



**Susan G. Komen**

**Research Grants – Fiscal Year 2015**

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**The consequences of centrosome amplification in breast cancer**

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**Public Abstract:**

Metastatic breast cancer is a major cause of death among women in the western world. Thus, there is a pressing need for gaining a deeper understanding of the phenomena underpinning breast cancers and developing targeted and efficient therapies to prevent or treat metastasis. One biological difference between normal mammary epithelial cells and many breast cancers is the number of cellular structures called centrosomes: normal cells contain two centrosomes during cell division, while many cancers, particularly breast cancers, contain extra centrosomes (more than two, also called centrosome amplification).

Our results show that centrosome amplification can induce cell invasion and unstable contacts between neighboring cells, the first step leading to metastasis. Importantly, we have evidence that cells with centrosome amplification induce increased migration and proliferation. Based on our results, we propose that the presence of centrosome amplification can lead to elevation and persistence of proliferation and collective motility, which in the long run can lead to the induction of metastatic potential.



In our previous work, we have identified an attractive therapeutic target for cancer cells with centrosome amplification: the HSET protein. This study has motivated the development of HSET inhibitors by several pharmaceutical companies; our results may suggest a role for HSET inhibition in preventing metastasis. HSET is not required for cell division in normal cells, but becomes essential for normal division in cancer cells with extra centrosomes. This observation will enable me to test the hypothesis that destabilization of organization of amplified centrosomes may unfocus the internal machinery that controls invasive protrusion formation and proliferation. In summary, this study aims to gain new mechanistic insight into the complex interplay between key intracellular processes and the tumor microenvironment in breast cancer. In addition, this project will provide a better understanding of the causes of persistence of amplified centrosomes in malignant breast cancers, in contrast to spontaneous loss of such centrosomes in normal cells. Confirmation of the hypothesis that perturbation of centrosome amplification impairs cell invasion and proliferation represents an important first step toward a novel therapeutic strategy of inhibiting breast cancer metastasis, and ultimate eradication of this deadly disease.

