Susan G. Komen
Research Grants – Fiscal Year 2014

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Determining the role of somatic mutations in SERM-resistant breast cancers

Investigator(s): Sean Fanning, Ph.D.; Geoffrey Greene, Ph.D. (Mentor)
Lead Organization: University of Chicago
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Public Abstract:
Breast cancer will affect 12.5% of women in the United States in their lifetime. Responses to the female hormone estrogen lead to tumor growth in approximately 70% of breast cancer cases. Selective estrogen receptor modulators (SERMs), such as tamoxifen and raloxifene, belong to a family of drugs which blocks the actions of estrogen and arrests the growth of estrogen-dependent breast cancers. While the combination of SERMs with other drugs has dramatically reduced number of deaths from estrogen-dependent breast cancers, approximately 11% of patients still die within five years of diagnosis (American Cancer Society, 2010). Breast tumors that are initially SERM-sensitive often become insensitive to these drugs as the disease progresses. Unfortunately, these patients are subsequently transferred to cytotoxic chemotherapies, resulting in a dramatic decrease in quality of life, before ultimately succumbing to the disease. We, along with our collaborators at the Memorial Sloan-Kettering Cancer Center have recently identified a possible mechanism which explains why some breast cancers become insensitive to SERM/SERD/AI treatment. SERMs work by competing with estrogen for its binding site within proteins called estrogen receptors. We identified mutations near the SERM binding site of the estrogen receptor in patients who have previously undergone SERM/SERD/AI treatment (average of 5 years). These mutations generate a receptor that is active even in the absence of estrogen and less sensitive to existing SERM/SERD/AI therapies, thereby allowing these metastatic breast cancers to progress even when ER-targeted therapies are administered. We believe that a comprehensive understanding of exactly how these mutations impact the function of the estrogen receptor and allow it to resist SERM inhibition will lead to new, more potent SERMs. To achieve this goal, we have established collaborations with several institutions and investigators. We believe that an integrative approach will yield the best results within the lifetime of this fellowship and beyond. These results will be directly used to guide clinicians treating SERM resistant metastatic breast tumors as well as lay the groundwork for the rapid development of new drugs that will ultimately lead to disease remission for a large population of breast cancer patients.