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**JAK2-STAT5 Pathway Blockade to Prevent Breast Cancer**

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**Awarded:** $900,000.00

**Grant Mechanism:** Investigator Initiated Research

**Public Abstract:**
Each year, approximately 200,000 new breast cancer cases are diagnosed in the U.S. Reducing breast cancer incidence even by a small percentage can have a profound impact on saving lives and reducing the huge cost associated with treatment. Since the invention of antiestrogens, unfortunately there has been little further development in breast cancer prevention. Early lesions of the breast such as atypical ductal hyperplasia (ADH) sometimes but not always progress to invasive cancer, but what causes a small subset of these premalignant lesions to progress is not yet known. This knowledge could provide new molecular targets for breast cancer prevention. Studies in a number of tissue types have shown that apoptosis (the common form of cell death) is activated in human early lesions, serving a barrier to progression. This barrier must be overcome for early lesions to develop full-blown cancer. Using novel mouse models, we have preliminary data showing a role of the STAT5 protein in the suppression of apoptosis during mammary tumor initiation, and that a novel STAT5 inhibitor developed by the co-PI of this application can prevent breast cancer. Therefore, we hypothesize that activation of STAT5 in patients harboring premalignant lesions promotes the progression of these lesions to malignancy by lowering the apoptosis anticancer barrier; therefore, inhibition of STAT5 could prevent breast cancer. We predict that even transient inhibition of STAT5 in early lesions could devitalize them and could lower the risk of invasive breast cancer, while the possible adverse effects and inconvenience to women would be small, so that they would not be discouraged from participating in this potentially highly-effective cancer prevention strategy. Specific Aims are as follows: (1) To establish that forced activation of STAT5 in oncogene-activated mammary cells weakens the apoptosis barrier and promotes the progression from an early lesion to malignancy in mice. (2) To demonstrate that genetic blockade of STAT5 causes mammary early lesions to undergo apoptosis and prevents these lesions from progressing to cancer in mice. (3) To determine whether a short-term treatment with a STAT5 inhibitor causes mammary early lesions to undergo apoptosis and prevents these lesions from progressing to cancer.