



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Fibulin-3 as a novel biomarker and target in the breast tumor microenvironment

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Grant Mechanism: CCR Basic and Translational

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Public Abstract:

Scientific Objective and Rationale: The dual tumor suppressor/tumor promoter role of the TGF- β signaling pathway suggests tight control and regulation of this pathway during breast cancer progression. However, this dual role makes targeting the TGF- β pathway difficult. Thus, it is important and necessary to investigate how the TGF- β pathway is regulated during breast cancer progression, especially by the microenvironment, which can be readily targeted. In addition, TGF- β also plays important roles in tumor associated-angiogenesis, the process which provides the tumor with oxygen and nutrients, and facilitates metastasis. However, angiogenesis only occurs during specific processes, including during development and breast cancer progression, suggesting that the microenvironment is also important for regulating breast cancer associated angiogenesis, potentially via TGF- β signaling. This proposed project is designed to investigate a fundamental and important question of how breast cancer and breast cancer associated angiogenesis are regulated by fibulin-3, a novel TGF- β regulator, in the breast cancer microenvironment. Thus, this project will yield novel insights into the how the dichotomous function of TGF- β signaling is regulated by the microenvironment during breast cancer progression. These studies will 1) aid in better understanding the impact of the breast cancer microenvironment on TGF- β signaling, breast cancer progression and tumor associated angiogenesis, 2) provide a novel mechanism by which fibulin-3 regulates TGF- β signaling and function in breast cancer and endothelial cells, and 3) define how fibulin-3 expression level in the microenvironment is changed and regulated during breast cancer progression.

Research Applicability: In the proposed work, we will investigate the roles of fibulin-3 in TGF- β signaling, breast cancer metastasis and breast cancer associated angiogenesis in vitro and in vivo. If successful, both the TGF- β signaling pathway and fibulin-3 could serve as potential anti-metastasis and anti-angiogenesis targets for the treatment of breast cancer patients. In addition, as fibulin-3 is a secreted protein, and serum fibulin-3 levels have already been proposed as a blood based biomarker for pleural mesothelioma, serum fibulin-3 levels could be used as a diagnostic, predictive or prognostic biomarker for breast cancer patients. Moreover, if fibulin-3 promotes breast cancer metastasis and tumor associated angiogenesis, as proposed in specific Aim 3C, recombinant fibulin-3 or agents based on fibulin-3 could potentially be used to treat breast cancer patients. Along those lines, we propose to assess the effects of fibulin-3 on tumor metastasis and angiogenesis directly in pre-clinical models of breast cancer. These pre-clinical studies could provide the rationale for the design and organization of phase I clinical trials of fibulin-3 based agents for patients with metastatic breast cancer (~4-5 years).