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

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Targeted therapy for micrometastatic minimal residual disease to prevent breast cancer recurrence

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

Public Abstract:
Despite treatment with surgery, radiotherapy, chemotherapy and/or hormonal therapy, many breast cancer survivors will experience recurrent disease following a period of remission. While treatments exist, recurrent breast cancer is typically an incurable disease. For many types of human cancer, residual tumor cells – referred to as minimal residual disease – remain following treatment that are not detected by conventional clinical testing. In the case of breast cancer, analyses of bone marrow samples indicates that disseminated tumor cells are present in 20-40% of primary breast cancer patients lacking any clinical or histopathological signs of metastasis. These cells have the ability to survive in a dormant state within tissues for extended periods of time. Ultimately, residual cells re-emerge from their dormant state and resume growth, leading to cancer recurrence. As such, micrometastasis, tumor dormancy, and recurrence constitute fundamental clinical manifestations of tumor progression that together are responsible for the vast majority of breast cancer deaths. Despite the unrivaled clinical importance of these aspects of breast cancer progression, however, the mechanisms underlying them are largely unknown. Residual neoplastic cells constitute the cellular reservoir from which tumor recurrences invariably arise and thereby constitute a major obstacle to the successful treatment of human cancers. Accordingly, understanding the biology of residual tumor cells and elucidating the molecular pathways and cellular processes that contribute to the survival of micrometastatic cells, tumor dormancy and tumor recurrence is a critical priority in breast cancer research. These issues are the focus of this application. A particular difficulty in studying micrometastasis, dormancy, and recurrence in breast cancer has been the challenge of identifying and isolating residual neoplastic cells in patients, and the lack of animal models that recapitulate these key features of breast cancer progression. To address this critical gap, we have developed and validated a series of doxycycline-inducible transgenic mouse models for HER2/neu, MYC and Wnt1-overexpressing breast cancers that display key features of human breast cancer progression, including micrometastasis. In this application, these models will be used to investigate the pathways that contribute to the dormancy and recurrence of micrometastatic tumor cells. We have used a genome-wide expression screen to identify a lipid kinase that we hypothesize functionally contributes to breast cancer recurrence. Cerk is a regulatory molecule that promotes cell survival by altering intracellular ceramide levels and potentiating the NF-?B signaling pathway. We have found that Cerk is markedly up-regulated in three different mouse models for breast cancer recurrence induced by oncogenes important in human breast cancer. Consistent with a role for Cerk up-regulation in human breast cancer recurrence, high Cerk levels predict an increased likelihood of relapse in women with breast cancer. Together, these findings suggest that Cerk may

functionally contribute to breast cancer recurrence. This proposal will use a novel series of mouse models for breast cancer recurrence to determine the functional contribution of Cerk to mammary tumor recurrence, and the potential role played by NF-?B signaling in this process. Specifically, we will test the hypotheses that up-regulation of Cerk is sufficient to promote mammary tumor recurrence, that Cerk down-regulation is required for mammary tumor recurrence, and that the ability of Cerk up-regulation to promote breast cancer recurrence is mediated by activation of the NF-?B pathway. Reducing breast cancer morbidity and mortality will ultimately require a substantially improved understanding of micrometastasis, tumor dormancy, and recurrence than currently exists. In the past, achieving this objective has been hampered by a lack of animal models that faithfully recapitulate these fundamental steps in tumor progression, and by the lack of sufficiently powerful methods to analyze these steps in vivo. This application will directly address these critical biological problems. By probing the functional role of Cerk in the biology of residual tumor cells and recurrence, these efforts should advance the therapeutic goals of preventing breast cancer recurrence. There are currently more than 10 million women worldwide with breast cancer. Historically, cancer pharmacology has focused on identifying drug targets involved in primary tumorigenesis. However, in recent years it has become increasingly clear that the molecular pathways underlying breast cancer recurrence may be distinct from those of primary tumorigenesis. These pathways present a wealth of potential new drug targets that could hold the key to the development of more effective treatments for this stage of disease. We believe that Cerk represents such a target. As such, these studies have the potential to enable the development of more effective therapeutic approaches that could dramatically alter the treatment options available to millions of breast cancer survivors.

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