



**Susan G. Komen**

**Research Grants – Fiscal Year 2015**

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**Targeting PI3K and CDK4/6 in breast cancer: integrative biomarkers of response**

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**Lead Organization:** Vall d'Hebron Institute of Oncology

**Grant Mechanism:** CCR Basic and Translational

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**Public Abstract:**

The PI3K/Akt/mTOR cell signalling pathway is inappropriately activated in 70% of breast cancer patients. Initially there was great excitement over the discovery of new drugs that can inhibit the PI3K pathway, which would have been able to treat this large group of patients. However, clinical results have not met these high expectations. We need to be able to predict which patients will benefit the most from PI3K-blockade, and understand why. In addition to the PI3K pathway, the cell cycle machinery, which are the molecules that drive cells to divide, also seems to be continuously “ON” in some tumors when it should normally be tightly controlled. Both the PI3K and the cell cycle pathways play central roles in cancer progression, by regulating processes such as cell growth and survival. Thus, new drugs that block these pathways have recently been developed, and there are currently numerous phase I/II/III clinical trials testing several different drugs and their combinations with chemotherapy or other so-called targeted therapies. However, predictive biomarkers other than mutation of PI3K for PI3K inhibitors or ER expression for CDK4/6 inhibitors, have not been identified. These biomarkers are insufficient to select the population of patients most likely to respond.

Our proposal seeks to identify predictive biomarkers of response to single agent and to combined PI3K and CDK4/6 inhibitors in breast cancer to improve their impact. To do this, we will use state-of-the-art patient-derived tumor xenografts (PDX) and patient-derived tumor cells (PDC). Our first aim is to



develop a three-dimensional ex vivo assay that recapitulates the in vivo response of our PDX. This will allow us to perform pharmacogenomic screening of a "Discovery set" of PDC samples (N=40). Further, we will identify genetic factors in the tumor (mutations, copy-number alterations or epigenetic events) that correlate with the tumors responding to or being resistant to the PI3K and/or CDK4/6 inhibitors. Finally, we will develop an algorithm that will correlate the presence of these biomarkers with the likelihood that the tumor will respond to these drugs. To test the clinical validity of our findings, we will query a "Test set" comprising at least one hundred PDX, PDCs and tumor biopsies from patients being treated with these drugs in the clinic.

We anticipate that this proposal will identify patients that can be successfully treated with PI3K and/or CDK4/6 inhibitors, and, equally importantly, those who cannot. Subsequently, we foresee better stratification of patients into personalized treatments, improving treatment efficacy and reducing patient morbidity and mortality.

