# Sensitizing Bone Metastasis to Chemotherapy and Radiotherapy by Targeting Jagged1-Mediated Tumor-Stromal Interactions

Dr. Yibin Kang
Warner-Lambert/Parke-Davis Professor of Molecular Biology
Princeton University

More than 70% Stage IV breast cancer patients suffer from severe complications of bone metastasis. Although bisphosphonates and denosumab, combined with traditional cancer treatments such as chemotherapy and radiation, can alleviate some of the symptoms associated with bone metastasis, none of these treatments improve the overall survival of breast cancer patients with bone metastasis. One major reason is the existence of a tumor-supporting environment in the bone, which consists of various "stromal" cells normally residing in the tissue. Therefore, effective therapeutic targeting this tumor microenvironment may offer new ways to effectively eliminate bone metastasis and improve the survival of advanced stage breast cancer patients.

The bone-building osteoblasts and and bone-degrading osteoclasts are two major stromal cell types in the bone. The functional importance of osteoclasts has been studied for decades, leading to the discovery of anti-osteolytic agents such as bisphosphonate and denosumab for the treatment of bone metastasis. Recent studies have started to reveal the functional contribution of osteoblast cells that may form a nurturing "niche" for the survival and expansion of metastatic breast cancer in bone. In our recent preliminary studies, we discovered that Jagged1-expressing osteoblasts support the survival of tumor cells in the bone microenvironment. In our proposed study, we will further investigate whether osteoblast-derived Jagged1 promotes bone colonization and therapy resistance. More importantly, we already developed a functional blocking antibody (15D11) against Jagged1, which is ready to be tested in mouse models and human patients (as the antibody is already humanized). We will first test the therapeutic effect of 15D11 in pre-clinical mouse models, either alone or in combination with chemotherapy, radiotherapy or osteoclast-targeting treatments. Positive data from the proposed experiments in mouse models will provide strong supporting rationale for launching clinical trials in human breast cancer patients.

To systematically understand the functions of osteoblast cells in breast cancer bone metastasis, we also propose to use genomic wide gene expression profiling of tumor cells and osteoblast cells upon chemotherapy. We expect to identify additional signaling molecules/pathways that cause therapy resistance. These candidate genes/pathways will be further studied in the future to discover new candidates for therapeutic targeting. Results from the proposed studies have great potential to have an immediate impact (within 5 years) on developing a new and effective treatment for bone metastasis, and subsequently reducing the mortality from metastatic breast cancer.