Susan G. Komen

Research Grants – Fiscal Year 2015

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Targeting CDK8 to overcome resistance to targeted therapies in breast cancer

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Lead Organization: University of South Carolina - USC

Grant Mechanism: PDF Basic and Translational **Grant ID:** PDF15329865

Public Abstract:

Scientific objective and rationale:

Therapies such as letrozole or tamoxifen which target breast cancers (BC) expressing estrogen receptor (ER) and trastuzumab which targets BC expressing HER2 have significantly improved the outcome for BC patients and opened up an era of cancer treatment known as targeted therapy. Unfortunately, many patients either fail to respond to targeted therapies despite the presence of the target receptor in their tumors, or respond initially but go on to develop resistant disease. The treatment options for these highly aggressive and ultimately lethal tumors are extremely limited. The purpose of this study is to utilize a dual treatment strategy combining ER or HER2 targeted therapies with an inhibitor developed by our team that targets a protein called CDK8, expression of which is associated with poor response to treatment in BC patients Our preliminary results show that combining either ER or HER2 targeted therapies with CDK8 inhibition strongly inhibits BC growth, even in cancer cells that exhibit resistance to a targeted therapy. We found that inhibition of CDK8 with our drug is preventing a specific signaling event (phosphorylation of STAT1) within the cancer cells that may prime such cells to be killed by the targeted drugs.

Therefore we are proposing to test whether CDK8 provides a new target to improve the treatment and survival of patients with ER and/or HER2 positive BC. We will do this by treating multiple cancer cell lines, some of which are sensitive to ER/HER2 targeted therapies and others which exhibit resistance,

with combinations of the CDK8/ER inhibitors to investigate the anti-BC efficacy of such drug combinations in cell culture and in animal studies. We will also determine if CDK8 inhibition will prevent BC cells from becoming resistant to ER- nd HER2-targeting drugs. We will also analyze CDK8 expression and STAT1 phosphorylation in samples from normal and cancerous human breast tissue, to confirm the clinical relevance of our laboratory studies.

Ultimate applicability of the research:

Successful completion of this project will provide a very strong rationale for clinical trials combining CDK8 inhibitors with ER inhibitors in ER-positive BC and with HER2 inhibitors in HER2-positive BC. The overall goal of the research that we propose is to provide a new treatment strategy for those breast cancer patients who at present have no viable treatment options available to them. We hope that this project will contribute to changing the lives of the millions of women who will develop breast cancer within and beyond our lifetimes.