Susan G. Komen for the Cure
Research Grants – Fiscal Year 2011

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Specific detection of metastases of breast cancer and imaging response to IGF-1R drugs by MRI

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Awarded: $599,975.00
Grant Mechanism: Investigator Initiated Research
Research Focus: Early Detection

Public Abstract:
Many patients with breast cancer have local and distant recurrence or metastases of their primary breast cancers, and this often happens, while they are on other therapies. One reason is that we do not yet have reliable means of predicting who will metastasize or the ability to detect micro metastatic disease early in the progression of breast cancer. A second reason for this is due to development of resistance to the therapy they are on. To decrease breast cancer mortality from metastatic disease we need to identify new targets, develop drugs against them and test their ability to inhibit metastases. A protein found on the surface of cancer cells called type I insulin-like growth factor receptor (IGF-1R) stimulates growth and the ability of tumor cells to migrate and move. Several drugs have been developed against it and are being tested in clinical trials. We have also shown that these drugs are remarkably effective in blocking metastases of estrogen receptor negative and Her2 negative breast cancer cells in preclinical animal models. Preclinical studies have shown also that blocking IGF-1R action with drugs is an attractive target in triple negative tumors, which lack estrogen receptor, progesterone receptor and Her2. These tumors cannot be treated with anti-estrogens or trastuzumab (an antibody against Her2) and have limited options for therapy besides chemotherapy. These triple negative tumor more aggressive and patients often develop metastases. Thus, IGF-1R drugs and inhibitors could be an attractive and effective treatment option for patients with triple negative metastatic disease. However, a problem with all targeted therapies is how to identify which patients would most benefit from it and develop surrogate biomarkers of response to the therapy. While clinical trials with IGF-1R drugs are on going we still have not yet identified reliable biomarkers that would allow selection of patients or monitoring response to these drugs. Our hypothesis is that a novel magnetic resonance imaging (MRI) technique called SWIFT combined with magnetic nanoparticles that will be targeted to breast cancer cells growing at a metastatic site such as the lung will allow earlier detection of micro metastatic disease, the ability to identify if breast cancer cells that have metastasized express IGF-1R and monitoring of response to IGF-1R targeted therapy. We will test our hypothesis by developing these targeted particles conjugated to an antibody against IGF-1 R that will target them to the breast cancers. Using two different models of metastasis in mice we will explore the ability of SWIFT to specifically detect such metastases. We will also measure metastatic tumor burden with a conventional MR technique and verify the detection using histological staining of sections of lungs from mice with metastases. Finally, we will test if this technology can also be used to monitor response to two different drugs against IGF-1R that we know block metastases in the models here. This research will have immense impact on patients with metastatic breast cancer. Improved MRI methods that lead to earlier detection of metastases, new drugs that can inhibit metastases and the ability to monitor anti-

metastatic response early will improve outcomes for breast cancer patients. An additional advantage of SWIFT is that it can acquire 3-dimensional (3D) images in scan times similar to, and in some cases, faster than conventional 3D MRI sequences. Further, development of non-invasive approaches that can measure expression of specific cancer cell surface proteins at sites of metastases of breast cancer (such as lungs and bone) will allow selection of patients whose metastatic can be treated with a drug against that protein. Thus, in the case of the proposed work, the ability to non-invasively measure if a patient's metastatic tumor expresses IGF-1R will allow for selection of patients who should be treated with IGF-1R drugs. An ability to predict which patient will benefit from this new class of drugs will accelerate the approval of a new class of drugs for women with triple negative metastatic breast cancer.

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