Susan G. Komen

Research Grants – Fiscal Year 2015

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Overcoming or preventing therapeutic resistance to HER2 targeted therapies

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Lead Organization: Duke University School of Medicine

Grant Mechanism: Komen Scholars **Grant ID:** SAC110033

Public Abstract:

Although there have been significant advancements in the treatment of inherently aggressive HER2+ breast cancers, the development of resistance to therapy has limited the clinical efficacy of HER2 targeted therapies, particularly in women with advanced stage breast cancer. If we cannot cure metastatic breast cancer we should strive to convert it to a manageable chronic disease similar to high blood pressure or diabetes. Resistance to HER2 targeted therapies does not appear to be caused by a single mechanism. Treatment strategies to overcome or prevent the onset of resistance to HER2 targeted therapies will require tailoring therapy based on a tumor profile predictive for the development of resistance via a specific mechanism(s). This requires identification of the mechanisms involved in the development of therapeutic resistance. In Aim 1, we will study the role of a variant form of HER2, which we refer to as p85HER2 in promoting resistance to HER2 targeted therapies used in the clinic. Relatively little is currently known about the function of p85 in breast cancer cells, information that could lead to improved treatments for women with advanced p85-expressing breast cancers. The best cure for breast cancer is to prevent it. While studying p85 and related variant forms of HER2, we discovered that a protein that protects cells against the damaging effects of noxious environmental stimuli (some of which has been linked to breast cancer risk) and importantly, in response to expression of cancer causing genes (oncogenes) promotes the earliest steps in converting a normal cell to a cancerous cell. This protective protein is called Hsp72. Our preliminary findings show that a novel Hsp72 inhibitor, discovered and developed by our lab and collaborators at Duke, can block the conversion of a

normal cell to a breast cancer cell. In Aim 2, we seek to demonstrate that Hsp72 can prevent/delay the formation of tumors caused by expression of a cancer causing gene in non-malignant breast cells, or in response to chronic exposure to cadmium, a breast cancer causing heavy metal environmental contaminant. We will also determine whether Hsp72 inhibition prevents tumor formation in a mouse model of human breast cancer. We also seek to establish a relationship between the level of Hsp72 expression in clinical breast samples and risk of developing breast cancer in a high risk population. In addition, we will determine whether Hsp72 levels in blood lymphocytes correlate with blood levels of heavy metals from lower socioeconomic women living in an industrialized area. The work proposed here can be rapidly translated into the clinic for further validation of Hsp72 expression in clinical samples from high risk individuals, and ultimately test an Hsp72 inhibitor as a novel mechanism-based preventative strategy in high risk individuals who have been identified based on Hsp72 levels measured in their blood cells or from breast tissue/aspirates.