Susan G. Komen
Research Grants – Fiscal Year 2014

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Microenvironmental and epigenomic mechanisms of therapeutic resistance

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Lead Organization: Oregon Health & Science University
Grant Mechanism: KS **Grant ID:** SAC110012

Public Abstract:
Amplification of the HER2 oncogene is a molecular aberration present in about 20% of breast cancers. These patients typically respond well to therapeutic agents targeted to the HER2 protein such as trastuzumab, lapatinib, pertuzumab and ado-trastuzumab emtansine. Unfortunately, the responses to these agents can be short, especially in metastatic disease. Clearly, work is urgently needed to understand and counter the mechanisms by which resistance arises. We now know that changes in the cancer genome and/or signals from the microenvironments in which the cells live signals can render the cells resistant to these treatments. This project focuses on understanding and countering the genomic and microenvironmental causes of resistance. Specifically, we will test the hypotheses that (a) subpopulations within individual HER2 amplified tumors undergo changes in differentiation status/pathway usage caused by genomic aberrations and/or as a result of signals from the microenvironments in which they grow and that these changes alter responses to HER2 targeted therapies and (b) that therapeutic responses can be made more robust by treating with combinations of agents that are specifically designed to manage the response heterogeneity found in individual tumors. We will assess the impact of differentiation status on therapeutic response to pathwaytargeted therapies by staining cells with markers that reveal differentiations status and analyze these using a quantitative automated microscope system. We will measure the impacts on differentiation status and therapeutic response of thousands of different combinations of proteins and growth factor from the microenvironments to which breast tumors metastasize. We will use information from these studies to design drug combinations that will counter the effects of genomic aberrations and microenvironmental signals that give rise to resistance to HER2 targeted therapies. We anticipate that translation of these combinatorial treatment strategies to the clinic will increase overall survival duration substantially – especially for patients with metastatic HER2 positive disease.