



**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.

Pathways and Barriers for Breast Cancer Patients in Salvador: An Assessment of the Breast Cancer Situation from Screening to Treatment

Investigator(s): Lapa Monteiro, Maria Do Carmo

Lead Organization: Viva Maria

Grant Mechanism: Global Strategy Programs

Grant ID: CAT14HSRBR02

Public Abstract:

The study aims to document the patient's journey around the breast cancer continuum of care from screening to diagnosis, treatment and follow-up care; and to identify the available resources and areas of opportunity for good and quality breast cancer care. This comprehensive assessment will be essential to establishing a baseline of the available infrastructure and quality of service delivery in public health services in Salvador de Bahia, Brazil. The study is being conducted by Viva Maria, a nonprofit organization native to Salvador and founded by a breast cancer survivor.



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Barriers, Needs and Opportunities in the Breast Cancer Continuum of Care in Women Living in Rural Communities and Indigenous Communities

Investigator(s): Maria Roquebert

Lead Organization: Geinsa Gestoria Integral

Grant Mechanism: Global Strategy Programs

Grant ID: CAT14HSRPAN02

Public Abstract:

This is an analysis of the breast cancer continuum of care in four provinces of Panama aimed at understanding the factors that determine whether women enter the breast cancer continuum of care, and the barriers that prevent women from completing the continuum. The assessment will focus in women in areas outside of Panama City and indigenous communities that face unique challenges to access breast cancer care beyond medical factors. The study will look at health care system factors within the primary, secondary and tertiary care levels, as well as at community level.



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Diagnosis of the quality, infrastructure and barriers related to Breast Cancer (BC) Care Programs in the Metropolitan Area of Guadalajara (MAG).

Investigator(s): Laura Chavez

Lead Organization: Fundacion Mexicana para la Planeacion Familiar, A.C. (MexFam)

Grant Mechanism: Global Strategy Programs

Grant ID: CAT14HSRMEX02

Public Abstract:

This study conducted by Fundación Mexicana para la Planeación Familiar A.C. will perform a diagnosis of the quality, infrastructure and barriers related to breast cancer care programs in the Metropolitan Area of Guadalajara (MAG). The objective of this assessment is to understand not only the effective ways in which women enter the breast cancer continuum of care, but also the specific health system issues, barriers and needs that delay a woman's transition through the continuum of care, affect the quality of care or prevent a woman from completing the cycle of care.



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Replicating Success: The Chicago Model to reduce racial disparities in breast cancer mortality.

Investigator(s): Ann Marie Murphy, Ph.D.

Lead Organization: Metropolitan Chicago Breast Cancer Task

Grant Mechanism: Community Health/Special Grant

Grant ID: CHGR15CHIBCTF

Public Abstract:

The Metropolitan Chicago Breast Cancer Task Force (the Task Force), through its various programs, including the Chicago Breast Cancer Quality Consortium (the Consortium) has established innovative, well defined methodologies for the ecological assessment of area breast care resources, variation in mammography quality, breast care needs and barriers or facilitators to optimal breast care quality at the healthcare systems level, particularly for women of color. These programs were established to analyze Chicago's large and growing racial disparity in breast cancer mortality and devise interventions to reduce and eventually eliminate this disparity. In addition to the documented success of some of our interventions, a recent analysis of the breast cancer mortality trends in Chicago showed, for the first time, a decrease in the disparity between Black and White women [1]. Thus the Chicago model shows promise as a means for understanding root causes of a location's disparity with a goal of positively intervening.

Susan G. Komen funding will allow the creation of a platform for disseminating this evidence-based success through a variety of means. Possible dissemination methods may include roundtables in cities with high disparities, webinars, or other presentations designed to engage interested participants in a discussion around disparities in breast cancer outcomes and to develop a plan of action, using lessons learned from Susan G. Komen's investment in the Chicago Model. The project will utilize the knowledge gathered by the Task Force over the past 6 years and test a pilot replication site so as to transform the Task Force's work into a rigorous, replicable methodological framework for analysis of any location with breast cancer disparities understanding that each location will vary in its environment and able to stimulate tailored solutions to address the challenges of each specific location with high breast cancer disparities.

The project will begin by choosing an initial replication pilot site and establishing a community wide advisory board with an on the ground team to implement the assessment. Intensive training would be provided by Consortium staff. Data collected would be analyzed by the Consortium so that direct comparisons can be made to the Chicago data. As additional funding becomes available, additional locations could join the replication efforts.



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Implementing breast cancer care efficiency in Zambia through specialized health provider training and health evaluation of patient outcomes

Investigator(s): Groesbeck Parham, M.D.

Lead Organization: University of North Carolina

Grant Mechanism: Global Strategy Programs

Grant ID: GSP15UNC002

Public Abstract:

The project is a collaboration between UNC and the IARC to (1) develop a training program for health care providers to efficiently scale breast cancer awareness, screening, and diagnosis and (2) evaluate the impact of the training on breast cancer outcomes. The training is focused on seven critical components of the breast cancer continuum of care: health promotion, clinical breast examination for down staging disease, on-site ultrasound and ultrasound-guided biopsy of palpable breast masses, point of care touch preparation cytology of breast core needle biopsies, psychosocial counseling, and surgical training. The impact of the training on breast cancer outcomes will be assessed through patient interview at diagnosis and follow-up of women using a mobile health-based patient navigation platform. The evaluation will assess whether referral times are shortened, whether this impacts on earlier stage at diagnosis, and thereafter whether it improves survival outcomes. The breast cancer training will be led by Groesbeck Parham, in collaboration with Kennedy Lishimpi and CDH, UTH and CAPRAZ. The outcomes assessment by Valerie McCormack at the IARC, and the IARC team. Valerie, together with Isabel dos Santos Silva from the London School of Hygiene & Tropical Medicine are the PIs of the African Breast Cancer Research Network Disparities in Outcomes program (ABC-DO; see <http://abc-do.iarc.fr/backgroundaims/backgroundaims.php>), a Komen funded study that commenced this year on breast cancer outcomes in several African countries. Valerie and Isabel have the study set up and running in three countries (Namibia, Uganda, Nigeria); hope to start soon in the fourth, South Africa; and have agreed to form a further site in Zambia that will serve to evaluate the effectiveness of the training. This is a unique opportunity to train health professionals in breast cancer and also strengthen referral systems and patient navigation.



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Disseminating BHGI guidelines in a Knowledge Summary format among policy stakeholders in Peru, a Middle-Income Country

Investigator(s): Benjamin Anderson, M.D.

Lead Organization: Fred Hutchinson Cancer Research Center

Grant Mechanism: Komen Scholars

Grant ID: SAC150001

Public Abstract:

While high income countries (HIC) have well-developed health services, many low and middle-income countries (LMIC) have limited resources allocated to healthcare. This impacts women's health in very concrete ways. Eighty percent of women diagnosed with breast cancer in the U.S., live at least 5 years after their cancer diagnosis, and many live much longer. In comparison, women living in LMICs have much lower survival rates – only 20-60% (depending on the country) of women are alive 5 years after diagnosis of breast cancer. Why does this difference exist? Many HICs have early detection programs for breast cancer, such as mammography, which aim to detect cancers at an early stage in their development when they are more easily treated. Unfortunately, many LMICs lack financial resources to allocate to similar programs. Women who aren't screened regularly have breast cancers diagnosed at later stages when the cancer has spread, making it harder to treat, and reducing women's chances of survival. How can we change outcomes for women in LMICs? One option is to implement breast cancer early detection methods that are less expensive, but equally effective. For example, mammography requires specialized equipment and training and women often have to travel long distances to mammography centers. An alternative example of an early detection method might be clinical breast examination (CBE), where a trained health-care professional examines women's breasts using a standardized protocol. Results have shown that CBE can successfully down-stage breast cancer– i.e. more women are diagnosed at an earlier stage. Over the past 12 years, the Breast Health Global Initiative (BHGI) has been developing guidelines for early detection, diagnosis and treatment of breast cancer in LMICs. These guidelines are stratified by available resources: for example, a HIC might use mammography and ultrasound; LMICs might promote breast awareness and CBE for screening, which would be a better use of limited resources in the target country. In 2014 using Komen funds, the BHGI, NCI, Pan American Health, and UICC collaborated to develop Knowledge Summaries (KS). The KSs are designed to educate health policy makers and patient advocates, among others, on what type of early detection methods are available, and what might be appropriate to different countries.

