Susan G. Komen for the Cure
Research Grants – Fiscal Year 2011

This research grant was approved by Komen's national board of directors for FY2011 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

Enhancing Efficacy of Chemotherapy in Triple-negative/Basal-like Breast Cancer by Targeting Macrophages

Investigator(s): Lisa Coussens, PhD, Shelley Hwang, MD and Hope Rugo, MD
University of California at San Francisco, California
Awarded: $6,500,000
Grant Mechanism: Promise Grants
Research Focus: Biology

Public Abstract:
General Public/Lay Abstract: Although breast cancer (BC) incidence in the United States is lower among African American women than Caucasian women, studies consistently show reduced BC survival among African American women with BC. Racial differences in access to screening, diagnosis and treatment have been cited as important determinants of disparities in BC survival. However, recent studies now indicate that there exist important biologic factors that likely contribute to differences in BC survival. Gene expression analysis has shown that African American women exhibit a higher proportion of the most aggressive tumors, called basal-type, or "triple-negative" breast cancers (TNBC) which are more likely to be resistant to standard chemotherapy regimens and associated with poor prognosis. Importantly, basal tumors are often characterized by a marked increase in immune cells, chief among them the tumor-associated macrophages. Data from our lab show that tumor-bearing mice treated with a drug that reduces infiltration of macrophages into tumors, PLX3397, enhances sensitivity to chemotherapy, thereby reducing the spread of cancer to the lungs and prolonging survival. In addition, antibodies targeting macrophages resulted in similar effects, confirming that targeting macrophage function is an important mechanism for increasing response to chemotherapy. PLX3397 is a novel drug that is completing early phase testing in humans. Preliminary results indicate that this drug has few side effects, and shows promise in treatment of advanced staged tumors. In this proposal, we will determine the clinical benefit of this entirely novel approach to the treatment of TNBC. We seek to achieve the following aims: 1) expand our preliminary results in an animal model of TNBC using PLX3397 and 3 different types of chemotherapy in order to find the most effective combination regimen; 2) evaluate 120 consecutive patients undergoing surgery for BC to identify characteristics on MRI, tumor analysis, and blood testing which are associated with the highest density of functional macrophages and therefore most amenable to macrophage targeted treatment strategies; and 3) test the best regimen identified in the animal experiments in women with metastatic TNBC to confirm safety of the drug combination in humans, and to determine whether this combination has potential to impact outcome in this poor-prognosis group of patients. Our team consists of Lisa M. Coussens, Ph.D., Professor, UCSF Dept of Pathology and Co-Director of the Program in Cancer Immunity and Microenvironment, and an expert in cancer-associated inflammation and mouse models of cancer; E. Shelley Hwang. M.D., Professor and Chief of Breast Surgery at UCSF whose research focuses on premalignant breast disease and identification of predictive and prognostic biomarkers; and Hope S. Rugo, M.D., Professor of Medicine and Director of Breast Oncology and Clinical Trials Education at UCSF who is an international

expert in breast oncology and clinical trial design. Kimberly Blackwell, M.D., Associate Professor of Medicine and Director of the Breast Cancer Program at Duke University, and Ingrid Mayer, M.D., Assistant Professor of Medicine and Clinical Director of the Breast Cancer Program at Vanderbilt University, both experts in breast oncology, translational medicine and clinical trials, will collaborate on the multi-center clinical trial and contribute to trial design, patient enrollment, tissue collection, data analysis, and reporting. The research team will be enhanced by the efforts of 4 experienced patient advocates: Ms. Susan Samson will lead the advocate effort, and will collaborate with Ms. Lynne Cargen (Vanderbilt), Ms. Mary Jackson and Ms. Valarie Clark Worthy (Duke), to provide input on clinical trial design, consent form wording, patient educational materials, patient recruitment, data analysis and reporting. Targeting tissue-associated macrophages is a completely new way of treating cancer and laboratory data indicate that it could be highly effective in treatment of advanced stage BCs, with potential to prolong survival in advanced stage disease and cure chemotherapy resistant disease. Successful completion of our aims would provide patients with metastatic TNBC access to this treatment in the next 3 years, and could allow for its use in a clinical trial for early stage patients in the next 5 years. The proposed approach will represent a significant advance in the treatment of TNBC and will help address the biologic basis of racial disparity in breast cancer outcomes.