

Modeling Therapeutic Strategies for Breast Cancer Metastasis to Bone

Christopher H. Contag, PhD

Professor, Departments of Pediatrics, Microbiology & Immunology, and Radiology

Bonnie L. King, PhD

Instructor, Department of Pediatrics

Princeton University

Metastasis is the process through which cancer cells depart the primary tumor to colonize and grow in distant organs. Metastatic spread is responsible for most breast cancer deaths. Bone is the most common site of breast cancer metastasis and the presence of small numbers of cancer cells in the bone marrow at the time of diagnosis is linked to the later development of metastatic disease. Small numbers of breast cancer cells appear to travel to the bone marrow during the earliest stages of breast cancer development. In some cases the cells remain inactive and never grow, whereas in other cases they grow aggressively, leading to the destruction of the mineralized bone tissues of the skeleton. During this stage, known as Stage IV metastatic breast cancer, breast cancer cells produce factors that lead to the break down of bone. This in turn results in the release of substances that stimulate more breast cancer cell growth. This positive feedback loop, which fuels both breast cancer cell growth and bone destruction is called the “vicious cycle of bone metastasis.” While current treatments help reduce the symptoms of this process, there are currently no curative therapies for this stage of bone metastasis.

Breast cancer metastasis is usually studied in mice, but these experiments take many weeks or months, and human breast cells do not always grow well in the mouse skeleton. In addition, it is difficult to study specific breast cancer cell responses within the bone tissues of a mouse. We have developed a novel culture system in which human breast cancer cells are grown in small human bone tissue fragments.

Previously we have developed methods to study the early steps leading up to bone metastasis, including methods to measure how breast cancer cells migrate into and colonize human bone tissues. In this grant application we propose to study the “vicious cycle of bone metastasis” in our human bone culture model. We will: 1) Develop methods to measure how much bone is being broken down, 2) Demonstrate that we can reverse bone destruction in our model with bone targeting drugs currently used to treat bone loss in osteoporosis and metastatic cancer, and 3) Measure the effects of these drugs on breast cancer cells growing in human bone tissues. These experiments will show that we can measure the cell and tissue responses that occur during late stage bone metastasis, and modify them with current drugs. This will prove that our model can be used to test new, more effective approaches to prevent and treat breast cancer metastasis to bone.