We propose to test these KSs as a tool for communicating concepts of resource stratification for early detection of breast cancer in a target audience of policy stakeholders including health policymakers, health administrators and breast cancer advocates in Peru, a LMIC which lacks an early detection program and where the incidence of breast cancer is increasing and 40% of women present with late-stage disease.

We hypothesize that the KSs will (1) increase policy stakeholders' knowledge of breast cancer early detection methods; (2) allow them to identify those methods that are more appropriate to LMICs; and (3) become aware of BHGI as a tool for developing resource-stratified early detection methods appropriate for Peru. We will also assess participants' perception of KSs' utility, ease of use and ability to inform target audiences. If these KSs are an effective tool for communicating these concepts to LMIC policymakers, they can be used to guide selection and implementation of effective early detection methods that their economies can afford. This will have a direct impact on the number of women accessing early detection methods, thus improving outcomes for women.



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Examining the role of cholesterol metabolites on the estrogen receptor signaling pathway

Investigator(s): Kimberly Blackwell, M.D.

Lead Organization: Duke University

Grant Mechanism: Komen Scholars

Grant ID: SAC150063

Public Abstract:

There are increasing associations between obesity and cancer, particularly estrogen receptor positive breast cancer, but the reasons for this are unclear. A leading hypothesis is that obesity is linked to estrogen receptor positive breast cancer through high cholesterol and high levels of cholesterol byproducts. A recent breakthrough paper in *Science*, showed that higher levels of cholesterol byproducts were associated with more aggressive breast cancers. They also found that in the presence of increased amounts of cholesterol, breast cancers were more likely to be resistant to standard treatments. These interesting findings have never been evaluated in human breast cancer patients.

We propose a study of 12 breast cancer patients on anti-hormone treatments for their estrogen receptor positive breast cancer to evaluate the total cholesterol and cholesterol byproducts in their blood prior to anti-cholesterol treatment and then at three time points on anti-cholesterol treatment. Additional studies on pre-treatment breast cancer biopsies in the laboratory will provide information about the characteristics of the tumor including levels of cholesterol byproducts, tumor aggressiveness, and gene expression. We would then have each patient undergo two additional biopsies of the tumor to repeat these same tests while on anti-cholesterol treatment. We will evaluate the optimal dose of rosuvastatin, the anti-cholesterol medication, the safety of rosuvastatin in these patients, and, with the blood work and tumor studies, determine if there are ways of predicting which patients would benefit from this treatment the most. We believe that estrogen receptor positive breast cancer patients will respond better to standard anti-hormone treatment while on anti-cholesterol treatment. We believe that rosuvastatin is a safe, inexpensive treatment with few side effects and it is taken by mouth as a daily tablet, unlike most cancer treatments.

This project is particularly interesting because anti-cholesterol medications, such as rosuvastatin, are inexpensive and widely available. Therefore, this study could have immediate clinical impact and rapidly provide better treatment options for breast cancer.



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Biomechanical profiling as a biomarker for breast cancer progression

Investigator(s): Gerard Blobel, M.D., Ph.D.

Lead Organization: Duke University

Grant Mechanism: Komen Scholars

Grant ID: SAC100002

Public Abstract:

The normal cellular functions of breast epithelial cells are controlled by a family of related proteins that make up the transforming growth factor-beta (TGF- β) superfamily. The TGF- β superfamily normally inhibits breast cancer formation. However, most human breast cancer cells become resistant to these tumor suppressor effects. We have demonstrated that most human breast cancers lose expression of one of the proteins on the cell surface that binds TGF- β superfamily proteins, the TGF- β receptor, T β RIII. When breast cancer cells spread, they often stop appearing like, acting like and expressing proteins like normal epithelial cells, instead appearing like, acting like and expressing proteins like cells that make up connective tissue in the body in a process called epithelial to mesenchymal transition (EMT). The TGF- β superfamily and T β RIII both have a role in EMT, and EMT appears to have an important role in the progression of breast cancer from localized cancer to metastatic cancer. While we know that the ability of breast cancer cells to move and invade in the laboratory is a good measure of how aggressive an individual's breast cancer might be, these studies take hours to days to perform. More rapid measures that could predict how an individual's breast cancer will behave are needed to make better and more individualized treatment decisions. One potential measure is to examine the stiffness of the cell and the cell's outer membrane. With our collaborators, we have developed a system to measure these biophysical properties and have used this system to assess the role of T β RIII in cancer, defining a role for T β RIII in regulating the stiffness of cancer cells relative to normal epithelial cells. We now propose to investigate whether loss of T β RIII expression during breast cancer progression is responsible for the decrease in cancer cell stiffness that allows the breast cancer cells to become more motile and invasive. We will address this question by (1) measuring the properties of breast cancer cells before and after EMT, including their ability to move and invade and then correlating that with the stiffness of the cancer cells; (2) optimizing our ability make these same measurements on specimens from mouse models of breast cancer; and (3) examining the stiffness of cancer cells from these mouse models and correlate these biophysical properties with more standard biomarkers for breast cancer behavior and clinical outcomes. Our ultimate goal is to use these measurements on breast cancer tissues to assess how breast cancers form, how each individual's breast cancer is different and which therapies might work best. These biophysical measurements could also create new, rapidly obtained biomarkers to diagnose or decide how to treat breast cancer patients on an individual basis.



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Analysis of the integration of cell-cell adhesion & Yap networks regulating tumor growth & invasion

Investigator(s): Joan Brugge, Ph.D.

Lead Organization: Harvard Medical School

Grant Mechanism: Komen Scholars

Grant ID: SAC130057

Public Abstract:

Interactions between breast epithelial cells play critical roles in regulating cellular processes that are critically important during tumor initiation and progression, e.g. contact inhibition, invasion, dissemination, metastasis. These interactions are misregulated in a high percentage of breast cancers, most prominently in lobular carcinomas where loss of the major receptor for cell-cell interactions, E-cadherin, is associated with almost all cases of this subtype and is a parameter in its clinical diagnosis. However, at the molecular level, E-cadherin-mediated cell-cell adhesion is much less understood than other adhesion processes such as cell matrix adhesion. Emerging new evidence indicates that E-cadherin feeds into the control of the recently identified pathway referred to as the Hippo-LATS pathway. Disruption of this pathway in model systems leads to oncogenic transformation in culture and tumorigenesis in mice. This pathway regulates organ size during development via regulation of two proteins called YAP and TAZ. Both cadherin and YAP/TAZ pathways have independently been implicated in contact inhibition of cell proliferation, yet the details of how these pathways integrate remain unclear. Our proposed research will characterize key aspects of E-cadherin mediated cell-cell adhesion and YAP/TAZ pathways and their crosstalk. Using combined proteomics and siRNA approaches we have identified multiple novel proteins that regulate cell-cell adhesion, four of which are strongly dysregulated in triple negative breast cancers. We are currently characterizing the novel adhesion regulators to define mechanisms whereby they regulate cell-cell adhesion and to establish how their alterations in tumor cells affect cancer invasion. We have also defined a signature associated with YAP in lobular carcinomas and are evaluating YAP regulation of this signature and the importance of this signature in tumor cell growth and survival. In addition, if we validate YAP/TAZ as targets in lobular carcinoma, we will collaborate with others to promote development of therapeutic strategies to inhibit YAP/TAZ in treatment of lobular carcinoma.



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Hereditary breast cancer: cause and effect

Investigator(s): William Foulkes, M.D., Ph.D.

Lead Organization: McGill University

Grant Mechanism: Komen Scholars

Grant ID: SAC110008

Public Abstract:

Hereditary breast cancer is an important type of breast cancer because it offers the possibility of prevention in the setting of a high prior risk. We are conducting a broad research program to investigate hereditary breast cancer, starting from a discovery study of new genes that might help us to evaluate risk of breast cancer to a much more "clinical" project where we implement new testing protocols for women with breast cancer, via a bench-based study of how some of the known breast cancer susceptibility genes cause breast cancer. In this way, we tackle not only basic issues, but also practical questions relevant to women with breast cancer. If we can identify women at risk for breast cancer before they develop it, we have a real chance to reduce mortality from breast cancer by the most effective means known — preventing the incidence of breast cancer.



