



**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.

Optimizing Akt/mTOR targeted breast cancer therapy

Investigator(s): Funda Meric-Bernstam, M.D., Ph.D.

Lead Organization: UT M.D. Anderson Cancer Center

Grant Mechanism: KS

Grant ID: SAC100006

Public Abstract:

Rationale and hypothesis: Greater understanding of the fundamental biology of breast cancer has identified cellular pathways that are altered in cancer cells that can be potentially targeted for therapy, which may be more effective than current treatments. Akt/mammalian target of rapamycin (mTOR) pathway is one of these cellular pathways and can be activated in breast cancer. mTOR is a central regulator of breast cancer cell growth and proliferation. Rapamycin is a well-studied agent that binds and inhibits mTOR. Rapamycin analogs (rapalogs) are in Phase III clinical trials in combination therapy. However, single agent rapalogs have induced objective responses in only a subgroup of breast cancer patients. Therefore, there is a pressing need to find markers which can be used to identify the patients who are going to benefit from or show resistance to treatment with rapalogs. In our preliminary work, we identified several genes whose expression was not previously known to be regulated by rapamycin. These markers may take part in rapamycin-mediated growth inhibition and may have potential as novel markers of response. In addition to rapalogs, there are new generation mTOR and Akt kinase inhibitors. Although they inhibit the same pathway, we found significant differences in their downstream effects and sensitivity to these inhibitors. The central hypothesis of this proposal is that Akt/mTOR modulates cell growth and survival in breast cancer, and that breast cancers with differing molecular subtypes may be differentially sensitive to rapamycin, Akt and mTOR kinase inhibitors. Research aims and design: We will (1) characterize predictors and downstream effectors of rapamycin response. We will use a cell line panel, including cell lines with intrinsic and acquired rapamycin resistance, identify and validate markers that respond to treatment with inhibitors. Then we will determine their effect on cell growth and rapamycin sensitivity. (2) In our previous work, we identified a 28-gene panel that is regulated by rapamycin treatment in three breast cancer cell lines. We will identify the role of these genes on cell growth. (3) To extend our preliminary work, we will use the new generation mTOR and Akt kinase inhibitors and test their downstream effect under various conditions, such as in cell lines with different genetic background. We will determine the effect of these conditions on treatment by looking at inhibition of cell growth. We will also test combination treatments with other pathway inhibitors or chemotherapeutic agents that are currently being used to treat breast cancer. Expected outcomes: We expect to be able to identify patients in advance who would benefit more from mTOR pathway inhibitors, and determine the best combinatorial approaches to treat patients likely to be resistant to single agent rapalog therapy. This is very timely research since rapalogs are now in the clinic, and mTOR and PI3K/mTOR inhibitors are entering clinical trials. Thus the findings of this project can be quickly translated into clinical care.