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.

Estrogen receptor reactivation for treatment of advanced breast cancer

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Lead Organization: Dartmouth College

Grant Mechanism: CCR Basic and Translational **Grant ID:** CCR15330848

Public Abstract:

Estrogen hormones interact with estrogen receptor alpha (ER) inside breast cancer cells, which typically drives cancer growth. Approximately 70% of breast cancers have ER. Anti-estrogen drugs that block ER activation are used to prevent cancer growth and recurrence. While anti-estrogens are among the most effective anti-cancer drugs in history, ~20% of patients with breast-localized cancer removed by surgery and treated with anti-estrogens ultimately develop recurrent cancer that is metastatic or locally advanced (~180,000 new cases per year worldwide). In nearly all cases, metastatic breast cancer eventually becomes resistant to standard therapies and is fatal, making ER+ breast cancer responsible for more deaths than all other breast cancer subtypes combined.

Before anti-estrogens were developed, ESTROGENS were used to TREAT breast cancer. This may seem counterintuitive because estrogens and anti-estrogens have opposite effects on ER, but these therapies elicit similar degrees of response in patients with metastatic breast cancer. Estrogens are most effective against breast cancer following a period of estrogen suppression, suggesting that ER reactivation is toxic to cancers that adapted to estrogen-independent growth. Withdrawal of anti-estrogen therapy can also induce anti-cancer effects, further suggesting that ER reactivation can be therapeutic. Anti-estrogens were subsequently developed and have been a treatment standard for over 30 years, while estrogens were relegated to rare use. However, estrogen therapies are being resurrected through recent clinical trials in patients with anti-estrogen-resistant breast cancer, including our POLLY trial (clinicaltrials.gov identifier NCT02188745).

We postulate that adaptation to anti-estrogens induces changes in breast cancer cells that render ER reactivation toxic. We will test this concept through studies in breast cancer cells, mice bearing breast tumors

derived from patients and cultured cells, and tumor samples from patients treated with estrogen therapy. These studies will reveal the mechanism and timing underlying the anti-cancer effects of ER reactivation, tumor-specific markers that predict subsequent tumor response, and ways to enhance the anti-cancer effects of ER reactivation. Such information is critical to the incorporation of estrogen therapy as a legitimate, inexpensive, widely available, relatively safe and tolerable treatment option for patients with anti-estrogen-resistant breast cancer, and to limit its use to patients with cancers likely to respond. Our early data suggest that inactivation of the protein EZH2 may be involved in the anti-cancer effects of ER reactivation. Anti-EZH2 drugs are undergoing initial testing in cancer patients.

Demonstrating that EZH2 inhibition blocks the growth of anti-estrogen-resistant breast cancer cells and tumors in mice would support testing of anti-EZH2 drugs in patients with anti-estrogen-resistant breast cancer.