Susan G. Komen
Research Grants – Fiscal Year 2014

This research grant was approved by Komen's national board of directors for FY2014 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

A novel therapeutic and diagnostic target in triple negative breast cancers

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Grant Mechanism: PDF Basic and Translational **Grant ID:** PDF14298952

Public Abstract:
The current proposal focuses on identification of a new diagnostic and therapeutic target in invasive breast cancer, the deadliest form of disease that is the major cause of mortality from breast cancer. Although the focus of this project is on Triple Negative Breast Cancers (TNBCs), the results are likely to impact other types of invasive breast cancers. All TNBCs are treated through the standard strategy of surgery, radiation and/or chemotherapy. Some respond well, while a large proportion do not, mostly because of the heterogeneity of the disease and lack of personalized molecular targeted therapies. Additionally, despite decades of research, we are still unable to predict which invasive cancers will relapse/metastasize, and how to restrict the use of toxic chemotherapy to those that need it the most, and spare others. We have recently identified a new protein that is used by tumor cells to invade and spread. This protein, named GIV, is able to integrate and simplify signaling downstream of multiple types of cancer causing proteins. Like a computer chip, numerous signals converge onto the protein like a central hub, and the cell can modify how signals are emitted from it by modifying the expression and functions of this protein. Therefore in my project I sought to reengineer this protein chip, by altering its protein sequence, so that the signals that are delivered to it are used to arrest the growth or destroy the cancer cell. I also propose to screen for drugs that will interfere with the ability of this protein to transmit its signals. And finally, I plan to test the level of expression of this protein in breast tumors and in the cancer cells shed from the tumor that are already in circulation, and see if high expression of our protein can predict which patients have aggressive form of the disease that is likely to spread and cause death. This study has many impacts, but most important of them all is that if we can establish GIV as a new target for therapy, it can potentially reduce the mortality from invasive breast cancer and offer a target in TNBCs, a subset that currently has no good targeted therapies. Demonstrating that signaling from multiple receptors can be funneled through this protein would change the way we approach the decision and regimen for cancer chemotherapy. Our study will provide critical proof-of-concept data that targeting GIV, a central hub will permit us alter cellular signaling downstream of multiple cancer causing proteins. This is conceptually superior to current chemotherapies because it will circumvent some types of therapy resistance. More importantly, because not all tumors express this protein, its presence or absence in tumors could guide the decision of whether annihilation of this hub would be an effective therapeutic strategy in that given patient. Thus, our studies have the potential of defining a new portal for personalized therapy in patients with breast cancers.