

Public/Lay Abstract

Avoiding the possibility of cancer recurrence at metastatic sites is the driving force behind many therapeutic strategies and is constantly on the minds of cancer patients. In breast cancer, the majority of breast cancers make estrogen receptor (ER+), which informs clinicians that the cancer cells grow in response to the hormone estrogen. Despite successes seen in treating patients with ER+ breast tumors with estrogen- and estrogen receptor-based hormone therapies, approximately 33% of these treated patients will develop recurrent metastatic tumors after hormone therapy. These recurrent tumors primarily metastasize to bone and either do not respond to or recur after current treatment options. The bone architecture gives cancer cells in bone an easy entryway to other tissues, ultimately increasing their spread throughout the body. To reduce patient mortality with stage IV breast cancer, we must determine why bone metastasis occurs and determine how to stop and reverse it.

My laboratory's ultimate research goal is to identify therapeutic strategies for patients with metastatic breast cancer. Identifying what causes this resistance and therapeutically targeting this process will identify effective second line therapies for recurrent tumors and will significantly improve patient outcomes. Towards this goal, we identified the gene ZNF217 as prognostic of reduced outcome in breast cancer patients. ER+ breast tumors of patients who develop the worst outcomes produce high amounts of ZNF217. Our data suggest that ZNF217 contributes to ER function and stage IV breast cancer. Importantly, we recently discovered that ZNF217, growth factors, and their signaling pathways together change expression of certain genes that ZNF217 and ER control, ultimately causing cancer cell resistance to endocrine therapies. These genes are known regulators of metabolism. Therefore, through our proposed preclinical research program, we will investigate if ZNF217 causes endocrine therapy resistance by reprogramming metabolism in the metastatic bone niche using both cell culture and *in vivo* experiments. Our approach will uncover previously unknown pathways that cause endocrine therapy resistance in tumors metastasized to bone. We also will determine if deficiency in one of these genes is sufficient to overcome endocrine therapy resistance of breast cancer metastasized to bone, which would provide a rationale for using inhibitors as therapeutics. Since patients with metastatic tumors overexpressing ZNF217 represent most breast cancer patients with poor prognosis, this project may significantly impact the design of future clinical trials with these therapeutics and ultimately improve patient outcome.

Future studies derived from the proposed study will develop ZNF217 and its target genes as biomarkers of bone metastasis and endocrine therapy resistance and, significantly, will identify personalized treatments to target these genes in breast cancer patients with ER+ tumors metastasized to bone who have exhausted treatment options. Since patients with tumors metastasized to bone currently have few treatment options, successful completion of this project will have significant translational potential and will bring hope for patients living with stage IV metastatic breast cancer.