

Lay Abstract

Bone is the most common site of first metastasis for breast cancer patients, but further metastasis to soft tissues (lung, liver, brain) is the primary cause of breast cancer patient death. Unfortunately, metastatic tumors need to grow to a size of more than 10 million tumor cells before these tumors are detectable with current clinical imaging methods (like MRI or PET/CT). This clinical imaging limitation means that patients with existing bone metastases can not be monitored carefully enough, which increases the risk of their disease progressing further to soft tissue metastasis which is often more lethal. It is important to improve the sensitivity of monitoring of bone metastases, so that patients can be treated earlier and the most effective therapies chosen to reduce the risk of further metastatic spread.

Liquid biopsies are cancer detection tests that can be conducted using blood samples. The isolation of either circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) from patient blood samples has been shown to be a predictor of metastasis and patient survival. In addition, these liquid biopsies provide a method to measure the amount of cancer throughout a patient's body, even when metastatic tumors are difficult or impossible to reach with more traditional tissue biopsies.

This project will use a preclinical model to establish metastatic tumors in the bones of mice and then test two independent liquid biopsy methods based on ctDNA and CTCs to more accurately monitor the growth of these tumors. The sensitivity of liquid biopsy methods will be compared to whole-body bioluminescence imaging and MRI detection of metastatic tumor growth (Aim 1). Live CTCs will also be isolated from blood samples and analyzed for metastatic phenotypes on microfluidic cell tethering chips (TetherChip) patented in the Martin lab (Aim 2). Five FDA-approved chemotherapies for triple-negative breast cancer (Doxorubicin, Carboplatin, Capecitabine, Vinorelbine, Paclitaxel) will be tested to identify the drug that most strongly reduces metastatic phenotypes. In Aim 3, the most effective drug will be used together with the 4 different detection methods (ctDNA, CTCs, bioluminescence, MRI) to determine whether introducing therapy at the earliest possible point can more effectively reduce the ability of bone metastases to spread to soft tissues.

Completion of this study will define how liquid biopsy detection can improve the treatment of existing bone metastases. In addition, methods to use live CTCs to identify the most effective therapy for individual patients will be advanced. Since the project will use 5 FDA-approved standard of care drugs, the results can be more rapidly translated to clinical studies. By improving both the detection of bone metastatic tumor growth and the optimization of drug treatments to reduce metastatic phenotypes, this project will help identify better ways to reduce the risk of existing bone metastases spreading to soft tissues to improve survival outcomes for breast cancer patients.