Susan G. Komen
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Targeting metabolic pathways to circumvent endocrine resistance in breast cancer

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Public Abstract:
Breast cancer is the second leading cause of cancer death in women. Growth of the majority of breast tumor depends on a female hormone, estrogen. In mammary cancer cells, estrogen binds to its receptor protein named estrogen receptor (ER) and activates it. Activated ER then binds to DNA and stimulates synthesis of genes which promotes tumor growth. Common modes of treatment of ER-positive breast cancer patients is to block the circulating levels of female hormone estrogen by aromatase inhibitors, or compete with estrogen for binding to its receptor with tamoxifen. Thus ER activation is hindered and breast cancer growth is blocked. Unfortunately, half of ER-positive breast cancer patients either fail to respond to these therapies or become resistant to long-term therapy. Indeed, the risk of an ER-positive breast cancer recurrence extends for decades after treatment and recurrent ER-positive breast cancer has a high mortality rate. Thus understanding the biological-mechanisms associated with drug resistance will provide us the opportunity to develop novel therapeutics. Our hypothesis is that resistance develops due to activation of 'unknown' escape pathways which provide tumor cells necessary resources for survival. We have identified a powerful metabolic enzyme named PFKFB4 which is one of the prime regulators of glucose-derived energy-generation process in breast tumor cells. In addition, we also found that PFKFB4 is responsible for activating an ER-binding protein steroid receptor coactivator-3 (SRC-3) which is frequently activated in tamoxifen-resistant breast cancer patients. In this proposal we wish to study the role of PFKFB4-driven-SRC-3 activity in the process of energy generation and synthesis of biomolecules required for tumor cell growth. Finally, using a mouse model and tamoxifen-resistant breast tumor cell line we will test the importance of this pathway to develop tamoxifen resistant breast tumors. Our current understanding about the mechanisms of drug resistance in breast cancer patients is limited. There have been no new effective endocrine agents introduced into the clinic in more than a decade and it is clear that new strategies to block this complex system are needed to prevent both early and late recurrences of breast cancer. Cutting off the predominant energy generation process in recurrent breast tumors will substantially halt the tumor growth, and eventually reduce the mortality rate and cure the disease. Currently investigations are ongoing to discover specific inhibitors targeting PFKFB4 for treatment of other types of cancer, and this study will provide a strong rationale for a Phase I trial in endocrine-resistance breast cancer patients.