Background information: ***Bone metastases*** are present in the majority of women with advanced stage IV breast cancer; indeed, bone is the most common site of first relapse. Tumors that express estrogen receptors (ER+ breast cancers), for unknown reasons, are much more likely to form bone metastases and are also notable for their tendency to form bone metastases even decades after the initial diagnosis. ***How is this possible?*** It appears that breast cancer cells can spread to bone very early, even in early stage disease at the time of diagnosis, where they remain dormant (and therefore resistant to hormone or chemotherapy) until poorly understood signals trigger their proliferative growth into clinically evident bone metastases. Having dormant tumor cells in bone increases a woman's risk for developing metastatic breast cancer. Importantly, in women diagnosed with stage IV breast cancer, the presence of dormant tumor cells in bone remains an independent risk factor for disease-related death. All of these facts suggests that therapies aimed at eliminating dormant breast cancer cells in bone could improve survival in women with stage IV breast cancer. ***How can this be achieved?*** Recent research has revealed that breast cancer cells can become "tethered" to bone cells via binding of a receptor on their cell surface (the CXC receptor 4 [CXCR4]) to its preferred docking site ("ligand") on bone cells. This tethering mechanism not only binds the cells to bone, but it also helps to maintain their quiescence. A study in animals has recently shown that breaking this tether, using a CXCR4 disruptor that is already FDA approved for another purpose, can cause the release of breast cancer cells from bone. **But is this a good thing?** Potentially, yes, since breaking the CXCR4 linkages can lead to a special form of cell death in ER+ breast cancer cells ("anoikis*").* Breaking this tether may also restore the cells' responsiveness to chemotherapy. However, the usefulness of "CXCR4 untethering" in improving survival and limiting bone metastases in stage IV breast cancer has not yet been tested because pre-clinical models of breast cancer bone metastatic dormancy are not available.

Clinical significance of the proposed research: The overarching goal of this research is to determine whether treatments that disrupt CXCR4 tethering (and are already FDA approved for use in other settings) can alter the number and proliferative state of dormant breast cancer cells in bone and thus improve survival in women with stage IV breast cancer.

Specific research approach and goals: In the studies proposed here, we will test the effect of FDA-approved drugs that are known to disrupt CXCR4 tethering on "dormant cell load" in a unique animal model of ER+ breast cancer bone metastatic dormancy that our laboratory has just developed, as well as assessing their effects on clinical outcomes (bone metastasis formation).

Unique features of this research and expected findings: These studies are only possible due to our laboratory's recent development of animal models of ER+ bone metastases, which are also CXCR4+ and can be manipulated to include a distinct period of dormancy. This is a unique and exciting development, not only because dormancy models have been lacking, but also because most commonly used breast cancer bone metastasis models, unlike the situation in women, do *not* express ER. We anticipate that clipping the CXCR4 link that binds quiescent ER+ cells to bone through the use of ***CXCR4 inhibitors*** will limit bone metastases progression in these models by hastening the demise of dormant cells either by directly triggering their death, or by making them more responsive to chemotherapeutic agents to be tested ***in combination*** (specifically, ***CDK4/6 inhibitors [e.g. Verzenio, Ibrance, Kisqali]*** that are currently used to treat ER+ stage IV breast cancer).

Clinical Benefits: The therapeutic effectiveness of targeting CXCR4 in bone metastatic breast cancer has not been previously been tested; however, CXCR4 disrupting agents are already clinically available, making these studies high risk, high reward with a potential for rapid clinical translation. In addition, while CDK4/6 inhibitors have known benefits in ER+ stage IV breast cancer, no pre-clinical studies have ever examined their specific effects on bone metastases, raising the possibility that information gained here may also enhance our understanding, and therefore use, of CDK4/6 inhibitors for targeting ER+ bone metastases.