the lung to the bone. With this controlled model, I will identify the genes and pathways that affect how cancer spreads from the lungs to the bones but not from the breast to the lungs using CRISPR-Cas9 technology, a tool that allows scientists to precisely and programmatically delete specific genes.

Overall, my research approach is unique from traditional studies that largely focus on the processes that occur within primary tumors that help them initially spread. Given that the interaction between tumors and the immune system is crucial for cancer to spread and that the spread from one metastatic site to another significantly worsens the disease, I believe it's vital to broaden our view beyond the traditional approach. The technologies that I propose in this METAVivor Early Career Investigator Award application will enable this expansion in research focus and have the potential to inspire entirely new therapeutic avenues for stage IV metastatic breast cancer patients.