

LAY ABSTRACT

Breast cancer remains the second most common cancer, affecting women. A predominant site of breast cancer metastasis is bone. Invasion of tumor cells to the bone stops the patient's immune system from fighting against the tumor because of inhibitory signals produced by tumor cells. These signals act as double-edged sword by not only affecting patients' immune cells from fighting the cancer, but also feeding into aggressive bone destruction by activating bone-destroying cells called osteoclasts. More recently, we identified that this vicious cycle also benefits metastatic breast cancer from an immunosuppressive cell type that additionally functions as osteoclast producers. This group of cells function as a double-edged sword by promoting immunosuppression and bone damage thereby paving way for the tumor cells to proliferate and evade immune surveillance. Patients with metastatic breast cancer typically develop severe bone disease, which predominantly affects the skull, ribs, vertebrae, pelvis, and proximal long bones. Characterized by the presence of bone pain and pathologic fractures, osteolytic bone disease represents a major cause of morbidity in patients with metastatic breast cancer.

Current treatment options for breast cancer patients with bone metastasis is quite ineffective mainly because of acquired resistance to chemotherapy. This has triggered a renewed search for new therapy alternatives. A major limitation for the failure to cure breast cancer with bone pathology so far is current therapies focus on one particular aspect of tumor growth in order to decrease tumor burden. Such approaches largely ignore the effects of dangerous signals from not only tumor cells, but also other cells in the tumor microenvironment, which enable resistance to chemotherapy, but promotes secondary pathologies described above. Thus, it is critical for new therapies to simultaneously address immunosuppression and underlying bone damage.

Towards developing a unique dual-axis therapy targeting bone morbidity and immune suppression, the proposed study will determine the potential of a combination genetically engineered regenerative cell therapy and immunotherapy approaches, respectively. Both cell therapy and immunotherapy platforms proposed in this application have been FDA approved in different disease contexts. Hence, using them for unique combination therapies proposed in this application will enable faster translation to the clinic. Using a highly relevant preclinical mouse model of metastatic breast cancer that recapitulates the disease pathology in human patients, outcomes of this translational study is expected to benefit patients in the near future.