



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.

The role of RAGE-ligand signaling in breast cancer progression and metastasis

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Lead Organization: Miller School of Medicine of the University of Miami

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15331076

Public Abstract:

A major limit of the vast majority of breast cancer research conducted to-date is that it has focused primarily on what is wrong only with the cancer cell itself. This tumor cell centric approach has not until recently taken into account the role of normal cells of the breast, nor of immune cells circulating in the blood. We now know that other diseases and conditions that come with the aging process such as diabetes, obesity and other inflammatory states can influence the outcome of breast cancer. Whilst these conditions have nothing to do with the many genetic changes that occur in the cancer cells themselves, these inflammatory states can drive the cancer cells to be more aggressive and spread to other tissue more readily.

One of the ways that cancer cells and cells that surround the tumor can “talk” to each other and sense this state of inflammation is through a protein called “RAGE”. RAGE (Receptor for Advanced Glycation End-products) is a receptor present on the surface of normal cells which gets switched on by many of the inflammatory proteins produced in cancer. What is not clear in breast cancer, is how RAGE makes different cell types communicate, and if its importance is on cancerous or non-cancerous cells. We are especially interested how RAGE activates breast cancer cells, and how it makes cancer worse by recruiting a normal cell type from the blood known as myeloid derived suppressor cells (MDSCs). MDSCs have recently been shown to be major regulators of the amount of inflammation in a tumor and how aggressive breast cancer can become. Our preliminary data presented in this proposal, demonstrates clearly that RAGE makes breast cancer cells more aggressive, and ligands for RAGE (s100a8/9) are



responsible for getting MDSCs into the tumor. Furthermore, we show that a new drug that specifically blocks RAGE makes breast cancer cells less invasive. We will test whether RAGE is important for the malignant function of breast cancer cells versus MDSCs in cell culture and in animal models. To show the human importance, we will perform analysis of RAGE protein levels in patient tissue samples to see if RAGE levels are predictive of invasiveness and metastasis. Finally, we will also test in mice if our RAGE drug inhibitor affects breast cancer progression and metastasis.

The potential clinical applications of our work is the rapid translation to clinical trials of our RAGE inhibitor in patients with invasive and metastatic breast cancer. Together with our experience in translating scientific findings to the clinic, and the resources at the University of Miami, these patient related outcomes could feasibly be accomplished in 5-10 years. The results of this study have great potential to impact clinical practice and treatment of breast cancer, and thus have the potential to make a significant difference in the lives of breast cancer patients.

