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

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## Interrogating the function of the oncogene TLOC1 in breast cancer

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**Public Abstract:**
Breast cancer is a collection of diseases with different mutations in varying frequency across different breast cancer subtypes. By focusing on molecular changes specific to breast cancer, targeted cancer therapies may be more effective than other types of treatment, including chemotherapy and radiotherapy, and less harmful to normal cells. As such, deeper exploration of the genetic changes that drive breast cancer will reveal new therapeutic targets. Therefore, in the proposed study, we aimed to define novel cancer driver genes, study their molecular mechanism to promote tumor formation and design targeted treatment based on these discoveries. TLOC1 was recently identified by our laboratory as a novel tumor driver gene amplified in 31.7% of human breast cancers. Overexpression of TLOC1 drives breast cell transformation by regulating messenger RNA (mRNA) translation, a fundamental biological process in which cellular machinery creates proteins. Further studies in our laboratory demonstrated that overexpression of TLOC1 was able to drive the oncogenic transformation of mammary epithelial cells through proteins involved in mRNA translation. Deregulation of this process correlated with worse clinical outcome and decreased breast cancer survival. The proposed research will address how TLOC1 acts as an amplified oncogene to drive breast cancer initiation by regulating mRNA translation and test whether inhibitions of mRNA translation could be an effective targeted therapeutic strategy for TLOC1-amplified breast tumors, which account for one third of all human breast tumors.The proposed research will use a comprehensive approach to translate our basic biological discovery to clinics. First, I plan to investigate the detailed molecular mechanism how TLOC1 promotes breast cancer formation by biochemical, bioinformatic and microscopic methods. These specific aims will bridge the gap from chromosome region 3q26 amplification to the biology of breast cancer. Understanding the molecular mechanism of translational regulation by TLOC1 and molecules involved in the signaling pathway will assist us to design therapeutic strategies targeting TLOC1 or molecules downstream of TLOC1 and search for available pharmacological compounds that inhibit mRNA translation in susceptible tumors. Second, I will determine the molecular target of TLOC1 and test whether inhibition of mRNA translation could inhibit the TLOC1-amplified breast cancer. This aim will provide a solid foundation for targeted therapy for breast cancers that harbor TLOC1 or 3q26 amplifications. Thus, the proposed research may implicate a practical molecular biomarker for the breast cancer patients potentially responding well to drugs targeting mRNA translation. In summary, not only will my proposed research provide insights into the biology of breast cancer, but it will also potentially serve as a foundation for a targeted breast cancer treatment to reduce mortality within the next decade.