



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.

Disruption of the tumor microenvironment in Her2+ breast to brain metastases

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Lead Organization: USC/University of Southern California

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15332673

Public Abstract:

It is often unrecognized that 90% of deaths from cancer occur because of metastasis and the most dangerous area to which cancer can spread is the brain. This is particularly relevant for women with breast cancer with Her2+ subtypes in whom nearly 40% of women will develop this dreaded and life threatening complication. Worryingly, breast-to-brain metastases are increasingly a first site of relapse even while their extra-cranial disease is under control. While patients are living longer from the success of new systemic therapies, a new frontier has been unmasked which is breast cancer spreading to the brain. This clinical scenario is terrifying and worsened by the fact that we have no good treatment options to offer other than brain surgery and radiation. Improving upon this clinical problem for women with advanced breast cancer will affect both how long they live and how well they live from a quality of life perspective.

The brain is the most complex biological system in the body and poses unique obstacles but also harbors opportunities for discovery for new treatment. Much of what we know about the brain microenvironment comes from neuroscience. We hypothesize that the cellular responses in neurodevelopment and neuronal connectivity may guide us towards new perspectives in understanding how Her2+ breast cancer cells communicate with brain cells to form metastases and drug resistance.



Tumor cells are biologically heterogeneous and continually evolve, yet one unifying element is the critical role of the microenvironment for arriving metastatic cells. The distinct steps of tumor cell extravasation and subsequent metastatic colonization are mediated by a variety of receptor-ligand pairs on opposing cell type; therefore, interactions of tumor cells with components of the brain microenvironment are crucial determinants in their progression towards metastasis. Our previous research established that the physiologic microenvironment of the brain must become a tumor-favorable microenvironment for successful metastatic colonization by breast cancer cells. We further show breast to brain metastases display similar characteristics to brain cells and then can utilize the molecule GABA as a biological fuel for energy. Therefore, breast cancer cells that successfully metastasize to the brain may represent a subpopulation of tumor cells that best mimic neural cells and adapt to the resources available in the brain's microenvironment- the proverbial "wolf in sheep's clothing."

Accordingly, the proposed work is significant, because it exploits the unique brain microenvironmental adaptations to which breast cancer cells are dependent upon.