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Stress reduction in breast cancer survivors: intervention development and evaluation

Investigator(s): Patricia Ganz, M.D.

Lead Organization: University of California, Los Angeles

Grant Mechanism: Komen Scholars

Grant ID: SAC110009

Public Abstract:

During the past 6 months we have tried to evaluate a psychosocial intervention program for women living with metastatic breast cancer. In the process of attempting to recruit women for the study, we identified a number of barriers to program delivery and have now stepped back to re-assess how best to meet the needs of this target population. We are working closely with the Los Angeles Komen Affiliate and with this target population to develop and refine an intervention that is appropriate and will meet their needs. We are also collaborating with advocates and other scientists to write about the needs of this group of breast cancer survivors so that more resources can be used to address their concerns as they now live for an extended time with metastatic disease. The latter will take the form of a written commentary in a high profile peer-reviewed cancer journal. Secondly, we now have an opportunity to take what was learned in our earlier clinical trial testing a mindfulness meditation intervention in younger breast cancer survivors and move this into a multi-site clinical trial supported by the Translational Breast Cancer Research Consortium (TBCRC). Younger breast cancer survivors are a vulnerable group of women who are at risk for recurrence or second cancers and finding strategies to reduce their stress may improve their outcomes. We are now going to see if the mindfulness intervention program and a health education program can be delivered at sites outside of UCLA, and tested for their benefit on stress reduction and improvement in well-being in comparison to a group of women who will receive these interventions at a later date. The current Komen Scholar funding has allowed the research team to rapidly develop this protocol. This will allow extension of the research findings we have reported on earlier that were funded by this grant.



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Toxicities of breast cancer treatment

Investigator(s): Sharon Giordano, M.D.

Lead Organization: MD Anderson

Grant Mechanism: Komen Scholars

Grant ID: SAC150061

Public Abstract:

The overall objective of this proposal is to evaluate the comparative toxicities of treatments for breast cancer. Clinical trials have generated essential information on the 'efficacy' of new therapies. However, once new therapies are approved, their effectiveness and toxicity in real world populations is less clear. Patients who participate in clinical trials are highly selected: patients who are older, are minorities, have comorbidities, and who are at higher risk of side effects are under-represented or excluded from trials. Because of these strong selection factors, we hypothesize that the actual toxicities experienced by patients may be substantially higher than the data from clinical trials would suggest. Women with breast cancer have many possible treatment options with similar efficacy, but the risk of hospitalization and death may differ substantially between these treatments, especially in women with other co-existing illnesses. Concerns over the real-world toxicity profile of systemic therapies are worsened by the high costs of new therapies, to the extent that "financial toxicity" has become a new term in cancer research. In this proposal, we will evaluate treatment-related toxicities in patients with breast cancer, including comparisons between standard adjuvant chemotherapy and metastatic regimens and toxicity due to medication interactions. In addition, to investigate the comparative risks of therapy, we will also study the financial toxicity of therapy for breast cancer, quantified by the out of pocket payments for different therapeutic regimens and types of health plan. Furthermore, the financial burden from cancer treatment may affect adherence to medications for other chronic conditions. Thus, we will also explore the association of out of pocket payments for cancer treatment with adherence to antihypertensive and lipid lowering medications. If women are less adherent to these chronic medications due to the cost of breast cancer treatment, they may experience worse survival. Collectively, these studies will cover a diverse population of older and younger breast cancer patients, with a wide array of insurance plans and generosity of coverage. The findings from this study may be used to help prevent unnecessary toxicity, including hospitalizations and death, experienced by women with breast cancer. In addition, this study will provide insight into the financial burden faced by women with breast cancer and how this financial burden impacts the use of other medications that are known to improve survival among women with breast cancer.



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Muscle weakness associated with breast cancer bone metastases

Investigator(s): Theresa Guise, M.D.

Lead Organization: Indiana University

Grant Mechanism: Komen Scholars

Grant ID: SAC130013

Public Abstract:

Muscle weakness is a major contributor to impaired quality of life in patients with advanced breast cancer and is an extremely common public health problem; the reason for the weakness is unknown and no effective therapy that improves muscle function in breast cancer patients exists. The overall hypothesis is that breast cancer-associated muscle weakness is due to inflammation-induced molecular changes in muscle that cause impaired muscle contraction. This hypothesis will be tested using mouse models of advanced breast cancer which has metastasized to bone. Specific drugs directed against the inflammation and its consequences on the muscle weakness will be tested in these models and if successful will form the basis for new clinical studies to test these agents in women with advanced breast cancer. Thus, results from this proposal could lead to major improvements in the health and quality of life for breast cancer patients through the development of highly innovative therapies to improve muscle strength. Thus, the unique and novel findings addressed in this proposal raise the possibility of a completely new therapeutic approach to breast cancer-associated muscle weakness which would revolutionize cancer treatment.



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Using breast tissue expression patterns to inform our understanding of breast cancer risk factors

Investigator(s): Susan Hankinson, Sc.D.

Lead Organization: Brigham and Women's Hospital and Harvard Medical School

Grant Mechanism: Komen Scholars

Grant ID: SAC110014

Public Abstract:

Breast cancer results from the interaction of lifestyle, genetic, environmental and tissue-specific factors. This complex process is multi-step and takes years to develop. A number of lifestyle factors have been consistently linked to increases (e.g., alcohol intake, postmenopausal obesity) or decreases (e.g., physical activity, premenopausal obesity) in risk of breast cancer. However, how these increases (or decreases) occur at the cellular level is largely unknown. Several primary pathways have been identified (for example, obesity increases estrogen exposure, which in turn increases breast cancer risk) but there are likely multiple other pathways also playing a role. We believe that by looking at the correlation between breast cancer risk factors and gene expression in breast tissue, we may learn what some of these other pathways are. In the current project, we propose to examine detailed RNA expression profiles in both breast tumors and normal breast tissue collected from a subset of premenopausal women in the Nurses' Health Study II, as well as similar profiles derived from a subset of postmenopausal women from the Nurses' Health Study.

We will link these expression profiles to several lifestyle exposures assessed prior to cancer diagnosis. For all samples, the NuGen/Affymetrix Human Transcriptome Array platform will be utilized; in total we expect to have 600-650 matched pairs (tumor plus adjacent normal). All participating women have provided detailed data on breast cancer risk factors. Specifically, we propose to assess physical activity, vitamin D, obesity in premenopausal and postmenopausal women, and alcohol intake. Studies conducted to date suggest that physical activity reduces the risk of both premenopausal and postmenopausal breast cancer, and improves survival in women with breast cancer. Our project should help us identify why this happens. Studies also indicate that vitamin D may play a role in breast cancer risk, with the most convincing evidence coming from animal and laboratory studies; evidence from studies in humans is inconsistent. Increased postmenopausal obesity has consistently been shown to be associated with both increased risk of postmenopausal breast cancer as well as decreased breast cancer survival. This increased risk is likely in part through weight gain increasing estrogen levels, a well-established cause of breast cancer, but other factors (e.g., increased inflammation) also may play a role. Interestingly, premenopausal BMI consistently shows an inverse association with breast cancer risk. The reason for this association is unknown, but will be explored as part of this project. Finally, alcohol is known to increase the risk of breast cancer, and although multiple mechanisms have been proposed (e.g., increased estrogen or androgens, increases in oxidation), none have been confirmed. By identifying differences in RNA expression profiles in breast cancer as well as normal breast tissue associated with these breast cancer risk factors, we will provide new insight into biologic mechanisms underlying these exposures. Further, the identified expression signatures in normal breast and breast cancer may represent new therapeutic targets for breast cancer prevention and treatment.



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Novel devices to capture circulating tumor cells

Investigator(s): Daniel Hayes, M.D.

