

Targeting Growth-Factor Receptor Discordant Metastatic Breast Cancer

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When breast cancer is diagnosed in the early stages of disease the 5-year survival rate of patients is upwards of 99%. However, when a diagnosis is made after metastatic progression the 5-year survival rate drastically decreases to 24%. The unfortunate truth is that current therapies do not provide a significant therapeutic benefit for treating tumors that have metastasized to vital organs. Therefore, the overall objective of this proposal is to identify and target molecules that are specifically involved in how lethal metastatic tumors grow within vital organs.

Twenty to 25% of all breast cancers will overexpress Human Epidermal Growth Factor Receptor 2 (Her2). Targeting of Her2 with antibodies (Trastuzumab, Pertuzumab), small molecules inhibitors (Lapatinib) and antibody-drug conjugates (Trastuzumab-DM1) has drastically improved the outcome of Her2+ breast cancer patients. However, with the improved specificity of these next-generation therapies comes the drawback of disease resistance. An overriding theme of resistance to Her2-targeted therapies is the loss of Her2 expression in the metastatic tumor as compared to the primary tumor. This loss or discordance in Her2 expression in the metastatic tumor occurs in approximately 24% of patients. Recently, our laboratory has made the exciting finding that the role of tumor promoters, like Her2, can be lost as breast cancer cells exit the primary tumor and move throughout the body. We have discovered that highly metastatic tumor cells can actually utilize the unique surroundings within the metastatic organ to drive their growth. This switch in growth signals may be at the heart of resistance to Her2-targeted therapies. In fact, Her2 resistance can result due to switching to any number of secondary growth stimuli. Therefore, chasing after the next growth factor pathway in attempts to treat metastatic disease may be a futile effort.

During the execution of this proposal we will attempt uncover the precise mechanisms that allow metastatic breast cancer cells to switch from Her2 to other growth pathways. By uncovering and inhibiting these mechanisms we hope to establish a means to resensitize metastatic tumors to Her2-targeted therapies. To do this we will take advantage of our recently established cell culture system that restricts the growth of nonmetastatic cells but allows for the growth of metastatic tumor cells. Using this system we will screen over a 1000 drugs for their ability to resensitize discordant and metastatic tumors to Her2-targeted therapies. With these compounds in hand, we will move forward with our clinical collaborators to develop the use of new, therapeutic protocols to overcome metastatic drug resistance. The knowledge gained by this proposal will quickly translate into Phase I clinical trials aimed at improving treatments for patients with drug-resistant and metastatic disease.