

Susan G. Komen

Research Grants – Fiscal Year 2015

This research grant was approved for FY2015 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

Novel microRNA pathways regulating breast cancer stem cells and metastasis

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Lead Organization: Case Western Reserve University

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15332826

Public Abstract:

Breast cancer is the most frequent cancer among women in the United States with over 230,000 new cases and 40,000 deaths every year. As a major fatal problem, metastasis is often linked to therapy resistance. Our research demonstrated that breast tumor initiating cells (BTICs) with stem cell properties, also termed as breast cancer stem cells, are able to mediate metastasis as well as therapy resistance. To understand the underlying molecular mechanisms, we have identified miR-30c as a prognostic biomarker and a functional regulator of cancer invasion (early initiation step of metastasis) and chemotherapy resistance. In addition, we discovered miR-30c's upstream transcriptional factor GATA3 and downstream target IL-11, both associated with clinical outcomes and involved in regulation of invasion and/or chemotherapy sensitivity. These data suggest that the miR-30c signaling pathway may serve as promising targets of breast cancer treatment. However, the roles of the miR-30c pathway in the late stages of metastasis in vivo, such as circulating tumor cells and existing lung metastases, are not fully characterized.

This project will assess the effects of modulated expression of miR-30c and other two candidate genes, GATA3 and IL-11, in different stages of spontaneous metastasis in patient-derived xenograft models in immune-deficient mice as well as mouse tumor models with intact immune cells. We will further develop feasible neutralizing strategies to target the cytokine IL-11. As IL-11 has been used in the clinic to promote platelet production in cancer patients who receive chemotherapy, it is critical to dissect the potential oncogenic functions of IL-11 and develop a targeting strategy to block tumor metastasis and overcome chemotherapy resistance. We will also

utilize the cutting-edge optical imaging technology to facilitate the understanding of basic biology and applications of our discoveries into future clinical settings.