Lead Organization: University of Michigan

Grant Mechanism: Komen Scholars

Grant ID: SAC150015

Public Abstract:

Breast cancer spreads from the breast to distant organs, where it develops metastases, which are the primary cause of mortality. The metastatic process requires that the breast cancer cells escape from their site of origin and travel in the blood system to the distant organs. When these cells are in transit, they are called “circulating tumor cells,” or CTC. We and others have shown that the presence of CTC in the blood of patients with early breast cancer, or in patients with already established metastatic breast cancer, is associated with worse prognosis – in other words, the time to development of distant metastases, the time to progression if the patient already has metastases, and the time to mortality, is shorter for those patients with elevated vs. not elevated CTC levels. We have also shown that patients who do not reduce their CTC after one cycle of first-line chemotherapy appear to not be responding to that treatment, and appear not to respond to other types of chemotherapy either, and that their survival time is quite poor (median is approximately 13 months).

These data suggest that just counting CTC is not sufficient to direct patient care. Rather, CTC might serve as a “liquid biopsy,” permitting detailed characterization for markers that might predict benefit from “targeted” therapies, the goal of “Precision Medicine.” CTC might have several advantages over true biopsies. True biopsies are invasive, expensive, and difficult to perform repeatedly. Further, a biopsy only provides information about the specific site from which the tissue was drawn, while CTC in blood presumably come from all the sites, and therefore provide a more comprehensive portrait of the patient’s entire tumor burden.

Recently, our laboratory and several other investigators, have shown that CTC can, indeed, be characterized for expression of important breast cancer markers, such as estrogen receptor, BCL2, HER2, Ki67, apoptosis, and markers of epithelial-mesenchymal transformation (EMT), which appears to be an important step in metastases. CTC can also be characterized for genetic abnormalities that might predict specific therapeutic responses.

However, currently available methods to capture CTC are limited to a relatively small volume of blood (3-30 milliliters) which is drawn at a specific time. We have developed a prototype CTC capture system that is placed into a subject’s venous system (like an intravenous catheter) and stays there for several hours. Blood will be diverted from the vein into a capture device that the patient wears on her arm and then back into the patient’s venous system.

We hypothesize that this system will provide us with many more CTC for characterization, and that these CTC will be more representative of the patient’s cancer than is a single blood draw. We will test this hypothesis in three specific aims: 1) we will refine the prototype system and test it in a canine (dog) cancer-bearing model; 2) we will determine if CTC captured in this system can be characterized (we will determine the genetic and protein expression status) and if they can be cultured in vitro; and 3) we will conduct pilot trials in patients with metastatic breast cancer.



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MR imaging phenotypes of breast cancer

Investigator(s): Nola Hylton, Ph.D.

Lead Organization: University of California, San Francisco

Grant Mechanism: Komen Scholars

Grant ID: SAC110017

Public Abstract:

MRI is an information-rich imaging modality that produces clear anatomic representation of soft tissue and also reflects underlying tissue biology. The MRI signal can be sensitized to tissue properties including water/lipid content, vessel density and blood flow, water diffusion and cellularity. These properties can be characterized three-dimensionally over the entire breast. The standard method for performing MRI of the breast uses a contrast-enhanced technique to highlight areas of tissue with increased vascularity, a hallmark of malignancy. Contrast-enhanced MRI, using an injected gadolinium-based contrast agent, has shown greater sensitivity for breast cancer detection and better ability to demonstrate the extent of cancer in the breast than mammography and ultrasound. However, the low specificity of contrast-enhanced MRI of the breast limits its diagnostic utility. While most research is focused on improving the diagnostic specificity of dynamic contrast enhanced (DCE) MRI for cancer detection, there is considerable additional information contained in MR images that we do not currently exploit. The goal of this project is to develop high-resolution non-contrast enhanced methods for characterizing breast tissue, and to use these methods in conjunction with standard DCE-MRI to study the relationship between imaging phenotypes and clinical, molecular and genomic factors associated with breast cancer and breast cancer risk. We hypothesize that functional MR imaging approaches will improve the ability to characterize breast tissue heterogeneity leading to non-invasive methods for both breast cancer diagnosis and risk assessment. This project will develop high resolution approaches for evaluating breast tissue T2 (intrinsic relaxation parameter), diffusion and perfusion, and these techniques will be used in combination with standard DCE-MRI to explore the biologic heterogeneity of breast tumors and surrounding stromal tissue.



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Uncovering mechanisms contributing to metastasis and to drug resistance in breast cancer

Investigator(s): Nancy Hynes, Ph.D.

Lead Organization: Friedrich Miescher Institute for Biomedical Research

Grant Mechanism: Komen Scholars

Grant ID: SAC110041

Public Abstract:

Metastasis is the major cause of breast cancer-related death. If a woman presents with a non-invasive tumor that has not spread to the lymph nodes (LN), she has close to a 100% chance of being alive at 5-years. However, if the tumor has spread to the LNs or is present in distant organs her chances of being alive at 5-years go down to ~ 80% and 25%, respectively. Thus, we need to know more about the process of tumor dissemination and metastasis. Our hypothesis is that by further molecular analyses of breast cancer metastasis we will be able to identify new approaches to prevent this process.

Metastasis is a complex process whereby tumor cells acquire invasive properties and colonize distant sites. Our experimental plan has two aims. In the first aim, we will use models of breast cancer metastasis in the bone in order to test the effect of blocking the well-known Jak/Stat signaling pathway. Using bone metastasis models, in the past three years, our lab has shown that this pathway is consistently active in the bone environment. Jak is a tyrosine kinase and importantly, Jak kinase inhibitors, e.g., Ruxolitinib, are currently being tested in clinical trials. Thus, we hope that by analyzing different bone metastasis models for breast cancer, we will see if blocking this kinase has an impact on tumor growth in the bone.

Our second aim is to block metastatic spread using a novel antibody that targets an extracellular serine protease inhibitor (serpin), called PN-1. My lab showed some years ago, using a metastatic breast cancer model, that loss (knock-down) of PN-1 leads to a block in the metastatic spread from the primary tumor to the lungs (Fayard et al 2009). In the past few years we showed that the PN-1 blocking antibody (Ab11) prevents PN-1 from binding its receptor, named LRP1. The antibody has been tested in vivo in different metastatic breast cancer models. In all cases we found significantly fewer lung metastases in antibody-treated mice. Using intravital multiphoton imaging directly on the tumors in living animals, we found that Ab11 treatment has a dramatic effect on the tumor environment; we observed a decrease in blood vessel leakiness and a restoration of the collagen matrix surrounding the tumor, both of which could contribute to preventing metastatic spread. Our hypothesis is that by more closely examining the tumor environment from control and Ab11 treated mice we will uncover the mechanism by which metastatic dissemination is blocked.

The research we are proposing to accomplish in the next year will be important for two reasons: first we hope to gain information on the impact of Jak inhibitors on tumor growth in the bone. These inhibitors are now in early stages of clinical development and are being tested in breast cancer patients whose tumors show phosphorylation of Stat3, a transcription factor that is a direct Jak substrate. Second, we hope to uncover the mechanism underlying the anti-metastatic activity of the PN-1 blocking antibody.



**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.

Mechanisms of endocrine action: ER-induced apoptosis and HRT-associated breast cancer

Investigator(s): V. Craig Jordan, Ph.D.

Lead Organization: UT M.D. Anderson Cancer Center

Grant Mechanism: Komen Scholars

Grant ID: SAC100009

Public Abstract:

There is currently an enormous amount of interest in the new biology of physiological estrogen action since the publication of the results of the Women's Health Initiative (WHI) Trial of the impact of long term conjugated equine estrogen (CEE) alone as hormone replacement therapy for hysterectomized postmenopausal women (Anderson et al, Lancet Oncol 2012; 13:476-486). Remarkably, there was a significant decrease in the incidence of invasive breast cancer and this decrease was maintained for five years after stopping CEE treatment. These paradoxical clinical results have now opened a window of opportunity by using laboratory models to discover and amplify the mechanisms of estrogen-induced apoptosis to aid more women to either prevent breast cancer or to control breast cancer growth following the failure of conventional therapies. The results of the WHI are consistent with an emerging body of laboratory evidence that is currently deciphering the molecular mechanism of estrogen-induced apoptosis and applying this knowledge to the treatment of breast cancer following the failure of multiple anti-hormone therapies (tamoxifen or the aromatase inhibitors). This evidence has recently been summarized (Jordan Endocr Relat Cancer, 2015 Feb;22(1):R1-R31). Our current project is focused entirely on discovering the molecular mechanism of estrogen-induced apoptosis in our laboratory model systems with the ultimate goal of enhancing tumor responsiveness from about a 30% response rate to more than 50%. It is our intention through the study of molecular mechanisms in the laboratory, to amplify breast cancer responsiveness to physiological estrogen to trigger apoptosis and aid increased survivorship from breast cancer. If we can discover the molecular mechanism whereby estrogen triggers apoptosis through the breast cancer cell estrogen receptor (ER), we may in fact be able to induce cancer cell death with an entirely new group of medicines. Additionally, our work is now able to provide an explanation as to why combined CEE plus synthetic progestin (known as HRT) increases incidence in breast cancer in postmenopausal women. (Sweeney, et al. Cancer Res, 2014, 74:7060-8). We plan to advance work and create a safe, cancer-free HRT for postmenopausal women.



