Susan G. Komen
Research Grants – Fiscal Year 2014

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Estrogen receptor-positive breast cancer recurrence through dependence receptor pathway

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Lead Organization: Indiana University
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Public Abstract:
Not all cancer cells in a tumor get the same amount of nutrients and oxygen because of uneven blood supply. Regions of tumors lacking oxygen are called hypoxic region. Tumors have come up with a way to survive under hypoxic condition and genomic changes/mutations cancer cells acquire while surviving under hypoxia also enable these cells to withstand the effects of chemotherapy. In previous years of funding, we have observed the ability of estrogen (E2) to increase the expression of proteins that enable cancer cells to survive hypoxia. E2 increased the expression of proteins called UNC5A and Netrin1 (NTN1). UNC5A and NTN1 then increased another protein called BCL2, which helps cancer cells survive hypoxia. Cancer cells that have acquired the ability survive under hypoxia may hide in places like bone marrow with lower oxygen and are responsible for late disease recurrence. Late recurrence is a major clinical problem in patients with Estrogen Receptor (ER)-positive breast cancer who have been treated with anti-estrogens for five or more years. In this year of funding, we will investigate how UNC5A-NTN1-BCL2 axis alters response of cancer cells to anti-estrogen under hypoxic condition. Additionally, we will investigate which of the known pathways of anti-estrogen resistance upregulates NTN1 and BCL2. Since NTN1 is a secreted protein, which can be measured in blood, NTN1 can be developed as a biomarker of anti-estrogen resistance and potentially a therapeutic target. Furthermore, we will be testing the effects of a drug called ABT-737 to kill cancer cells under hypoxia. ABT-737 is an inhibitor of BCL2 and is in clinic for treating blood cancers. If ABT-737 proves effective, the findings can be translated into clinic.