Susan G. Komen
Research Grants – Fiscal Year 2014

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Biological consequences of novel PTEN pathway signaling defects in breast cancer

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Grant Mechanism: KS **Grant ID:** SAC110028

Public Abstract:
There are two major goals that the grant "Biological Consequences of Novel PTEN Signaling Defects in Breast Cancer" is trying to achieve. The first goal is to make a mouse model that reflects the most frequent genetic change that is seen in breast cancer in a setting of estrogen dependence. The second goal is to profile stem cell markers in mouse models of breast cancer to identify if any of the common cancer models are related to normal mouse mammary stem cells.
Goal 1. The most common form of breast cancer is Estrogen Receptor (ER) positive, which usually indicates that the cancer requires estrogen for its growth. The PIK3CA gene is mutated in approximately 40% of ER positive breast cancers, which represents the most common mutation in this form of the disease. PIK3CA encodes the catalytic subunit of the enzyme PI3-kinase alpha (PI3K) and is an oncogene. Tumor mutations of PIK3CA lead to increased PI3K catalytic activity. We have generated mice that have "knock-in" mutations that mimic mutations found in human breast cancer. We have engineered the mice so that expression of the mutant oncogene occurs only in the mammary gland and these mice develop indolent cancers at a low frequency. To better reflect the human condition, we will be testing the notion that estrogen supplementation will be able to stimulate the development of ER positive breast cancer in the setting of PIK3CA mutation in the mouse. We hope that this study will lead to a mouse model that accurately reflects a common subset of human breast cancer. Such a model would be a useful tool for improving therapy for ER positive disease.
Goal 2. Recent findings have identified that the human and mouse mammary glands contain stem cells that are able to regenerate a mammary gland when these cells are implanted into a recipient mouse. Analysis of these stem cell populations has revealed that they share similarities with human and mouse tumor cells. We hope to assess the enrichment of normal mouse stem cell populations in different genetically defined mouse models of breast cancer that have activated the PI3K pathway in different ways.