Susan G. Komen

Research Grants – Fiscal Year 2015

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Dual immunotherapy plus a HER2 vaccine reverses anergy to eliminate breast cancer

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Lead Organization: Providence Portland Medical Center

Grant Mechanism: CCR Basic and Translational **Grant ID:** CCR15329664

Public Abstract:

Patients with early stage breast cancer have excellent survival rates, however the outlook for women with metastatic disease remains poor. Therefore, new treatments for metastatic breast cancer are urgently needed. One exciting approach to address this unmet need is immunotherapy, which is a class of cancer treatments that utilizes the patient's immune system to destroy malignant cells. Unfortunately, the induction of immune suppression by cancer cells can severely limit tumor-specific immunity. Regulatory proteins known as immune "checkpoints" including molecules such as CTLA-4, PD-1, and PD-L1 serve to inhibit immune cell activation. Checkpoint blockade with anti-CTLA-4, anti-PD-1, or anti-PD-L1 monoclonal antibodies (mAb) releases the "brakes" on white blood cells (T cells), thereby enhancing tumor immunotherapy. Alternatively, stimulation of T cells with an activating drug called anti-OX40 mAb provides the "gas" for the immune system to seek out and destroy breast cancer cells. Despite the clinical activity of agents such as anti-CTLA-4, anti-PD-1, and anti-PD-L1 in diseases such as renal and lung cancer and malignant melanoma, to date, similar efficacy has been lacking in women with breast cancer. Thus, there is a critical need to understand the mechanisms that hinder efficacy and develop new immunotherapeutic approaches to elicit robust tumor regression in women with metastatic breast cancer. In this proposal, we demonstrate that dual anti-OX40/anti-CTLA-4 therapy was not sufficient to eradicate mammary carcinoma due to immune suppression by the tumor. However, the inclusion of a breast cancer-specific vaccine synergized with anti-OX40/anti-CTLA-4 therapy to rescue the function of "killer" T cells and eliminate mammary carcinomas. We hypothesize that this

combinatorial approach relieves immune suppression and elicits a unique immune profile in the “killer “ T cells that is associated with their enhanced ability to locate and destroy breast cancer cells. Our specific aims are: 1) Test the hypothesis that anti-OX40/anti-CTLA-4 therapy plus anti-DEC-205/HER2 mAb vaccination rescues anergic CD8 T cells and mediates tumor regression through a CCL3 and CCL4-dependent mechanism in orthotopic models of mammary carcinoma; 2) Test the hypothesis that ICOS-mediated Th2 polarization and suppression by FoxP3+ CD4 T cells (Treg) following anti-OX40/anti-CTLA-4 immunotherapy plus breast cancer-specific vaccination impairs complete eradication of mammary carcinoma; and 3) Test the extent to which ICOS blockade can further boost the efficacy of anti-OX40/anti-CTLA-4/HER2 vaccine immunotherapy. Ultimately, our goal is to translate this approach to the clinic, as generating a more robust and targeted therapeutic immune response against breast cancer cells would represent a significant advance in treatment, thus putting us closer to our goal of eliminating the morbidity and mortality associated with metastatic breast cancer.