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Abstract Submission Form

Poster Title: **Whole Genome Deletion of Wave3 Inhibits Progression and Metastasis of Triple Negative Breast Cancer Tumors.**

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Location of Laboratory: **Rammelkamp Building**

Category: **Cancer Biology**

Cancer metastasis is a complex process by which cancer cells migrate through the blood and the lymphatic systems to lodge and proliferate in distant sites and organs in the body. Metastasis is the main cause of death in patients suffering from cancer, including those patients with breast cancer. Breast cancer (BC) is the most frequently diagnosed malignancy in women and is one of the leading causes of death due to the cancer's invasion, metastasis, and resistance to therapies. Among its variants, triple-negative breast cancer (TNBC) is considered the most aggressive due to its early invasive and metastatic properties with poor prognosis. WAVE3, a member of the WAVE/WASF actin cytoskeleton remodeling proteins, has been associated with the pathogenesis of several types of cancers of epithelial origin. Our previous studies have established the role of WAVE3 as a major regulator of the invasion-metastasis cascade in breast cancer by controlling several hallmarks of cancer in tumor cells. The contribution of mammary glands WAVE3 to the process of tumor progression and metastasis has, however, not been investigated. Accordingly, we generated a global genome knockout of the Wasf3 locus, including in the mammary glands using a CRISPR/Cas9-based editing strategy. Loss of WAVE3 has no deleterious effects on mammary glands development, mouse development and fertility, and lactation in mice bearing the WAVE3 deletion phenotype, as well as their progeny. However, in a syngeneic mouse model of TNBC, the loss of WAVE3 in the mammary glands inhibited tumor growth and metastasis in mice inoculated with the aggressive murine TNBC EO771 cells when implanted directly in their mammary fat pads. Injection of the same EO771 cells via the lateral tail veins, also resulted in significant inhibition of lung tumor colonization, suggesting that loss of WAVE3 in the lungs may also play a role in the lung dissemination and establishment of metastases in this organ. These results are being replicated in a second mouse syngeneic model using the more aggressive HML2-derivative clone. Mechanistically, we are investigating the effect of loss of WAVE3 in mammary glands on tumor stemness through the regulation of the cancer stem cell phenotype, in a similar manner that our published studies showed that cancer cell WAVE3 regulates this oncogenic pathway in TNBC tumors. Thus, our findings strongly suggest that WAVE3 supports BC oncogenesis in both the tumor cells and the mammary epithelial cells as well as in the secondary metastasis organs. Therefore, therapeutic strategies targeting WAVE3 in both the cancer cells and the mammary glands may be necessary for a successful inhibition of BC tumors.