



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

This research grant was approved by Komen's national board of directors for FY2014 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

Mechanisms of Endocrine Resistance in Estrogen Receptor Positive Breast Cancer

Investigator(s): Matthew Ellis, Ph.D.

Lead Organization: Baylor College of Medicine

Grant Mechanism: KS

Grant ID: SAC130059

Public Abstract:

ER+ breast cancer, also called luminal-type breast cancer, is stimulated by the presence of estrogen and standard treatment is to reduce estrogen in the body for long periods of time using a class of drugs called aromatase inhibitors. When this "endocrine" treatment is given prior to surgery, it is called "neoadjuvant" endocrine therapy. Although most patients with estrogen receptor positive, HER2-negative (ER+/HER2-) breast cancer have excellent outcome, a significant number experience recurrence, often after a long period of being cancer-free. The mechanisms that cause these late recurrences are not fully understood, but likely to be a result of genetic changes (mutations) within the tumor cells that provide an advantage for the cell to grow and survive, sometimes even in the presence of drugs that were previously effective. Our objective is to learn how to more effectively kill luminal breast cancer so that disseminated cells do not persist to later mutate and take the patient's life. Our long-term objective is to sequence as many breast cancers treated in neoadjuvant endocrine therapy clinical trials as possible so that the genetic changes in the tumor cells can be interpreted in the context of the marked variability in response to estrogen-lowering treatments. Sequencing of patient's tumor DNA and comparing it to their normal cell DNA allows us to observe genetic alterations that are specific to the cancer cells in an unbiased way. We can repeat this analysis in each case over time to observe changes in the tumor genome that are associated with resistance. It is also important that we sequence the RNA from the tumors in parallel with the DNA analysis. The RNA sequence provides information about which of the many mutant genes detected by DNA sequencing are active in the tumor cell and therefore which are really important for driving the growth and drug resistance or sensitivity. We therefore plan to examine the DNA and RNA from luminal breast cancers treated in two Phase 2 neoadjuvant endocrine therapy clinical trials testing experimental drugs that are being combined with an aromatase inhibitor to increase tumor regression before surgery. We have chosen these studies because they are testing aromatase inhibitors in combination with a second drug that targets a critically important pathway for breast cancer development. From large scale sequencing studies, we know that approximately one-third of patients with ER+ breast cancer have a mutation in the PIK3CA gene. In one of the studies we are therefore testing MK2206, a PIK3CA pathway inhibitor. In a second parallel study we are testing a drug called palbociclib in patients without a mutation in PIK3CA. This drug has shown promising results for patients with advanced disease as it inhibits a critical growth stimulation pathway involving enzymes called CDK4/6, which regulate a cell growth "gate keeper" called RB.

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