Public Abstract

Breast cancer patients with bone metastases suffer from life-threatening hypercalcemia, pathologic fractures, spinal cord compression, excruciating pain, limited mobility and eventually death. Bone metastases are not a rare event, occurring in approximately 70% of patients with advanced breast cancer. Current treatments include anti bone-resorbing drugs such as denosumab that have not consistently improved progression free or overall survival. To be more effective, combination therapy will be necessary. However, denosumab has been linked to increased risk of serious infections and combining it with immunotherapy drugs is problematic. Also, because it is a biological agent (monoclonal antibody), it is expensive. Denosumab blocks the function of an important cell surface receptor known as RANK that is critical for stimulating the formation of bone degrading cells. RANK receptor has several intracellular motifs that activate different cell signaling pathways leading to various cell functions including stimulating immune cell development. We recently performed a high-throughput small molecule screen to identify compounds that interact with specific motifs in RANK to block pathways involved in the formation of bone degrading cells while sparing the pathways necessary for immune cell development. ***Our ultimate goal*** is to develop more effective and safer small molecule drugs that block specific RANK motifs for treating established bone metastases and has the potential to significantly improve current therapeutic targeting strategies. The objectives of this METAvivor Research Award proposal are to use pre-clinical animal models to evaluate the safety and efficacy of two lead compounds to treat established breast cancer bone metastases and to design, synthesize, and characterize 25-30 new analogs of the lead compounds with improved drug-like properties. Successful and timely development of effective and safe anti-RANK small molecule drugs will have a profound impact on current breast cancer patients with bone metastasis. First, the drugs will not affect the ability of RANK to activate signaling pathways known to regulate immune cell development and are unlikely to exert any effects on the immune system making them safer than denosumab in treating breast cancer bone metastasis. Second, due to the expected better safety profile for these drugs, they have the potential to achieve higher efficacy in reducing the debilitating bone related issues in breast cancer patients with bone metastasis compared to denosumab. Third, since these drugs are unlikely to affect the immune system, they have the potential to significantly improve progression free or overall survival of breast cancer patients with bone metastasis. Due to the same reason, they also have the potential to be used in combination with existing or emerging immunotherapy drugs to increase the likelihood of permanently eradicating breast cancer bone metastasis. Fourth, these drugs will be significantly cheaper than denosumab because manufacturing costs of small molecules are lower than biological agents. This will reduce the financial burden on patients and their families. Finally, as small molecules, they will permit oral administration, which is a preferred method for delivery. Positive outcomes from the studies in this proposal will form the basis of a larger grant application for development of these compounds into clinically useful drugs.