



**Susan G. Komen**

**Research Grants – Fiscal Year 2015**

This research grant was approved for FY2015 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

**Targeting breast to bone metastases via bone seeking metalloproteinase inhibitors**

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**Lead Organization:** H. Lee Moffitt Cancer Center & Research Institute

**Grant Mechanism:** PDF Basic and Translational

**Grant ID:** PDF15332812

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**Public Abstract:**

In 2014, the American Cancer Society predicts that approximately 40,000 women will succumb to breast cancer. The primary cause of death is due to metastasis, that is the spreading of cancer cells from the breast to other part of the body. Studies have shown that the skeleton is one of the most prominent sites of metastasis for breast cancer. In bone, metastatic breast cancers induce extensive bone destruction by manipulating normal bone building cells known as osteoblasts and bone destroying cells known as osteoclasts. Excessive bone destruction causes a great deal of pain to women with bone metastasis and can lead to bone fracture. This in turn greatly impacts the patient's quality of life. Despite medical advances, the treatments available to women with bone metastases remain limited and geared toward pain management rather than actually curing the lesions. By understanding the factors through which metastatic breast cancer cells interact with the normal cells of the bone, we can develop new therapies to prevent that interaction. The Lynch Lab has demonstrated that an enzyme, matrix metalloproteinase-2 (MMP-2), is expressed by both breast cancer cells and bone cells. Importantly, we have found that MMP-2 is a key regulator of cell-cell communication and in allowing the cancer cells to grow in the bone environment. We therefore think that targeted inhibition of MMP-2 would be a valuable therapy in preventing the growth of metastatic breast cancer in bone.

To specifically target MMP-2, I have built a novel inhibitor that specifically prevents MMP-2 enzymatic activity. I have built this inhibitor on a bisphosphonate foundation. Bisphosphonates are chemicals that



can specifically stick to areas of bone undergoing remodeling and they prevent bone destruction by killing the bone destroying osteoclasts. Therefore, by integrating MMP-2 inhibition into bisphosphonate structures, I have generated a powerful inhibitor of MMP-2 that can specifically target breast cancer cells growing in bone. This is important because the MMP inhibitor targets the skeleton where the breast cancer is growing (thus reducing whole body side effects). In my preliminary studies using a mouse model of bone metastasis, I have shown that bone seeking MMP-2 inhibitors (BMMPs) are very effective in preventing the growth of breast cancer in bone. In my Susan G. Komen fellowship, I propose to expand upon these preliminary findings in this grant application. Importantly however, I believe that these studies will be critical for the development of the BMMPs and their rapid translation to the clinic for the treatment of women with bone metastatic breast cancer. I expect that at the end of the study period I will have built up a body of data that will allow me to generate very competitive future grant applications so that I can transition to an independent investigator dedicated to finding cures for breast cancer.

