High Impact Therapeutic for the Elimination of Breast Cancer Metastasis to Bone

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Despite new therapeutics and improved screening/detection methods, the survival rate for Stage IV metastatic breast cancer patients remains heartbreakingly low. Most patients with metastatic disease suffer from bone metastases where painful osteolytic lesions result from bone resorption and lead to increased morbidity and mortality. From the work proposed here, we plan to develop a novel anti-inflammatory therapeutic with a low side-effect profile that would be beneficial to patients by reducing or eliminating breast cancer bone metastasis and prolonging lives. This drug would work by inhibiting the action of a protein called oncostatin M (OSM).

OSM is an inflammatory protein important in normal wound healing and disease states such as arthritis and cancer. In breast cancer, OSM is made by cells of the immune system as well as tumor cells. When OSM binds its receptor (OSMR) on the tumor cells, it signals many events that promote a favorable microenvironment conducive to the survival of metastatic cells in the bone. For one, OSM upregulates cancer cell-secreted products that are involved in both metastatic tumor cell growth and the differentiation and activity of osteoclasts, the cells responsible for bone resorption. Second, our important published results demonstrate that OSM is critical for osteolytic bone metastasis in breast cancer. The fact that aggressively metastatic breast cancer cells both make more OSM and express more of its receptor than normal breast cells emphasizes the need for a drug targeting the OSM signal. Therefore, we hypothesize that an OSM small molecule inhibitor (OSM-SMI) can be used as a therapeutic for breast cancer metastasis to bone. Our goal for this proposal is to perform preclinical studies and identify up to three OSM small molecule inhibitors (OSM-SMIs) that reduce bone metastasis and prolong survival. Therefore, we propose two specific aims: 1) Prioritize OSM-SMI analogs developed through rational drug design; and 2) Assess the preclinical therapeutic efficacy of OSM-SMIs in a mouse model of human metastatic breast cancer.

In the first aim, we will use computer modeling to improve OSM-SMIs that have been already identified for their ability to insert between OSM and its receptor and block downstream signaling. These OSM-SMI analogs will be prioritized and synthesized. In aim 2, the fifteen most promising compounds will be assessed for in vitro efficacy and then will enter preclinical trials. These animal studies will utilize a model of human breast cancer metastasis to bone in mice with an intact immune system. Data obtained from this proposal will be used to obtain NIH R01 funding.

Our long-term goal is to develop an FDA-approved drug for the treatment of OSM-regulated bone metastasis that will decrease the mortality associated with Stage IV breast cancer. Individuals who have had their primary tumor surgically removed and whose tumor cells express high levels of OSM and/or OSMR would be ideal candidates for this anti-OSM therapy. Because OSM drives inflammation, blocking OSM could also reduce inflammatory symptoms of the disease, as well as improve other inflammatory conditions including arthritis, gingivitis, and inflammatory bowel disease (IBD). Potential risks would be those associated with a reduced inflammatory response, such as slower than normal wound healing. With the conclusion of this work, we will have identified up to three compounds targeted against the OSM/OSM receptor axis that should offer new therapeutic options for metastatic breast cancer. As almost 80% of all women with metastatic breast cancer have metastasis to bone, a novel therapeutic

with a low side-effect profile would be beneficial for patients by reducing or eliminating breast cancer bone metastases and prolonging lives.