



**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.

**Endocrine therapy resistance of ER+ breast cancer caused by ESR1 gene aberrations**

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**Lead Organization:** Washington University in St.Louis

**Grant Mechanism:** CCR Basic and Translational

**Grant ID:** CCR14300139

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**Public Abstract:**

Breast cancer is a deadly disease affecting millions of women worldwide. The most common subtype (luminal cancer) expresses the estrogen receptor protein (ER) which is the key driver of cancer cell growth. One unique feature of ER that has been successfully exploited in clinics is that its activity depends on the binding of estrogen to the hormone-binding domain. This is the mechanistic basis for the wide spectrum of endocrine therapies aiming to either block estrogen production (aromatase inhibitors) or to directly compete for estrogen binding (antiestrogens e.g. tamoxifen and fulvestrant). Nevertheless, 50% of patients receiving endocrine therapies develop resistance, and are left with few treatment options except chemotherapies that are usually less specific and more detrimental. Mechanisms causing endocrine therapy resistance are complex but are important to understand in order to develop more effective therapies. This grant focuses on understanding a novel mechanism (mutations in ER gene itself) that has been under-appreciated in the past but is now suggested to be present in 10% or more of advanced luminal breast cancer patients. Our data suggest that direct alterations in the ER gene occur in several different ways, and each may require structurally tailored targeting approach. They include: point mutations in the hormone-binding region of ER making it active without estrogen, truncation of ER gene removing its hormone-binding region but maintaining its hormone-independent activity, and ER gene amplification producing excess wild type ER protein to compensate for the low estrogen levels. Of particular importance, all three types of ER gene alterations appear to result from long-term hormone deprivation, explaining why they are more prevalently detected in the advanced-stage post-treatment samples as opposed to pre-treatment primary samples. The major goal of this grant is to identify new therapeutic options for hormone resistance caused by these ER gene aberrations based on our existing knowledge of their molecular structures and using our unique preclinical mouse models derived from patients naturally harboring these aberrant ER genes. Specifically, we will test the hypothesis that ER point mutations and amplifications, though resistant to aromatase inhibitors, can still be effectively targeted by standard antiestrogens (e.g. tamoxifen and fulvestrant) and/or alternative antiestrogens with higher potencies. In contrast, truncated ER genes (which lack the hormone-binding domain) cannot be targeted by antiestrogens and demand alternative therapies indirectly regulating its activity. This inevitably requires better understanding of their biological properties which we will also investigate in this grant. Together, experiments in this grant, if successful, will generate data that can be quickly incorporated into clinical trials that will help many thousands of breast cancer patients harboring these ER gene aberrations.