Susan G. Komen

Research Grants – Fiscal Year 2015

This research grant was approved for FY2015 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

Hippo pathway activation in chemo-sensitive and -insensitive breast cancer

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Grant Mechanism: PDF Basic and Translational **Grant ID:** PDF15331014

Public Abstract:

Breast cancers are generally divided into subtypes based on the presence, or lack, of receptors found within the tumor: estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2). The most successful treatments for breast cancer are hormonal and targeted therapies for these receptors. Unfortunately, none of these receptors are found in women with the triple negative breast cancer (TNBC) subtype and patients are treated with nonspecific chemotherapies. While 20-30% of TNBC patients respond to chemotherapy treatment, TNBC patients with residual disease post-therapy have low overall survival rates. Even patients who do respond to chemotherapy treatment are likely to have recurrence and metastasis years after the initial treatment. It is therefore necessary to develop novel and improved therapies for patients with TNBC. We propose to interrogate the difference between Hippo pathway activation in chemo-sensitive and –insensitive TNBC cell lines and patient samples using our novel MIB/MS (multiplexed inhibitor beads and mass spectrometry) technology. Kinases themselves are highly tractable molecular targets that have been shown to be disregulated in many cancers, and cancer cells have been shown to respond to targeted kinase inhibitor therapies. The Hippo pathway is an evolutionary conserved regulator of tissue growth and cell fate that has been shown to be disregulated in many cancers, including breast cancer. Therefore, determining kinome activation states within the Hippo pathway in response to chemotherapy in TNBC should enable understanding of why some tumors respond to chemotherapy and others remain insensitive. Our studies will define kinase dynamics within the Hippo pathway that can be used to target specific kinases

with small molecule inhibitors to enhance the sensitivity of chemo-resistant tumors to combination therapies. Using these methods, we hope to find better treatment options for patients with TNBC.