**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.

Molecular and clinical characterization of breast cancer heterogeneity in Israel

Investigator(s): Bella Kaufman, M.D.

Lead Organization: Chaim Sheba Medical Center

Grant Mechanism: Komen Scholars

Grant ID: SAC110019

Public Abstract:

Breast cancer is composed of different diseases which vary according to the origin of the cancer cell types as well as their location. Breast cancer originates and progresses as a result of molecular processes. Our aim in this study is to understand the molecular processes that are the basis of breast cancer development, progression, metastasis and resistance to therapy.

As cancer progresses, new mutations (genetic alterations) occur and accumulate in the cancer cells. Our working hypothesis is that early identification of such genetic signatures will shed light on tumor evolution and will lead to the development of rationally targeted and individualized therapy.

We address several clinically relevant questions and plan to detect and analyze the genetic differences underlying the following processes:

1. To understand the molecular mechanism(s) of the development of invasive cancer (IDC – invasive ductal carcinoma) from locally confounded cancer (DCIS – ductal carcinoma in-situ). We propose to investigate tumor evolution by analyzing the mutational spectrum of a certain patient's tumors at different stages of disease progression.
2. Characterization of breast cancer evolution throughout the timeline of pre-operative (neo-adjuvant) chemotherapy. We plan to identify expression signatures that predict recurrence at the biopsy stage. Overall, in addition to the contribution of this study to the improvement of breast cancer prevention and management, it also has the potential to contribute to cancer study in general. The produced data from these studies have the following potential: 1) providing the research community with a basic understanding of the tumorigenic process, and 2) detecting a set of potential biomarkers involved in these processes. Identifying the cases prone either to resist therapy, cause tumor progression, or recur, would justify more aggressive therapy while avoiding unnecessary morbidity. On the other hand, identification of low-risk patients can help reconsider the most appropriate treatment management, thus avoiding short- and long-term morbidities, as well as side effects undermining patients' quality of life.
3. The mechanism(s) leading to the significant difference in the response rate to treatment (pathological complete response) between young and older patients receiving pre-operative chemotherapy (neo-adjuvant).



**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.

Gene Discovery for Inherited Breast Cancer Using Next Generation Sequencing

Investigator(s): Mary-Claire King, Ph.D.

Lead Organization: University of Washington

Grant Mechanism: Komen Scholars

Grant ID: SAC110020

Public Abstract:

The discoveries of BRCA1 and BRCA2 changed breast cancer prevention and treatment in remarkable ways. It is now possible for women to learn if they carry cancer-predisposing mutations in BRCA1 and BRCA2, and if so, to take steps to prevent breast and ovarian cancer. One of our greatest frustrations is to discover that a family severely affected with breast cancer carries no detected mutation in any gene. In our studies of extended families at high risk of breast cancer, we have confronted this frustration many times. Our analyses of >800 severely affected families suggest that many mutations and genes for breast cancer predisposition remain to be found. Indeed, most severely affected families remain unresolved.

There are at least 18 genes with mutations responsible for inherited breast cancer. BRCA1 and BRCA2 are the best known, conferring extremely high risks of breast and ovarian cancer. Inherited mutations in TP53, CDH1, PTEN, and STK11 are associated with a high risk of breast cancer in the contexts of rare syndromes. Inherited mutations in several genes in pathways critical to genomic integrity confer 2- to 4-fold increased risks of breast cancer; that is lifetime risks of 20% to 50%. These genes include Abraxas, ATM, BARD1, BRIP1, CHEK2, PALB2, RAD51C, RAD51D, ATR, BAP1, CHEK1, and GEN1. Recommendations for care of women with mutations in these more recently characterized genes include increased surveillance, including tools such as MRI that are not offered universally.

In this Komen project, we will screen for novel mutations in the non-coding regions of breast cancer genes. Such mutations regulate when and where genes are expressed. The integration of high throughput genomics with information on regulatory elements with the genetic material and clinical information provided by our participating families provides an ideal opportunity to identify novel mutations and new mechanisms for inherited breast cancer.

We will identify regulatory mutations specifically from families severely affected with breast cancer. If successful, our results will allow preventive management strategies to be extended to many families for whom the genetic cause of breast cancer is currently unknown. This proposal has the potential to improve patient care in the next few years by yielding a more comprehensive genomic profile of breast cancer predisposition. The short-term goals are to better identify women at risk, and to allow closer surveillance. The long term goals are to contribute to the design of new prevention strategies and a better understanding of the mechanisms involved in breast cancer development.



**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.

Mechanism by which BRCA1 elicits a state of mammary epithelial differentiation control

Investigator(s): David Livingston, M.D.

Lead Organization: Dana-Farber Cancer Institute and Harvard Medical School

Grant Mechanism: Komen Scholars

Grant ID: SAC140022

Public Abstract:

We have generated results that suggest the existence of a new step in the process by which breast cancer develops in women with BRCA1 mutations. This step involves the function of a group of proteins: BRCA1 and another protein, BRG1, that is involved in the formation of normal organs. Our results from studying BRCA1 in normal mammary epithelial cells with BRCA1 mutations, predict that BRCA1 ensures the normal development of the human breast by maintaining the normal function of this complex. A breakdown in this process would likely support the development of additional mutations that may lead to malignancy. Our proposal is to test this hypothesis. Positive results would highlight the function of BRCA1/BRG1 complexes in normal mammary gland development and BRCA1-driven breast cancer suppression. Positive results would create opportunities for the discovery of novel BRCA1-based strategies leading to breast cancer prevention.



**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.

Combinatorial adaptive resistance therapy in breast cancer

Investigator(s): Gordon Mills, M.D., Ph.D.

Lead Organization: UT M.D. Anderson Cancer Center

Grant Mechanism: Komen Scholars

Grant ID: SAC110052

Public Abstract:

The ability to target HER2 with Herceptin or Lapatinib has greatly improved outcomes for patients with amplified HER2. Unfortunately, only a subset of breast cancer patients with amplification of HER2 benefit from therapies targeting HER2. We have new data that indicates that when cells are cultured in systems that mimic the growth of tumors in patients, resistance to targeted drugs is due to signals induced by the drug itself. The striking observation is that targeting the events induced by the drugs results in a massive death of the tumor cells. We call this ability to identify rational combinations of drugs ‘combinatorial adaptive response therapy’ or CART. We have explored CART with three drugs targeting the HER2 family (Iressa, Lapatinib and Neratinib). As a result, we discovered a number of possible drug combinations that could increase the activity of each of these drugs. We will explore this further to identify rational drug combinations that would increase the response of patients to HER2 targeted drugs.



**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.

Translating breast cancer genomics in the clinic

Investigator(s): Olufunmilayo Olopade, M.D.

Lead Organization: University of Chicago

Grant Mechanism: Komen Scholars

Grant ID: SAC110026

Public Abstract:

The unacceptable consequence of the marginalization of Africans and African Americans in science, reflected by their nearly complete exclusion from discovery research, has been the delayed delivery of important scientific advances - including technologies and treatments – to already vulnerable minority populations. Ironically, these are the populations most likely to benefit from these breakthroughs in science. As we know, black women die at a disproportionately higher rate from breast cancer than white women in the United States. In West Africa - the founder population of most African Americans - and for that matter in all sub-Saharan Africa, breast cancer is almost always fatal. In our study in Nigeria, we have found the majority of women presenting with a breast cancer diagnosis to be under 50 years of age and in the advanced stages of the disease. In another study from Barbados, a historically-isolated group with strong African ancestral origins, the reported incidence and mortality rates of breast cancer is the highest in the Caribbean. The significantly higher incidence of early-onset breast cancer in women of African ancestry is likely due to a correspondingly high prevalence of pertinent genetic risk factors.

