Susan G. Komen

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Research Grants – Fiscal Year 2015

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Mechanisms of normal-to-malignant transformation in the breast.

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Lead Organization: McGill University

Grant Mechanism: CCR Basic and Translational   **Grant ID:** CCR15331358

Public Abstract:

Breast cancer remains a devastating disease with over 200,000 new cases and 40,000 deaths per year in the US. Women at high risk for developing breast cancer may be eligible for preventative therapy, however, existing treatments only prevent some breast cancers and the net benefit is limited by serious side effects. Identifying novel targeted therapies will reduce breast cancer incidence, but a major barrier to this is a limited understanding of the mechanisms underlying early stages of breast cancer development.

Breast cancer progresses step-wise, with normal mammary ducts made of tubes comprised of a single layer of cells, becoming multilayered and eventually a solid mass of cancer cells. The initial loss of organization is accompanied by increased cell proliferation, which drives cancer growth. Therefore, loss of organization is a key early event that may be essential for breast cancer initiation.

Fibroblasts are cells that surround mammary ducts play a supportive role in tissue maintenance. They become reprogrammed as breast cancer progresses, which further promotes the growth of breast cancer cells. Sometimes these reprogrammed fibroblasts are present in the normal margins of breast cancers that are removed surgically. We predict that cancer fibroblasts left behind may make it easier for cancer cells to develop again.

aPKC is an enzyme that regulates tissue organization and is over-expressed in breast cancer. Increasing its expression in normal cells causes disorganized growth, similar to cancer cells. Inhibiting aPKC in cancer cells, it blocks loss of tissue organization and overgrowth, restoring them to a more normal state. The precise

mechanism by which normal cells transform into cancer cells, how aPKC regulates this, and whether the process is reversible is not understood.

Our hypothesis is that loss of cell organization initiates the earliest stage of breast cancer and that blocking it will prevent breast cancer development.

Aim 1 of our project will provide an indepth analysis of the expression of aPKC and other genes that regulate tissue organization by examining samples from breast biopsies. Since the patient outcome is known, we can identify if these genes predict whether an early lesion is likely to progress to breast cancer. Aim 2 of our project will examine how normal cells transform into cancer cells. Using a 3-dimensional (3D) culture system that closely recapitulates the normal organization of cells, we will induce the expression of cancer-causing genes and make videos of cells as they change. This will allow us to literally watch cancer cells form. We will then inhibit aPKC to learn its function in cancer initiation. We will establish a screen to identify other genes that interact with aPKC and are also involved in establishing a cancer state. In Aim 3 we will modify our 3D culture system to include fibroblasts and cancer-associated fibroblasts and determine how they affect the normal-to-cancer transformation.