



**Susan G. Komen
Research Grants – Fiscal Year 2014**

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Harnessing altered ER turnover in invasive lobular carcinoma for improved therapy

Investigator(s): Sreeja Sreekumar, Ph.D., Steffi Oesterreich, Ph.D. (Mentor)

Lead Organization: University of Pittsburgh

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Public Abstract:

Invasive ductal (IDC,80%) and invasive lobular (ILC,10-15%) carcinoma are the two main histologic subtypes of invasive breast cancers. Although the incidence of ILC is “only” ~15%, annually ~34,000 women are diagnosed with ILC, which exceeds the number of ovarian and melanoma cases. ILC always tends to be diagnosed at an advanced stage compared to IDC due to the difficulty in mammographic detection. There has been a significant increase in ILC cases over the last two decades. However, ILC has not been well studied and there is a striking lack of understanding of the disease, compared to IDC. Estrogen hormone is implicated in the etiology of breast cancer. Biological effects of estrogen are mediated by cellular receptors called estrogen receptor (ER). ER subtype ERα is implicated in breast cancer pathogenesis and is the primary target for endocrine therapies. A group of drugs called SERMs (e.g. tamoxifen) are currently used in endocrine therapy. ILCs show increased levels of favorable prognostic markers including ER. The proportion of ER+ tumors is higher in ILCs than IDC and our preliminary studies show that ILC cell lines show higher ERα levels than IDC cell lines. Yet, recent evidence suggests that ILC patients have fewer clinical benefits from endocrine therapy compared to IDC patients. The molecular biology of this paradox needs to be unraveled. Why are ER levels different between IDC and ILC cells? Previous studies have shown that ligand binding decreases ERα protein levels by targeting the receptor for destruction by proteasome. Is altered ER level in ILC due to increased synthesis or decreased degradation? In our preliminary studies, the natural ligand, Estradiol(E2) induced ER degradation in IDC cells, but not in ILC cells. However, another class of drugs called SERDs (e.g. ICI 182,780) degraded ER in both IDC and ILC cells. These results suggest that ERα degradation is regulated differently in ILC cells. My project aims to identify these signals by comparing ER turnover in ILC and IDC cells. My preliminary data also raises the interesting and potentially clinically important question whether increased ERα levels confer greater susceptibility of ILC to SERDs compared to SERMs? I will perform experiments using IDC and ILC cell lines and mouse models bearing ILC tumors to provide answers for these challenging questions. We believe that by targeting the molecular cues regulating altered ER turnover in combination with effective SERDs will be an efficient tumor subtype specific (“personalized”) treatment for ILC which is now understudied but increasing in incidence in our society. I have discussed my research proposal with Ms. Heather Hillier, a patient advocate (ILC survivor) of University of Pittsburgh Cancer Institute (UPCI) and she has kindly agreed to be a key-personnel in our project. The interactions with Ms. Hillier and incorporating her suggestions will provide a patient perspective in the proposed study.