

Bankhead-Coley Cancer Research Program

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2007 Program
New Investigator (3-year project)

Project Title: Parvovirus B19-Based Vectors for Gene Therapy of Breast Cancer Bone Metastases

Project Summary: Breast cancer patients do not die from regional disease but from systemic metastases in vital organs. Bone is the most common site of breast cancer metastasis. Bone micrometastases have been detected in bone marrow aspirates in 34 percent of patients with no known distant disease (TNM stage M0) and 74 percent of patients with overt metastatic breast cancer (M1). Adjuvant chemotherapy is ineffective in eliminating single dormant micrometastatic breast cancer cells. The recently introduced anti-HER2 (human epidermal growth factor receptor 2) antibody therapy has been shown to be effective in targeting HER2-positive cancer cells in vivo and prolonging—but not saving—patients' lives, warranting the search for more effective therapies to target bone metastatic breast cancer cells. HER2 gene amplification and HER2 protein over-expression occur in 5-20 percent of invasive breast cancers and are associated with a poor prognosis, but are rarely observed outside breast cancer. A high incidence of HER2 expression has been observed on micrometastatic breast cancer cells. In this research grant, we will develop a breast cancer bone metastasis-targeting system that takes advantage of the high HER2 expression on metastatic breast cancer cells and exploits the bone marrow tropism of the human parvovirus B19 combined with a novel viral co-receptor function-inducing feature to specifically target metastatic breast cancer cells in the human bone/bone marrow compartment. Parvovirus B19 is a small, single-stranded DNA virus of human origin that has evolved a remarkable tropism in that it enters the human body through the upper respiratory route and 'travels' to the bone marrow space where it is able to replicate exclusively in erythroid progenitor cells. The virus uses the blood group P antigen (globoside) as receptor to bind to the cell surface. We have identified the adhesion receptor $\alpha 5\beta 1$ integrin, which is present on every nucleated cell, as a co-receptor for parvovirus B19 internalization and demonstrated that $\alpha 5\beta 1$ integrin is recruited as viral co-receptor only after its functional activation. $\beta 1$ integrins are expressed on metastatic breast cancer cells; however, their functional activation through complex formation with the urokinase plasminogen activator receptor (uPAR) has been found to be disturbed in metastatic breast cancer cells leading to a non-proliferative or dormant state of these cells. The breast cancer metastases-targeting parvovirus B19 vectors combine three features to ensure specificity for bone metastatic breast cancer cells: (1) enrichment in the bone marrow compartment based on the natural bone marrow tropism of parvovirus B19; (2) replacement of the erythroid-specific P antigen binding site by a HER2 binding epitope inserted into the viral capsid; (3) activation of the $\beta 1$ integrin viral co-receptor for virus entry into target cells, and induction of re-entry of targeted cells into the cell cycle to enhance their susceptibility to the parvovirus B19 vector-mediated expression of a cell death-inducing gene product.