Susan G. Komen

Research Grants – Fiscal Year 2015

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Elucidating ER transcriptional network associated with endocrine resistance

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Lead Organization: Dana-Farber Cancer Institute

Grant Mechanism: SAB Grants **Grant ID:** SAB1000008

Public Abstract:

Over 200,000 women in the US will be diagnosed with breast cancer this year, and close to 40,000 will die of it. Most (75%) breast cancers in developed countries are estrogen receptor positive and endocrine treatments are the mainstay therapy for breast cancer. The most common endocrine treatments include either targeting the ER for inhibition using the antagonist tamoxifen, or reducing ER activation by suppressing endogenous estrogen production using aromatase inhibitors in postmenopausal women. These endocrine treatments in the adjuvant setting reduce the risk of disease recurrence by up to 60%. However, women treated with adjuvant endocrine treatment still have a 1-2 % annual risk of recurrence, and in the metastatic setting, such endocrine treatments achieve response rates of only 20%-40%, underscoring the need for new effective therapies. Unfortunately, nearly all women with advanced ER+ breast cancer will eventually progress through all endocrine treatments and chemotherapy options, and ultimately die of their disease. Such loss of responsiveness to endocrine therapies represents acquired resistance, and determining its mechanisms is a major challenge in the field and the goal of the proposed research.

Clinical and pre-clinical data both suggest that acquired resistance is not associated with ER mutations or loss of ER expression and targeting the estrogen receptor and associated factors remains a key therapeutic approach capable of improving outcomes and reducing mortality. Therefore, in the proposed research we will investigate the key changes that occur in the ER transcriptional network in acquired endocrine resistance by studying both breast cancer cell lines as well as primary metastatic breast cancer cells. We will also develop new assays, which will facilitate the study of human metastatic tissue specimens both in culture system and xenograft models, which has been limited because of the paucity of such tissue specimens. Finally, these assays will be employed to study novel treatment targets in acquired endocrine resistance that will arise from our studies of the ER transcriptional network.