



**Susan G. Komen**

**Research Grants – Fiscal Year 2015**

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**Clinical identification and regulation of cancer stem cells in TNBC**

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**Lead Organization:** Baylor College of Medicine

**Grant Mechanism:** PDF Basic and Translational

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**Public Abstract:**

Approximately 15% of human breast cancer cases are triple negative (TNBC), which is associated with high tumor grade, increased risk of visceral or cerebral metastasis, and poor survival after recurrence. TNBC has a strikingly higher rate of mortality and distant recurrence within the first 5 years of diagnosis compared with non-TNBC. Breast cancers may be driven by a small population of cancer stem cells (CSCs), and these cells are particularly abundant in triple-negative disease. CSCs are a subpopulation of tumor cells with the ability to undergo self-renewal and recapitulate the entire tumor population in vitro and in vivo, and they are responsible for tumor growth and recurrence as well as treatment failure. Therefore, examining CSCs in human breast cancer may help guide patient treatment and may lead to better drugs to subsequently target them.

While breast CSCs can be identified using sophisticated assays in a laboratory setting, until now CSCs cannot be easily assessed in a clinical setting on frozen or paraffin embedded tissues. Consequently, the value of CSC theory has not been fully harnessed to benefit breast cancer patients. Our preliminary data using both mouse models and human TNBC cell lines suggest that cytokeratin 6 is a novel marker of breast CSCs. Cytokeratin 6 is highly stable protein, and I have already developed an assay that is suitable for detecting cytokeratin 6 in frozen or paraffin embedded human breast cancer samples. Therefore, in this proposal I will validate cytokeratin 6 as a marker of CSCs in human TNBC samples. If successful, our data could have direct and immediate clinical implications.

We have found that these cytokeratin 6-positive CSCs produce a soluble protein, interleukin 1, that can maintain self-renewing potential of CSCs. This is novel because this type of protein was previously found to be made only by immune cells that infiltrate cancer, but not cancer cells themselves. I will test whether this interleukin 1 protein



indeed regulates CSCs in human breast cancer tissues that are grafted in mice. In addition, I will test whether targeting interleukin 1 and the signaling pathway that it controls can suppress CSCs and halt TNBC progression.

Scientific Impact: My work may lead to the identification of a new CSC marker for human breast cancer, and may implicate an interleukin-mediated signaling pathway as a key factor in controlling CSCs and TNBC progression.

Clinical impact: My work on K6a a CSC marker may lead to a new clinical assay for assessing CSCs in human breast cancer patients. My mechanistic studies on key factors regulating CSCs may implicate IL-1 signaling as a novel molecular target for treating TNBC patients. Moreover, my work may provide an efficacious adjuvant chemotherapy for preventing TNBC progression and relapse.