To advance the field we need to further examine the specific etiology of breast cancer and its subtypes and the only way to do that is to collect more data. In our Nigerian Breast Cancer Study, we have previously recruited 1233 cases and 1101 controls in Nigeria. The University of Chicago Breast Cancer Study has recruited over 600 African American cases and 600 controls. Our goal now is to replicate our initial findings of risk factors associated with specific breast cancer molecular, or aggressive basal-like subtypes, in a larger cohort. Needed is a large-scale epidemiologic study in Ibadan, Nigeria from which we can use state-of-the-art Next Generation sequencing, genotyping, and computational biology to analyze its data. Through funding provided by the Susan G. Komen Foundation, we hope to expand our Nigerian Breast Cancer Study to collect 1500 additional cases and 1500 controls. This will help us delve further into the impact of genetic and non-genetic factors on breast cancer risk and its molecular subtypes. To date, we have made gains in the field through developing fruitful collaborations with other investigators studying African American and African Barbadian women for comparative analyses across geographic boundaries. We have a unique opportunity to study the contribution of genetic factors to the high incidence of early onset breast cancer and overrepresentation of triple negative breast cancer in the African Diaspora. With improved access to relatively inexpensive high throughput technologies, we are now in a position to complete a comprehensive genetic analysis in a large cohort of women of African ancestry from across the globe, with well documented phenotypes. With increased numbers, we can develop a high-risk screening protocol so that individuals identified as carriers of deleterious mutations in breast cancer susceptibility genes can be enrolled in a longitudinal follow up to examine whether the outcomes can be vastly improved through family-based interventions. Funds from the Susan G. Komen Foundation will be used to enhance our recruitment and to translate findings from the genetic analysis of this cohort into meaningful interventions that hold the most promise for reducing the high mortality associated with early onset breast cancer both here and abroad.



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.

SRC-3 “Delta” 4 directs ERBB2 signaling to promote the conversion of DCIS to invasive ductal carcinoma

Investigator(s): Bert O'Malley, M.D.

Lead Organization: Baylor College of Medicine

Grant Mechanism: Komen Scholars

Grant ID: SAC140027

Public Abstract:

SRC-3 is a protein that can function as an oncogene when it is overexpressed in breast cancer cells. It not only functions to promote breast cancer development but also participates in tamoxifen and chemotherapy drug resistance. We recently demonstrated that when we block the expression of SRC-3 in breast cancer cells, they are more sensitive to doxorubicin-induced death. In an effort to identify proteins that are downstream of SRC-3 that are responsible for SRC-3's oncogenic function, we identified TRAF4 (TNF receptor associated factor-4), as a protein that can promote cell resistance to cytotoxic stress. We observed that SRC-3 expression is inversely correlated with the expression of p53-regulated pro-apoptotic genes in breast cancers and further found that SRC-3 and TRAF4 overexpression diminished cytotoxic stress-induced upregulation of the tumor suppressor p53 protein. We also demonstrated that TRAF4 is overexpressed in the tumors of breast cancer patients who have received adjuvant chemotherapy and/or radiotherapy and hormone therapy after surgical removal of the tumor. Also linked with SRC-3 driven breast cancer cell growth is another protein called ERK3 that can drive cancer cell migration and invasion by stimulating the expression of MMP proteins that are responsible for breast cancer cell invasion. Little is known, however, about the upstream stimuli and activators of ERK3. To better understand the ERK3 signaling pathway, we collaborated with Dr. Jun Qin, director of the Proteomics core laboratory in our institution, to identify the interacting partners of ERK3 by immunoprecipitation of ERK3 protein complexes, followed by the mass-spectrometry analysis. A total of 566 candidates were identified. In addition, a recent study of signal transduction protein interaction networks by yeast-two-hybrid screening identified 160 interacting proteins for ERK3. Importantly, among these candidates identified by these two analyses, there are 126 in common. Consistent with our recent finding about ERK3's role in promoting cancer cell migration and invasion, top ERK3-associated network functions identified by the analysis include cellular assembly and movement, cell-to-cell signaling and interaction, and tumor morphology. The involvement of ERK3 signaling in cancer progression and metastasis is further indicated by the identification of top ERK3-associated biological pathways including RhoGDI signaling, TGFP/BMP signaling, serine synthesis, and VEGF signaling, which are all responsible for breast cancer progression. Here, we plan to investigate the roles of TRAF4 and ERK3 in driving breast cancer cell growth in greater detail. Specifically, we plan to investigate how SRC-3 coordinately regulates TRAF4 and ERK3 to block apoptosis and drive cell motility and invasion, leading to aggressive, therapy-resistant breast cancer growth.



**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.

Breast cancer in young women

Investigator(s): Ann Partridge, M.D.

Lead Organization: Dana-Farber Cancer Institute

Grant Mechanism: Komen Scholars

Grant ID: SAC100008

Public Abstract:

When young women are diagnosed with breast cancer, they are more likely to suffer both physically and emotionally than older women. Many prior studies have tried to evaluate the reasons for this in various groups of women; however, there are rarely enough young women in any given study to learn about their unique issues. Recognizing that there are substantial limitations to the prior research, and especially given that most studies have not had enough young women with details regarding their disease, treatment, and medical and psychosocial outcomes, we started a large prospective study focused on young women with breast cancer. We have been asking women since 2006 to participate in this research in an effort to learn more about breast cancer in young women so that we can help to improve how they do in both the short and long run, both medically and emotionally. To date, we have enrolled over 1,200 women in our ninth year of the study and we have evaluated many issues using information provided by the women today regarding their disease presentation and characteristics, fertility concerns, surgical decision-making, and distress, coping, body image, and sexual functioning in the year after treatment. As the cohort matures, we will be able to evaluate later outcomes as well as evaluate for unique tumor biology and genetics of this large cohort of young women. To our knowledge, this is the only study of its kind and successful completion of this project will uniquely advance our understanding of breast cancer in young women and elucidate areas to target for intervention which will lead to reductions in breast cancer morbidity and mortality in this vulnerable population.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Breast cancer cell sensitivity to radiotherapy in the presence of targeted therapies

Investigator(s): Lori Pierce, M.D.

Lead Organization: University of Michigan

Grant Mechanism: Komen Scholars

Grant ID: SAC110029

Public Abstract:

Currently, breast conservation therapy for patients with localized invasive breast cancer includes surgical resection followed by radiation therapy, with chemotherapy given to selected patients. While molecular prognostic tools, such as OncotypeDx, can be used to help guide decisions regarding chemotherapy in subsets of breast cancer patients, no similar tools exist to inform decisions regarding radiation therapy. Therefore, there is a clear need to identify the inherent radiation sensitivity of each patient's breast cancer, and to develop approaches of combining targeted drugs with radiation therapy for patients with aggressive tumors that have a high chance of local recurrence following radiation alone. To this end, we have previously generated a radiation sensitivity signature, named RadiotypeDx, in a series of laboratory studies assessing the expression of genes which can distinguish between radiation-sensitive and radiation-resistant breast cancer cell lines. In the current proposal, we now seek to assess the performance of this signature in clinical specimens from patients with breast cancer, by using previously published gene expression data collected from tumor samples from cohorts of breast cancer patients. In addition, we hope to evaluate for associations between radiation resistance, as predicted by RadiotypeDx, and breast cancer cell line sensitivity to hundreds of drugs, as an approach for discovering potential therapeutic strategies which may overcome radiation resistance. Lastly, we plan to test the top therapeutic strategies, as nominated from our analyses, in laboratory models of breast cancer. We believe that successful completion of this project will allow us to identify and confirm biological markers of breast cancer resistance to radiation, and to develop new strategies for increasing the sensitivity of aggressive breast cancers to radiation therapy. In doing so, we hope that this project provides a scientific foundation for our next generation of clinical trials in this area.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Triple negative breast cancer: subtypes, molecular targets, and therapeutic approaches

Investigator(s): Jennifer Pietenpol, Ph.D.

