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.

Understanding and targeting IGF's role in G2/M progression

Investigator(s): Adrian Lee, Ph.D.
Lead Organization: University of Pittsburgh
Grant Mechanism: KS   **Grant ID:** SAC110021

Public Abstract:

Breast cancer is the second leading cause of cancer death among women with approximately one million new cases of breast cancer diagnosed worldwide every year. It is estimated that approximately 15-20% of women with breast cancer have triple negative breast cancer (TNBC). TNBCs are characterized as tumors that do not express estrogen receptor (ER), progesterone receptor (PR) and the human epidermal growth factor receptor 2 (HER2). TNBC do not respond to hormonal therapy or HER2-targeted therapies. It is estimated 65-80% of patients with TNBC often experience rapidly fatal clinical outcome within two years of diagnosis due to lack of targeted therapies and poor response to conventional chemotherapy. Hence there is an urgent need to develop novel therapeutic agents for the treatment of this aggressive subtype of breast cancer. Several preclinical studies have strongly implicated the role of the IGF system in breast cancer. IGF-1R is highly present in cancer cells than in normal breast and high expression of IGF-1R is reported in 90% of bre'ast cancer cases making it an attractive therapeutic target. Several studies have entered phase 1/11 clinical trials testing efficacy of anti-IGF-1R inhibitors either alone or in combination with chemotherapy; however results have been mixed, possibly due to lack of proper criteria in patient selection. Our laboratory has developed a gene expression signature based on genes induced or repressed by IGF-1 (IGF gene signature) which can predict the response to anti IGF-1R therapies. The IGF signature is correlated with poor prognosis in breast cancer and we observed high levels of IGF signature in TNBC cell lines and primary tumor. Previous findings in our lab have shown that anti IGF-1R therapy in combination with chemotherapy cause complete tumor regression in xenografts of primary TNBC tumor xenografts via mitotic catastrophe, a form of cell death that results from abnormal cell division. Understanding the role and mechanism of IGF-1R inhibitors in regulation of cell division is pivotal for development of efficient combination therapies. We will also investigate whether the synergism between anti IGF-1R/InsR treatment and Docetaxel is specific to agents targeting G2/M phase in primary TNBC xenografts. The findings from this study will benefit triple negative breast cancer patient population. We anticipate that inhibition of IGF-1R prolongs the arrest of cells in G2/M and cause cells sensitive to chemotherapy and induce cell death. Thus IGF-IR inhibition may in fact allow us to lower the dose of chemotherapy needed in combination treatments for efficacy in killing tumor cells; thereby we can minimize the toxic effects of chemotherapeutic agents. We can also identify biomarkers from groups that are sensitive or resistant to combination therapy (anti IGF-1R therapy and chemotherapy) and can use this information to predict responsiveness to the anti IGF-1R