Susan G. Komen

Research Grants – Fiscal Year 2015

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Novel therapeutic approach to triple-negative breast cancer: role of antioxidants

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Lead Organization: University Health Network - Toronto

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Public Abstract:

Cells are constantly exposed to reactive forms of oxygen termed “ROS” that are generated by their physiological functions. If ROS levels become too high, they damage tissues and kill cells. Cells use antioxidant systems to neutralize and control ROS. Tumor cells have genetic and metabolic defects that produce very high ROS, which they handle by increasing the activity of their antioxidant systems. Tumor cells may die if these systems are blocked, offering a rationale for a form of new anticancer therapy. My proposal seeks to characterize antioxidant molecules crucial for the survival of breast cancers with mutations in one of four genes, namely BRCA1, BRCA2, ATM, PALB2 and BRIP1. Women with breast tissue cells carrying alterations in these genes have a greater chance of developing an aggressive form of breast cancer known as Triple-Negative Breast Cancer (TNBC). Tragically, these cancers develop at a young age, are very hard to treat, and currently lack the targeted therapies that have been effective in treating other breast cancer subtypes. Recent studies suggest that BRCA1, BRCA2, ATM, PALB2 and BRIP1 (“TNBC genes”) are normally important for controlling ROS levels inside the cell because they regulate the activities of antioxidant molecules. When a TNBC gene is mutated in a breast cancer cell, this cell has only a low level of antioxidant factors and consequently accumulates high ROS. I hypothesize that such cancer cells then activate alternative mechanisms to control ROS and ensure their survival, and that inactivation of these alternative mechanisms might be a new route to TNBC therapy. My research proposal aims to identify which antioxidant molecules are controlled by TNBC genes, and which alternative mechanisms are selected by tumor cells with mutations in TNBC genes. In addition,

because research studies have theorized that administration of antioxidants to patients may interfere with their anticancer therapy, I will study whether the antioxidant vitamin E affects the response of TNBCs to two advanced chemotherapeutic drugs currently used for TNBC treatment: PARP inhibitors and PI3K inhibitors. The expected outcomes of my research are: 1) the identification of new factors that are essential for the survival of TNBC cells and thus may represent new potential drug targets for personalized cancer treatment, and 2) the clarification of whether antioxidants should be given to breast cancer patients. I envision that my research proposal will contribute to bridging the gap between basic science and clinical practice. Because my experimental approach includes human and mouse model systems of breast cancer that closely recapitulate the human disease, I believe my results will be readily translated into improved care for TNBC patients, bringing us closer to the ultimate goal of creating a world without breast cancer.