Lead Organization: Vanderbilt University

Grant Mechanism: Komen Scholars

Grant ID: SAC110030

Public Abstract:

Women with tumors that lack HER2 amplifications and estrogen or progesterone receptors, that are overrepresented in BRCA1 mutation carriers and in the African-American population, do not benefit from the current targeted therapies. These difficult-to-treat cancers are classified molecularly as triple-negative breast cancers (TNBC). Long-term follow-up on TNBC patients has shown that these individuals have an increased likelihood of distant recurrence and death compared to women with other types of cancer. There is an urgent need to create targeted therapies for patients diagnosed with TNBC. This can only be accomplished if faster, more efficient methods are developed to convert genetic information into new targeted therapies. From our recent integrated genomic analyses accomplished during the last two years of our Komen-funded research grant, we discovered that TNBC can be classified into six subtypes, each with distinct biologically relevant signaling pathways that drive tumor cell growth. Further, we identified 25 TNBC cell lines representative of these subtypes. Predicted 'driver' signaling pathways were pharmacologically targeted in these cell lines as proof of concept that analysis of distinct genomic signatures can inform therapy selection. Translating this pre-clinical work continues to be the overall aim of the current proposal. Our ongoing hypothesis is that an innovative combination of genomic data mining, molecular biology, and laboratory model systems can be used for streamlined 'target' identification within pathways that drive different types of TNBC; and, these pathways can be targeted for therapeutic benefit for patients and result in much more individualized, precision care for each TNBC patient. Common features of the majority of TNBC tumors is the inability of the tumor cells to repair DNA damage and the dependency of the tumor cells on 'robust' growth signals that come from a pathway referred to scientifically as the PI3K pathway. This continuation proposal will focus on analyzing the tumor tissue from patients enrolled in a novel clinical trial to determine if a set of genomic markers can predict sensitivity or resistance to the drugs tested in the trial, BRE1287. The trial is focused on evaluating the efficacy of cisplatin (a DNA damaging agent to which TNBC cells are very sensitive) and GDC-0032 (PI3K inhibitor from Genentech) versus cisplatin alone in patients with metastatic TNBC. This trial is based on our preclinical data generated in the past funding period. The trial will also test our ongoing hypothesis and importantly let us understand why specific patients will respond to the treatment and why other don't; and for the latter find better methods to target their tumors. The ultimate outcome of the proposed research is to successfully advance data from the laboratory to the clinic in the form of rationale, target-driven clinical trials as well as discover additional candidate targets as 'leads' for future investigation.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Plk2 function in mammary gland development and breast cancer

Investigator(s): Jeffrey Rosen, Ph.D.

Lead Organization: Baylor College of Medicine

Grant Mechanism: Komen Scholars

Grant ID: SAC110031

Public Abstract:

Breast cancer is the most common form of cancer found in women. Although mammography screening has decreased the incidence of breast cancer, there are still thousands of women that die every year as a consequence of the disease. One of the most aggressive types of breast cancers is the basal subtype. Within the basal subtype, triple negative cancers are characterized by the absence of steroid hormone receptors, such as estrogen and progesterone receptor, in addition to loss of HER2 growth factor receptor. Due to the absence of the hormone receptors, hormone therapy for patients with triple negative breast cancers is not an option. Currently there are no treatments for triple negative breast cancer and patients with this type of breast cancer have a poor prognosis and are associated with poor survival. This lack of treatment strategies is because there is little understanding of the signaling networks regulating triple negative breast cancers. Therefore it is critical to identify drugable pathways and the proteins involved in these pathways to provide new therapeutic targets. Recently we have identified Plk2 as a regulator of normal mammary gland development and a putative tumor suppressor in the basal subtype of breast cancer. Plk2 is involved in the cell cycle and loss of Plk2 leads to an increase in proliferation, misorientation of mitotic spindle and loss of polarity, processes which all have been implicated in tumorigenesis. Moreover, we have identified a drugable kinase downstream of Plk2, Plk1. The goal of this proposal is to develop a preclinical model that would allow us to test inhibitors of Plk1 to determine if tumors lacking Plk2 but with increased Plk1 activity are more sensitive to these inhibitors. By identifying a drugable candidate we may be able to rapidly translate our discoveries into a potential therapy for a subset of patients with triple negative breast cancers.



**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.

Overcoming or preventing therapeutic resistance to HER2 targeted therapies

Investigator(s): Neil Spector, M.D.

Lead Organization: Duke University School of Medicine

Grant Mechanism: Komen Scholars

Grant ID: SAC110033

Public Abstract:

Although there have been significant advancements in the treatment of inherently aggressive HER2+ breast cancers, the development of resistance to therapy has limited the clinical efficacy of HER2 targeted therapies, particularly in women with advanced stage breast cancer. If we cannot cure metastatic breast cancer we should strive to convert it to a manageable chronic disease similar to high blood pressure or diabetes. Resistance to HER2 targeted therapies does not appear to be caused by a single mechanism. Treatment strategies to overcome or prevent the onset of resistance to HER2 targeted therapies will require tailoring therapy based on a tumor profile predictive for the development of resistance via a specific mechanism(s). This requires identification of the mechanisms involved in the development of therapeutic resistance. In Aim 1, we will study the role of a variant form of HER2, which we refer to as p85HER2 in promoting resistance to HER2 targeted therapies used in the clinic. Relatively little is currently known about the function of p85 in breast cancer cells, information that could lead to improved treatments for women with advanced p85-expressing breast cancers. The best cure for breast cancer is to prevent it. While studying p85 and related variant forms of HER2, we discovered that a protein that protects cells against the damaging effects of noxious environmental stimuli (some of which has been linked to breast cancer risk) and importantly, in response to expression of cancer causing genes (oncogenes) promotes the earliest steps in converting a normal cell to a cancerous cell. This protective protein is called Hsp72. Our preliminary findings show that a novel Hsp72 inhibitor, discovered and developed by our lab and collaborators at Duke, can block the conversion of a normal cell to a breast cancer cell. In Aim 2, we seek to demonstrate that Hsp72 can prevent/delay the formation of tumors caused by expression of a cancer causing gene in non-malignant breast cells, or in response to chronic exposure to cadmium, a breast cancer causing heavy metal environmental contaminant. We will also determine whether Hsp72 inhibition prevents tumor formation in a mouse model of human breast cancer. We also seek to establish a relationship between the level of Hsp72 expression in clinical breast samples and risk of developing breast cancer in a high risk population. In addition, we will determine whether Hsp72 levels in blood lymphocytes correlate with blood levels of heavy metals from lower socioeconomic women living in an industrialized area. The work proposed here can be rapidly translated into the clinic for further validation of Hsp72 expression in clinical samples from high risk individuals, and ultimately test an Hsp72 inhibitor as a novel mechanism-based preventative strategy in high risk individuals who have been identified based on Hsp72 levels measured in their blood cells or from breast tissue/aspirates.



**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.

Prospective studies correlating pharmacogenetic biomarkers and survival outcomes in hormone-sensitive breast cancer

Investigator(s): Vered Stearns, M.D.

Lead Organization: Sidney Kimmel Cancer Center at Johns Hopkins University School of Medicine

Grant Mechanism: Komen Scholars

Grant ID: SAC110042

Public Abstract:

How the body interacts with drugs depends on how the body expresses many different genes. One gene, CYP2D6, makes an enzyme that changes how the body uses common drugs. It is possible that breast cancer patients who are poor drug metabolizers (low CYP2D6) will not have the same benefit from tamoxifen compared to patients with a moderate or high score. We will examine that relationship, and test several other genes that could also affect tamoxifen's benefit. We have also initiated a clinical registry to study other endocrine agents and to encourage patients of differing genetic backgrounds, such as African-American patients, to enroll in order to survey a more diverse section of the population to provide a more complete picture of the many ways the human body can work.



**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.

Validation and implementation of genomic testing for chemotherapy and endocrine sensitivity

Investigator(s): W. Fraser Symmans, M.D.

