

Public Abstract

Objectives and Rationale

Cancer is an abnormal growth of cells which proliferate in an uncontrolled manner and form a mass called a primary tumor. In some advanced stages of the disease, cancer will spread to other organs than the one primarily damaged and form secondary tumors called metastases. While progress has been made to treat primary breast cancer, long-term survival has not improved greatly in the past 30 years. Most breast cancer mortalities are not caused by the primary tumor, but rather, the formation of metastases. When cancer cells escape the breast and colonize other organs such as bone marrow or lungs, they fall asleep. In other terms, they stop growing, and therefore, they are not eliminated by chemotherapy treatments that are designed to target growing cells. These sleeping cells are called dormant cells and can remain in this state for decades before growing back and forming deadly metastasis. Little is known about mechanisms of cancer dormancy. We used a mouse model where we injected cancer cells in the primary organ and let the primary tumor grow and spread to distant organs before performing surgery to remove the primary tumor. At the time of surgery, mice present a primary tumor mass and disseminated dormant cells in their lungs. After surgery, we treated the mice for 4 weeks with an FDA approved drug called Fosinopril from the category of ACE inhibitors in an attempt to prolong dormancy of these cells with the underlying idea to prolong mice survival. Four weeks after treatment, we inspected the tumor site and lungs to count dormant cells and discovered that the treatment had completely cleared the cancer cells.

In this study, we want to investigate the mechanism of action of this treatment on dormant cells and evaluate its potential effect on breast cancer dormancy and metastasis formation. We will divide our research into two axes. First, we will demonstrate the effect of ACE inhibitors on disseminated breast cancer cells *in vivo* using mouse models and microscopy to track cell death *in vivo*. We will determine if the treatment prolongs the survival of treated mice in comparison to untreated mice. Then, we will investigate how the treatment affects the dormant cells and clears them to unveil the underlying mechanism of action.

Clinical applications and impact of the research to benefit stage IV metastatic breast cancer patients

ACE inhibitors were discovered in the early 80's and are commonly used as treatment for hypertension and heart failure. ACE inhibitors are a well-tolerated class of drugs and produce only a few side effects. As there are about 80 clinical trials using ACE inhibitors on healthy patients on clinicaltrials.gov, we believe that a clinical trial in breast cancer could be facilitated as there is already evidence of low toxicity of these drugs. The design of our experiments will highlight if these drugs can prolong the survival of patients with already metastasized breast cancer as well as an effect on earlier stages of breast cancer. If successful, this treatment could drastically improve the survival of breast cancer patients by neutralizing disseminated cancer cells and reduce the occurrence of deadly metastasis.

Dr. Di Martino's Career Goals in Breast Cancer

The work from this research proposal, the guidance, and mentorship of Dr. Bravo-Cordero, an expert in advanced imaging techniques and mouse models of breast cancer and the research environment at the Icahn School of Medicine at Mount Sinai will help me to develop into an independent breast cancer researcher. I am a woman in science and I hope my research will benefit women's health. Beyond a professional choice, investigating breast cancer progression mechanisms is a personal choice and I am strongly committed to achieve my goals to unveil each step of the metastasis development process in order to participate in the discovery of new long-term therapeutic solutions for breast cancer relapse.