



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150440

Project Title:
Effects of hormonal therapy on subclonal evolution of breast tumors with
ESR1 mutations

Award Mechanism:
Individual Investigator

Principal Investigator:
Fuqua, Suzanne A

Entity:
Baylor College of Medicine

Lay Summary:

The overall goals of this project are determine the role of estrogen receptor gene (ESR1) mutations in the progression and recurrence of hormone-resistant breast cancers. We originally discovered these mutations, but the paucity of reports in tumors led many to assume that ESR1 mutations were not there. It is now accepted that these mutations are indeed present in tumors with numerous recent publications validating our original discoveries. Since estrogen withdrawal with aromatase inhibitors (AIs) is the most effective endocrine therapy, and are preferred for the treatment of metastatic disease, tumors with ESR1 mutations may be resistant to estrogen withdrawal. Thus there is an urgent need to define the exact role of the mutations in hormone treatment of ER-positive breast cancer patients and to identify alternative therapeutic strategies. We have found that the mutations are dominant over normal wild-type receptor, and may confer resistance to all hormonal therapies, except the new antiestrogen fulvestrant. We will definitively determine the role of these mutations in treatment resistance and metastasis by conducting sensitive sequencing for them in a large number of clinical samples with valuable clinical information and follow-up. We will also explore their role in resistance using novel metastatic cell line models we have developed, and we will identify new ways to treat resistance with biologic targets. Our proposal could impact approximately 135,000 women diagnosed per year with ER-positive breast cancer. This proposal could also have a significant clinical impact because ESR1 mutations represent a frequent clinical target in ER-positive breast cancer. The use of ESR1 mutation status to guide the treatment of breast cancer is a new paradigm which can become a reality, and the PI is considered a pioneer in this clinical effort.