Susan G. Komen

Research Grants – Fiscal Year 2015

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Targeting serine and glycine metabolism in breast cancer

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Lead Organization: New York University School of Medicine

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Public Abstract:

Metabolic pathways are essential for maintaining a proper balance of small molecules within the cells, and in proliferative cells the demand to accumulate biomass requires substantial metabolic pathway alteration. Indeed, altered metabolism is a hallmark of cancer. To proliferate, a cell needs to synthesize or scavenge building blocks for creating another cell, such as membrane and protein components and DNA. Indeed, there is substantial evidence for upregulation of biosynthetic enzymes in cancer, often as a direct result of gene mutation. Indeed, several enzymes involved in biosynthesis are the targets of both well-established and emerging anti-cancer drugs. Recently and with the generous support of a Susan G. Komen Postdoctoral Grant, I devised a strategy to evaluate the impact of targeting hundreds of metabolic genes at once. I undertook this strategy directly in a growing ER-negative breast tumor in mice. Each cell in this growing tumor had a different metabolic gene inhibited, and they competed with other cells in the tumor to uncover which genes are most important for tumor formation and growth. This increased the number of genes that could be evaluated simultaneously and led to the discovery that the gene PHGDH is highly elevated in ER-negative breast cancer and important for the growth of such tumors. Here, I propose to engage in three pre-clinical experiments to evaluate the impact of targeting PHGDH on breast cancer prevention and treatment to impact breast cancer mortality within the next decade:

(1) We will study a PHGDH inhibitor, which we identified from evaluating hundreds of thousands of molecules, and assess the impact of this inhibitor on breast tumors in mice. We will determine whether other commonly used drugs work better in combination with this PHGDH inhibitor, and whether cancer cells treated with this drug have new dependencies that can be exploited for therapy.

(2) We will design a mouse that can model inhibition of PHGDH in the breast and assess the impact of PHGDH loss on normal breast tissue and the prevention of breast cancer.

(3) We will use a powerful new genetic technique to uncover the underpinnings of ER-negative breast cancer's high demand for serine, a key nutrient produced by PHGDH.

Thus, the research objectives outlined here are important because they evaluate, in the most direct way possible in a pre-clinical setting, the effect of inhibiting a promising new breast cancer target.