**Susan G. Komen**
**Research Grants – Fiscal Year 2014**

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## Characterization and targeted therapy of hormone-refractory breast cancer

**Investigator(s):** Sarat Chandarlapaty, M.D., Ph.D.
**Lead Organization:** Memorial Sloan-Kettering Cancer Center
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**Public Abstract:**
The estrogen receptor is the master regulator of tumor growth for the majority of breast cancers where its expression is detected. In essence, the hormone estrogen serves as a signal to tell breast derived cancer cells to grow and divide. Drugs targeted against estrogen signaling have had a greater benefit for patients than almost any other class of cancer drug in history. Despite this success, failure of antiestrogen therapy represents a common clinical dilemma and is a major contributor to both the morbidity and mortality from breast cancer. The basis for cancer resistance to antiestrogen therapy is not well understood. As a result, patients are moved away from therapy specifically targeted against the estrogen receptor and onto more generic and toxic chemotherapies that are rarely effective for a long time. Our hypothesis is that activation of other, non-hormonal signals is the reason for resistance in many patients. There are two ways in which we have observed these other growth signals to emerge. First, we have found that mutations arise in the DNA of the tumor cell. These mutations promote other growth signals. One such growth signal is from genes that encode for a specific growth pathway known as the PI3K pathway. But we have reasons to think that there are several other such mutations. To find these mutations, we propose to collect tumors after patients have developed resistance and determine if there are alterations that arose while the patient was receiving hormonal therapy. This will guide us towards newer therapies directed against such mutations. The second way in which new growth signals might emerge is through rapid adaptations in proteins that occur right after the drug is given. In this case, the tumor evolved (before a drug was ever given) to not be entirely dependent upon estrogen signaling. When the tumor is deprived of estrogen, it simply shifts to rely on the other growth signal. In order to identify such adaptive changes, we need to study the tumor immediately after a drug is given. So we propose to do this using both cell lines in the lab as well as patient tumor samples when patients just start out on hormonal therapy. Finally, there are already good drugs against the PI3K pathway in clinical trial testing now. Unfortunately, they are showing some signs of side effects like rash in many patients. This is limiting how well these drugs can be used. We propose to study giving the drug as a pulse rather than continuously as this may be more effective and have far fewer side effects – but the details on how best to do this need to be established. Overall, this proposal seeks to use laboratory models of cancer and small tumor biopsies from patients to determine the molecular basis for hormone resistance and then identify and optimize combinations of drugs targeting the "other signal" with hormone therapy. The final goal is to prolong lives by identifying better treatment strategies that evade drug resistance.