Susan G. Komen
Research Grants – Fiscal Year 2014

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Mitochondrial phospho-proteomic and metabolic analyses of HER2+ breast cancer

Investigator(s): Taro Hitosugi, Ph.D.
Lead Organization: Mayo Clinic
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Public Abstract:
The mutational activation of growth-promoting oncogenes drives cancer development and growth. In the case of breast cancer, the HER2 receptor tyrosine kinase is a key driver of the disease. Two HER2-targeted therapies, lapatinib and traztusamab, have activity in the disease, but patients often relapse. To improve the efficacy of such therapies, we propose to study the interaction between two common cancer hallmarks: HER2 signaling and HER2-dependent alterations in tumor metabolism that promote tumor growth by favoring the synthesis of proteins, nucleotides, and lipids. From our preliminary data from mitochondrial phospho-proteomic analysis of HER2+ breast cancer cells, we found that carnitine palmitoyltransferase 1A (CPT1A), a mitochondrial protein that facilitates fatty acid degradation, is tyrosine phosphorylated and activated by HER2 signaling. We thus propose to assess how this phosphorylation impacts breast cancer metabolism and growth. To address this, in addition to in vitro culture cell breast cancer model, we will use in vivo (HER2+ PDX) breast cancer models that accurately reflect the in vivo setting. Importantly, we will also assess how disabling CPT1A (using shRNAs and etomoxir, a small molecule inhibitor) affects tumor growth alone and in combination with lapatinib. Because etomoxir has been used in human clinical trials for metabolic diseases, our findings may uncover a novel therapeutic strategy that can be rapidly deployed in the clinic. We have contributed substantively to current understanding of the direct link between tyrosine kinase signaling and cancer metabolism and demonstrated that targeting a metabolic enzyme has therapeutic benefit in mouse xenografts. As such, we are in a unique position to push this field forward through the proposed studies that 1) will yield insights into the basic mechanisms by which HER2 programs tumor metabolism by regulating CPT1A and 2) may help develop novel therapeutic approach targeting CPT1A that can be combined with the already-effective HER2 therapies in breast cancer.