

Public/Lay Abstract:

Breast cancer is the most commonly diagnosed cancer among U.S. women. Over 43,000 women in the U.S. are projected to die in 2021 from breast cancer. Over the course of lifetime, 1 in every 8 women (almost about 13%) will develop invasive breast cancer. When cancer cells are grown outside the breast in other organs, this situation is known as metastatic breast cancer. Metastatic breast cancer will cause most of those deaths. Bone protects our body's vital organs and acts as a very fertile soil for the housing of this metastatic breast cancer. Bone metastasis drastically reduced the survival of breast cancer patients. Complications of bone metastasis are numerous, such as severe pain, risk of fracture, paralysis, poor quality of life. Bone is full of life; the task of replacement of old bone with the new one is fulfilled by bone-forming (osteoblasts) and bone-resorbing (osteoclasts) cells (like renovation of our house). Metastatic breast cancer cells camouflage these cells and take over the normal bone regeneration process to attract more cancer cells at the bone sites. Currently, no effective therapy is available. The available treatments options such as bisphosphonate, the antibody against RANKL (denosumab), and radiopharmaceuticals can only slow down the metastasis process but cannot treat. This shortfall is due to the lack of proper understanding of the disease and limited distribution of druggable targets (either cancer cells or bone cells). Simultaneous targeting of both arms is a better approach for advanced patients with bone metastasis.

We have first time found that a novel receptor known as GFRAL and RET are highly expressed in cancer cells that go to the bone. These high GFRAL and RET-containing cancer cells were forced to secrete GDF15 from bone-forming osteoblasts. This GDF15 binds to the GFRAL and helps cancer cells to grow more in the bone. We have also found that targeting RET with a recently known drug (Selpercatinib/LOXO-292) decreases bone resorption and kills the cancer cells, suggesting that targeting the GFRAL/RET is a new effective method to treat bone metastasis.

To address these questions, we propose the following specific aims:

Aim 1. Functional and clinical significance of the GDF15/GFRAL/RET axis in breast cancer bone metastasis. *This part of the proposal will first establish the importance of the GFRAL/RET axis in the preclinical syngeneic mouse model of BC bone metastasis. We will validate the importance of GFRAL and RET as a biomarker via analyzing the expression in metastatic breast cancer patients.*

Aim 2. Dual targeting of GFRAL/RET axis in breast cancer bone metastasis: *To determine the therapeutic benefits of combination therapy using FDA-approved highly potent RET inhibitor along with known osteoporosis drug in the pre-clinical syngeneic mouse model of bone metastasis.*

The current application addresses the main challenges with existing treatment. It will **(1)** define the role of the new therapeutic target of lethal metastatic breast cancer to reduce death and **(2)** develop treatments that improve outcomes for patients with lethal metastatic breast cancer.

This proposal has direct clinical applications. Since the FDA recently granted accelerated approval of the proposed drug (Selpercatinib) to treat metastatic lung and thyroid cancer patients. The side effect and tolerance of Selpercatinib is well known through the several clinical trials. If the preclinical study of the proposed drug will become successful, this drug can directly go for a clinical trial for bone metastatic breast cancer patients. Another proposed drug, an antibody against RANKL protein (denosumab or Prolia), is already in the market to treat osteoporosis and cancer patients. Since both drugs exist in the clinic, the proposed combination therapy can immediately be employed to bone metastatic patients without Phase 1 clinical trials. The successful completion of this proposal will be highly beneficial in the clinical setting lacking the adverse associated risk factors. The outcome of this highly innovative and clinically relevant proposal will be advantageous for millions of bone metastatic patients.