we believe that blocking the function of CSF1R acting through PU.1 in MPs and OCs may be a way to prevent or treat bone metastasis. A new class of drugs has been developed that reduces the function of certain genes by blocking the activity of a family of proteins called BET proteins. We have found that PU.1 and BET proteins bind and act together to promote the function of MPs and OCs. We then showed that if you treat MPs and OCs with BET inhibitors, PU.1 can’t function properly in controlling MPs and OCs. BET inhibitors are effective against BrCa cells grown in the laboratory. However, no studies have evaluated if drugs that block BET proteins can prevent the spread and growth of BrCa cells in other parts of the body. More specifically, no one has evaluated the effects of BET inhibitors on BrCa bone metastasis. CSF1R inhibitors only affect cells within the body that are descendants of the myeloid cell lineage, such as MPs and OCs. Therefore, they do not have any off-target effects on other cell types. To make BET inhibitors be able to specifically target MPs and OCs, in this proposal we are going to place this drug in small capsules called nanoparticles. These nanoparticles will be coated with a protein that binds to proteins on the surface of MPs and OCs. The MPs and OCs will consume these nanoparticles, the nanoparticle capsule will be broken down, and the BET inhibitor will then negatively impact MP and OC function.

More specifically, no one has evaluated the effects of BET inhibitors on BrCa bone metastasis. CSF1R inhibitors only affect cells within the body that are descendants of the myeloid cell lineage, such as MPs and OCs. Therefore, they do not have any off-target effects on other cell types. To make BET inhibitors be able to specifically target MPs and OCs, in this proposal we are going to place this drug in small capsules called nanoparticles. These nanoparticles will be coated with a protein that binds to proteins on the surface of MPs and OCs. The MPs and OCs will consume these nanoparticles, the nanoparticle capsule will be broken down, and the BET inhibitor will then negatively impact MP and OC function. The objective or goal of this study is to investigate the effects of CSF1R inhibitors and nanoparticle-encapsulated BET inhibitors, alone and in combination, on breast cancer bone metastasis. We will determine this by measuring tumor growth over time and then use molecular biology techniques to determine their direct effects on gene expression in tumor-associated MPs and OCs and their indirect effects on neighboring BrCa cells. This will be done in two clinically-relevant mouse models of bone metastasis – one using cells from the triple negative BrCa subtype and another using cells from the estrogen receptor-positive BrCa subtype. We believe that inhibiting CSF1R and BETs will reduce 1) tumor burden and 2) genes that drive cancer, metastasis growth, and tumor-associated MP and OC function. We also believe combination therapy with a CSF1R inhibitor and a nanoparticle-encapsulated BET inhibitor will be the most effective.

Research Impact: This proposal will use mouse models of BrCa bone metastasis to determine if our therapeutic approach using CSF1R inhibitors and nanoparticle-encapsulated BET inhibitors could help prevent the growth and resultant bone loss associated with BrCa bone metastasis. This would significantly impact a patient’s quality of life, by reducing bone pain and fracture, and prolonging survival in BrCa bone metastasis patients. If bone metastasis growth is reduced by either blocking 1) CSF1R acting through PU.1 or 2) PU.1 and BET proteins acting together, to promote MP and OC activity, it would be a major discovery in, and contribution towards, treating bone metastasis. By targeting tumor-associated MPs, our treatment approach may also inhibit primary BrCas and metastasis to, and growth in, other organs. This may also be useful for bone metastasis from other cancers and primary bone tumors. Positive results using our clinically-relevant mouse models of BrCa bone metastasis would be an interim outcome, but would definitely support clinical evaluation of our treatment strategy 1) for the management of bone metastasis, and potentially, other metastatic sites and 2) combined with other therapies. Identification of changes in individual genes and larger gene sets will identify patients with similar genetic changes before treatment that may benefit from our treatment strategy. Since the presence of a bone metastasis and its associated bone loss limits the efficacy of many chemotherapeutic agents, and increased OC activity drives this process, current therapies may now have greater efficacy when combined with our treatment strategy to limit bone destruction. Findings could have a major impact on treatment, quality of life, and survival of bone metastasis patients.