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

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GREB1: A Novel Prognostic and Therapeutic Target in Breast Cancers with Resistance to Endocrine Therapies

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Awarded: $600,000.00
Grant Mechanism: Investigator Initiated Research
Research Focus: Early Detection

Public Abstract:
Study Hypothesis: Our central hypothesis is that Gene regulated in breast cancer 1 (GREB1) protein is over-expressed in some endocrine resistant breast cancers and functions to support breast cancer cell proliferation and progression. Inhibition of GREB1 expression in these hormone refractory breast cancers (HRBC) as well as GREB1+ ER- tumor subpopulations using siRNA and GREB1-specific aptamers will result in a loss of cell proliferation, suggesting GREB1 is a potential new therapeutic target in these breast cancers. Rationale: Identification of new biomarkers that predict the therapeutic response to endocrine therapy and the development of novel therapeutic targets in HRBC are critical for the successful treatment of advanced breast cancers. GREB1 is an estrogen-regulated gene that mediates hormone-stimulated cell proliferation and is a candidate clinical marker for response to endocrine therapy. Surprisingly, we observed that GREB1 is over-expressed in some HRBC although its role in these tumors and their progression in unknown. Investigation of the role of GREB1 in breast cancers with resistance to anti-estrogen and ER signaling therapies as well as evaluation of GREB1 as a therapeutic target in endocrine-refractory breast tumors is justified. Objective and Experimental Design: The objective of this proposal is to examine the role of GREB1 protein in some HRBC and explore the potential of GREB1 as a therapeutic target in these challenging breast cancers. We will examine the incidence of GREB1 expression in HRBC cell lines and sections from primary tumor samples using a novel GREB1 antibody developed in our laboratory paired with a quantitative imaging system. To provide insight into the function of GREB1 in HRBC as well as the therapeutic potential of targeting this gene, we will employ interference RNA technology to inhibit expression of GREB1 in HRBC cell lines and evaluate changes in cancer cell behavior in culture as well as in immunodeficient mouse models. Finally, inhibitory small molecules called aptamers that have been selected to specifically inhibit GREB1 will be evaluated as a potential new therapeutic strategy targeting GREB1+ HRBC. Impact of the Proposed Research: The findings from the experiments proposed in this study will benefit a significant number of breast cancer patients whose endocrine-based therapy has failed to produce an effective and long-term response. Specifically, this study seeks to identify a novel biomarker (GREB1) over-expressed in some HRBC that may be utilized to predict response to therapy as well as target with novel therapeutic strategies in these progressive breast cancers. Furthermore, this proposal evaluates GREB1-specific DNA aptamers as potential therapeutic agents targeting the cell-proliferative function of this novel biomarker. Thus, the findings from this study will have clinical applications in both the diagnostic and therapeutic settings. The specific research aims outlined in this innovative proposal will have a direct

impact on the goal of eradicating cancer as follows: 1. Characterization of a potential new biomarker in HRBC for diagnostic and prognostic applications. In this proposal, we will measure the expression levels of GREB1 protein in HRBC cell lines and tumor samples using a novel monoclonal antibody (GREB1ab) developed in our laboratory. These initial experiments will form the basis for GREB1 as a biomarker in HRBC based upon unique expression profiles compared to sensitive breast cancers as well as advanced ER- malignancies. Therefore, utility for GREB1 as a potential prognostic marker for responsiveness to endocrine therapy would be a key finding. These results will have a direct impact on the clinical management of patients with breast cancer. 2. Identify GREB1 as a new therapeutic target in HRBC. Experiments utilizing inducible siRNA to specifically target GREB1 mRNA and reduce protein expression will provide definitive insight into the role of GREB1 in HRBC. If reduction in GREB1 expression results in inhibited cell proliferation and altered cancer cell phenotype as our preliminary data suggest, then GREB1 will be a candidate target for HRBC therapies. This would be a critical finding as there is an unmet need for new therapeutic strategies that target and possibly prevent the development of HRBC. This result would have a direct impact on eradicating HRBC as a new target would be identified to begin developing therapies based upon GREB1 inhibition. 3. Provide a new therapeutic strategy for GREB1+ HRBC. High affinity GREB1-specific aptamers will be evaluated for their ability to inhibit GREB1 function and prevent HRBC cell proliferation. If successful, this strategy will not only benefit patients with GREB1+ HRBC but will also provide a therapeutic option for patients with other types of GREB1+ breast cancers (ex: ER-/GREB1+ breast cancers). Collectively, these types of cancer cells compose a significant proportion of breast cancers over time. Therefore, this potential new therapy would have a direct impact on the treatment and eradication of breast cancer.

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