**Susan G. Komen**

**Research Grants – Fiscal Year 2015**

This research grant was approved for FY2015 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

## NLK inhibitor as new targeted agent for endocrine resistant breast cancers

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**Grant Mechanism:** PDF Basic and Translational **Grant ID:** PDF15333523

**Public Abstract:**

About half of the breast cancer patients treated with endocrine therapy will relapse eventually. There is no effective treatment to overcome endocrine resistance due to the lack of mechanistic insights and viable targets. Our lab has identified a new therapeutic target for endocrine resistant breast cancer called nemo-like kinase (NLK). NLK is a serine-threonine kinase overexpressed in ~30% of breast tumors. Prognostic analyses suggest that NLK overexpression significantly and specifically correlates with worse outcome in tamoxifen-treated patients.

My previous studies show that NLK may promote tamoxifen-resistance via phosphorylating ER and its key coactivator SRC-3. Most importantly, I have identified a selective NLK inhibitor that has been proven safe in phase I/II clinical trial for inflammatory diseases. In vitro studies suggest that this drug potentially sensitizes endocrine-resistant breast cancer cells to tamoxifen treatment. Combination of NLK and mTOR inhibition showed promising therapeutic effect in a xenograft tumor with acquired tamoxifen resistance. The objectives of this study are to further assess the therapeutic value of the NLK inhibitor in combination with other targeted agents such as mTOR inhibitors in endocrine resistant breast cancer, and identify the biomarkers that may predict the tumor response to the targeted therapy cocktails.

This study will have substantial basic and clinical impacts. Co-targeting ER and alternative survival pathways may be the most effective means to combat endocrine resistance; such strategies have shown promising results in clinical trials. Here we have identified a new survival mechanism associated with endocrine resistance, and this project will develop the cocktails of NLK targeted therapy in combination with other targeted agents to manage endocrine-resistant breast cancers, as well as identify the potential biomarkers to predict tumor response and optimize the regimen of the targeted therapy cocktails. The outcome of this study could quickly move into clinical development, leading to a new line of targeted therapy as well as predictive assays for precision treatment, which would benefit a substantial population of incurable breast cancer patients. This project will greatly enhance my career goals to apply multidiscipline approaches including genomics, cancer biology, preclinical and translational researches to better understand the breast cancer biology and translate the laboratory advancements into improved patient care.