



**Susan G. Komen
Research Grants – Fiscal Year 2014**

This research grant was approved by Komen's national board of directors for FY2014 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

LTBP1: A prometastatic factor linking pregnancy to breast cancer

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Lead Organization: New York University School of Medicine

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF14300709

Public Abstract:

Rationale and Objective: Pregnancy exerts dual effects on breast cancer risk: early pregnancy reduces breast cancer risk in later life, but all pregnancies, particularly those in older women, elevate breast cancer risk during pregnancy and for five years after childbirth. Thus natural changes that occur in breast during pregnancy and after childbirth are responsible for the heightened risk. Pregnancy Associated Breast Cancers (PABCs) that develop after weaning are highly metastatic and associated with very poor outcome. During this period, the supporting tissue of the breast undergoes extensive changes that are thought to promote metastasis. This proposal concerns Latent TGFbeta Binding Protein 1 (LTBP1), which forms a bridge between the supporting breast tissue and the breast cells. We have made the novel finding that breast cells lining the ducts dramatically upregulate LTBP1 during involution. Importantly, LTBP1s regulate the activity of TGFbeta, which can promote breast tumor cell movement. We hypothesize that LTBP1 may be a critical factor inducing the metastatic progression of breast cancers and that its elevation during involution could explain the poor outcome in women developing PABC post-partum. Supporting this concept, LTBP1 appears in two gene signatures that stratify breast tumors into those that metastasize to lung and brain respectively. The experiments in this proposal will test directly whether elevating LTBP1 stimulates tumor cells to metastasize and conversely whether eliminating LTBP1 prevents this. They will also assess if LTBP1 has promise as a breast cancer biomarker for metastatic risk of breast tumors. Impact: PABC has been increasing as more women delay childbirth until later in life. Although PABCs represent a small fraction of breast cancer, their propensity to metastasize contributes significantly to the poor outcome associated with young women's breast cancer. Currently, we do not understand the etiology of PABC and why PABCs are so metastatic. Thus, fundamental research into molecular links between involution and metastasis are prudent. Studies on this promising pro-metastatic candidate may provide valuable clues about this highly malignant form of breast cancer and be relevant for metastasis in general. In the short term, the proposed research has the potential to validate a novel biomarker indicative of a pro-metastatic tumor microenvironment. Markers that can identify patients with luminal tumors predisposed to become malignant are urgently needed to spare 70 % of patients from unnecessary treatment and permit resources to be directed to those who will benefit. If our hypotheses are correct, the longer-term impact of our work will be to shift breast cancer management away from its current focus on cure and towards a strategy of prevention during natural breast developmental windows of susceptibility. For example, use of available TGFbeta antagonists could be explored during the post partum period.