Susan G. Komen for the Cure
Research Grants – Fiscal Year 2011

This research grant was approved by Komen's national board of directors for FY2011 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

Investigating the signaling pathways involved in the ECM degradation by breast cancer cells.

Investigator(s): John Condeelis, PhD
Albert Einstein College of Medicine at Yeshiva University, NY
Grant Mechanism: Post Doctoral Fellowship - Basic Research

Fellow: Ved Sharma, PhD
Awarded: $180,000.00
Research Focus: Biology

Public Abstract:
In March 2010, Pfizer announced that it is stopping the development of its breast cancer drug "Sutent" because the drug failed to meet its goals in the two late-stage breast cancer trials. This is not an isolated news, and unfortunately, more and more, we are seeing that new drugs, which show exceptional results in the laboratory, fail miserably during the clinical trials. We think that the primary reason for these failures is due to an incomplete understanding of how different proteins interact with each other in cancer cells during the disease progression. New drugs are being screened by a "black box" kind of approach, where different types of cancer cells are exposed to hundreds or thousands of compounds and the ones which prove best at killing the cancer cells are then evaluated further. Slowly it is being realized that a better way of designing new drugs is to first understand how proteins interact at the molecular level in cancer cells. Drug target identification and subsequent drug development should be based on the sound understanding of how proteins interact with each other in cancer cells. Based on this reasoning, we would like to investigate the protein interaction at the molecular level, in the invadopodia of breast cancer cells. A growing body of research implicates invadopodia in cancer cell invasion and metastasis. Invadopodia are protrusive structures of the cancer cells, with a diameter around 0.5-1 micron and length a couple of microns. Primary function of these structures is to degrade the extra-cellular matrix, which creates a passage (like a tunnel) through the extra-cellular space, which cells utilize to migrate from the primary tumor site to enter the bloodstream and eventually metastasize at distant sites, e.g. lungs, to make secondary tumors. Metastasis is the leading cause of death in breast cancer patients, as opposed to the growth of primary tumor, which can be kept in check by surgery, chemotherapy and various drugs. Therefore, understanding the protein dynamics during the assembly of invadopodia in breast cancer cells is the crucial first step to design new drug targets, with the potential of lowering the rate of breast cancer metastasis. We hypothesize that the assembly of invadopodia is a sequential process, where some proteins arrive early, which then recruit other proteins to form the mature invadopodia. To test this hypothesis, our approach is to image the dynamics of different invadopodial proteins in breast cancer cells using fluorescence microscopy. Fluorescence microscopy involves tagging proteins in the cells with various fluorescent markers (e.g. GFP, green fluorescent protein, whose discovery lead to a Nobel Prize in chemistry in 2008), followed was visualizing the fluorescence with a microscope. Recently, we have built one such system, and our goal is to visualize the interaction of multiple proteins in breast cancer cells to elucidate the sequential order of arrival of different proteins during the invadopodia assembly. In our opinion, targeting proteins, which either arrive early at the invadopodia or the ones which help to stabilize the invadopodia, through

specific drugs, will lead to a reduction in invadopodia formation in breast cancer cells. This will lead to a reduction in the ability of those cells to metastasize to the secondary sites, a leading cause of breast cancer mortality.

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