Susan G. Komen
Research Grants – Fiscal Year 2014

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Elucidating Novel Mechanisms of Resistance to HER2-Directed Therapy

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Lead Organization: Dana-Farber Cancer Institute
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Public Abstract:
Approximately 20% of breast cancers are characterized by abnormally high levels of a cell surface signaling protein called HER2. These HER2-positive cancers typically have an aggressive behavior and poor outcome when treated with conventional therapies. However, the introduction of drugs specifically targeted against HER2, including trastuzumab (Herceptin), lapatinib, pertuzumab, and trastuzumab emtansine (T-DM1) has significantly improved outcomes for patients with HER2+ breast cancer. However, despite these new therapies, resistance to HER2-directed therapies, particularly in the metastatic setting, is an important clinical problem. Because of the development of resistance, metastatic HER2+ breast cancer remains largely incurable. It is thus critical that we identify the molecular mechanisms that cause resistance to these agents so that approaches to overcome these mechanisms can be developed. While a number of potential resistance mechanisms have been proposed based largely on laboratory based studies, none of these have been validated in metastatic tumor tissue from patients. We hypothesize, that based on work by our laboratory and that of our collaborators, that there are at least several potential mechanisms through which tumors can become resistant to HER2-targeted therapy. One mechanism is amplification of the Epidermal Growth Factor Receptor gene, a cell signaling protein similar to HER2. Amplification of this gene leads to overexpression of EGFR protein, which can allow the cancer cell to bypass the need for HER2. A second potential mechanism is through mutations in key cell cycle regulatory proteins that allow the cancer cell to replicate in unrestricted manner. A third mechanism may arise because cancers are heterogeneous, even in HER2+ cancers some cells within the cancer may have little or no expression of HER2, making these cells resistant to HER2-targeted agents. To validate these potential mechanisms in human cancers, and begin to develop approaches to overcome them, we propose the following Aims. 1) To confirm that EGFR amplification exists in metastatic tumor biopsies from patients with HER2+ metastatic disease and that its presence is associated with resistance to trastuzumab. 2) To use next generation sequencing to comprehensively identify the mutations that exist in a unique collection of metastatic tumor biopsies from patients with HER2+ metastatic disease and then evaluate the function of these mutations. 3) To conduct a preoperative trial of T-DM1 in patients with HER2+ cancers and determine if cancers that do have a subpopulation of HER2 negative cells are less likely to completely respond to T-DM1. Through these Aims, we will improve our understanding of the actual molecular mechanisms of resistance that occur in patients with trastuzumab-resistant cancers, leading to approaches to overcome these mechanisms.