Susan G. Komen
Research Grants – Fiscal Year 2013

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Role of TMEPAI in Breast Cancer Progression

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Public Abstract:
Breast cancer represents still one of the top causes of death (~ 40,170/year) among women in the United States. Although localized breast cancers are successfully detected and treated, invasive breast cancer still represents a lethal form of disease and poses a greater therapeutic challenge. The worst outcomes are mainly in the basal-like subtype with "triple negative" or other aggressive phenotypes and Her-2 positive luminal breast cancers. The basal-like triple-negative tumors, which frequently affect women of African-American and Hispanic descent as well as younger women of all races, demonstrate a high histological grade and proliferation index, and unlike the other subtypes, they lack appropriate targets that respond to available therapeutic agents such as hormonal therapy (anti estrogens and/or aromatase inhibitors) or Herceptin (targets HER2 receptor). In this study, we propose to explore the prognostic value and therapeutic significance of a novel protein (TMEPAI) expression in invasive breast cancers independent of their estrogen receptor or HER2/Neu status. Our study developed a better molecular marker that will not only identify subtypes at the time of primary diagnosis but help to predict accurately the clinical outcome of these invasive breast cancers. This proposal investigates a previously unrecognized role for TMEPAI in the development of invasive and aggressive breast cancers. This research will have great impact on our understanding of mechanisms whereby TGF-ß signaling is transformed from its normal role as tumor suppressor in early tumorigenesis to a tumor promoter in advanced cancers as well as on breast cancer treatment. It will identify TMEPAI as an attractive target for the development of drugs that may be superior to currently used toxic chemotherapies in many patients. Patients with triple negative or conventional therapy resistant breast tumors could be the primary beneficiaries of this approach. Thus, interventions that either decrease TMEPAI or abrogate its activity are expected to reconvert TGF-ß from its tumor promoting activity in advanced breast cancer, back to its normal tumor suppressor role. Targeting this important molecule downstream of TGF-ß receptors therefore avoids the dangers associated with complete overall TGF-ß signaling inhibition. Moreover, targeting TMEPAI may recover surveillance roles of both TGF-ß as well as immune cells. New therapies targeting this novel molecule may not only inhibit tumor growth but also prevent recurrence of breast cancer. Consequently, this work will pave the way for developing drugs that selectively downregulate TMEPAI without interfering with TGF-ß signaling in treating invasive triple negative breast cancer patients. Attainment of our objectives could lead to paradigm shifts in research on cancer progression and drug development.