Lead Organization: UT M.D. Anderson Cancer Center

Grant Mechanism: Komen Scholars

Grant ID: SAC110034

Public Abstract:

Measurements from a routine biopsy of HER2-negative invasive breast cancer at the time of diagnosis or surgery using a developed microarray-based predictive test could predict whether a person with newly diagnosed breast cancer would benefit from neoadjuvant or adjuvant chemotherapy containing a sequence of taxane and anthracycline-containing chemotherapy, and/or subsequent adjuvant endocrine (hormonal) therapy. An independent retrospective evaluation of this test showed that in 28% of patients who were predicted to be treatment sensitive their probability of being alive and without metastatic disease at three years after diagnosis was 92%, and this was significantly (18%) higher than the probability if they were predicted to be insensitive to the treatment.

This proposal is to conduct a prospective trial to establish the true prevalence of these prediction results in a representative population of people with newly diagnosed breast cancer, and to test the feasibility of routinely performing this test within the clinical pathology laboratory using tumor biopsy samples obtained from patients at the time of needle biopsy or at the time of surgery. The ability to obtain quality test results in more than 85% of biopsy samples will indicate the feasibility of using this predictive test. Recorded prediction results will subsequently be compared to the tumor response and survival outcomes of the patients who receive treatment that is relevant to the intended use of the test. This study has 80% power to confirm whether the probability of survival at three years of follow up is as high as was described in the previous (retrospective) study. This research will establish a higher level of clinical confidence in the performance and utility of genomic testing in a pathology diagnostic laboratory.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Optimizing therapy for early-stage triple-negative breast cancer

Investigator(s): Melinda Telli, M.D.

Lead Organization: Stanford University

Grant Mechanism: Komen Scholars

Grant ID: SAC150062

Public Abstract:

The current approach to the treatment of early stage triple-negative breast cancer (TNBC) has changed little in 15+ years. However, a growing body of evidence suggests that platinum chemotherapy drugs may be more active against tumors in BRCA1 and BRCA2 gene carriers and potentially other TNBC tumors with altered DNA repair function. Recent clinical trial data in all patients with TNBC suggest that platinum chemotherapy agents can increase the rate of favorable response when added to standard chemotherapy drugs given prior to surgery, yet toxicity is increased and the benefits do not appear to be equally experienced by all patients. Optimizing therapy for this high-risk group of patients, by giving platinum treatment to those most likely to benefit and sparing toxicity for those unlikely to benefit, is a high priority. Given the clinical potential of drugs such as platinum, new methods to assess the DNA repair capacity of tumors (functional versus dysfunctional) have been developed. We have shown that these tumor-based tests can identify TNBC patients, with and without an inherited risk of breast cancer due to BRCA1 or BRCA2 gene mutations, most likely to benefit from chemotherapy drugs like platinum. As such, the clinical trial proposed will directly address the customized chemotherapy treatment of women with newly diagnosed early-stage TNBC on the basis of the tumor's DNA repair function (functional versus dysfunctional). If successful, this trial will provide important evidence with great potential to lead to a shift in the treatment approach for newly diagnosed breast cancer with tumor DNA repair dysfunction.

Interestingly, recent studies have also documented that the body's immune system plays an important role in prognosis and chemotherapy response in TNBC. The presence or absence of the body's immune cells around a tumor in the breast has been shown to influence how likely that tumor is to respond to chemotherapy. Interestingly, we have shown that tumors lacking a normal capacity to repair DNA damage appear to be the same tumors that are more likely to have infiltrating immune cells around the tumor cells and are more likely to respond favorably to chemotherapy treatment. As part of this proposal, we will further evaluate this interplay between immune cell infiltration and DNA repair dysfunction in TNBC. A better understanding of the relationships between tumor immunity and DNA repair dysfunction may provide important insights regarding the response to both standard chemotherapy drugs and novel immunotherapy drugs currently in early clinical testing in TNBC.



**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.

Mammary stem cells and breast cancer

Investigator(s): Geoffrey Wahl, Ph.D.

Lead Organization: The Salk Institute for Biological Studies

Grant Mechanism: Komen Scholars

Grant ID: SAC110036

Public Abstract:

Breast cancer comprises a heterogeneous collection of diseases. Work by basic researchers and clinicians has produced drugs targeting specific types of breast cancers based on particular proteins that they require for their growth and survival. Herceptin is one such drug that has proven very valuable for treating only those breast cancers that express its target, the Her2 protein. Drugs that inhibit the estrogen receptor, which is expressed in about 2/3 of breast cancers, have also proven to be effective. Unfortunately, many women are diagnosed with cancers that do not have significant levels of the estrogen receptor, the related progesterone receptor and the Her2 protein. These so-called “triple negative” cancers are often very aggressive and, thus far, have no “targeted” therapies. While initially sensitive to chemotherapy, these “triple negative” cancers often relapse with a vengeance. Thus, an important goal for researchers is to find therapies that are effective in eradicating such tumors. Also, better ways of evaluating the diversity of cell types that characterize almost all cancers and the cellular mechanisms that lead to their ability to adapt to drugs and other challenges could lead to better prognostic and treatment strategies. Attacking both of these problems is at the root of the work we are doing. Over the past several years we have identified when mouse mammary gland stem cells first start to form at the earliest times of development. We isolated these rare cells and analyzed them and found that the genes they express are also expressed by the triple negative cancers referred to above. Thus, it seems that either the triple negative cancers contain cells that have the molecular characteristics of very primitive mammary stem cells OR the tumor cells have reprogrammed themselves to behave like these primitive cells to gain some of the growth and survival advantages they may have over their mature counterparts. The work we now propose is geared to better understand the cell signaling pathways that are essential to the growth and survival of the nascent normal mammary stem cells and to determine whether the same pathways are important in triple negative breast cancers. We also want to develop very sensitive, rapid and inexpensive methods to find cells with mammary stem cell characteristics even within the complex cellular makeup of a human cancer. Finally, we want to apply our detection methods to see if we can find evidence of these stem-like cancer cells in the blood stream as “circulating tumor cells”. If we can, we will then be able to determine whether the presence of these cells correlates with patient prognosis or if the cells are sensitive or resistant to various therapies used to treat triple negative breast cancers. Our hope is that these studies will lead to a better understanding of the types of cells that make these cancers so dangerous, and to better methods for eliminating them.



**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.

MRI Guided preoperative partial breast irradiation in early stage breast cancer

Investigator(s): Julia White, M.D.

Lead Organization: Ohio State University

Grant Mechanism: Komen Scholars

Grant ID: SAC110038

Public Abstract:

The goal of breast conserving therapy (BCT) for early stage breast cancer is to maximize cancer control in the breast and preserve breast appearance and sensation. Nearly 30 years of clinical trials has proven that the addition of radiation therapy (RT) following lumpectomy leads to equivalent local cancer control and survival in comparison to breast removal or mastectomy. Accelerated partial breast irradiation (PBI) is a recent development in radiation that has sought to maintain the goals of BCT while reducing the radiation exposure to normal tissue and minimizing the treatment burden for patients. Instead of treating the entire breast daily for > 5-6 weeks, PBI irradiates the breast tissue immediately around the lumpectomy cavity that is the most likely place of cancer recurrence in just 5-10 treatments typically over a period of several days. The current standard practice of delivering breast RT (including PBI) postoperatively has had two major drawbacks: (1) inaccurate targeting, and (2) unknown radiation response. The target volume for PBI has been, so far, the post lumpectomy cavity. This post surgery cavity may not necessarily direct the radiation toward the highest risk area of the breast around the tumor. Furthermore, the postoperative RT delivers radiation in the setting of disrupted blood and lymphatic supply that may theoretically be suboptimal in term of radiosensitivity and that eliminates the opportunity to observe radiation-induced tumor response. MRI has the capability of imaging gross tumor and can be used to guide RT more precisely than guiding surgery. The purpose of this proposal is to develop this potential technology and clinically test MRI-guided preoperative partial breast irradiation, a novel approach, for early stage breast cancer patients. A prospective clinical trial to test the safety and feasibility of delivering MRI-based preoperative PBI using the newly developed technology will be carried out. We hypothesize that the use of MRI for target definition and CT for treatment delivery for pre-lumpectomy PBI will (1) be feasible, (2) provide improved accuracy in target definition and treatment delivery, thus, improved treatment outcome, and (3) allow a means for evaluating the radio-responsiveness of breast cancer. A better understanding of radiation response of breast cancer combined with improved targeting and treatment delivery will encourage novel RT regimens that can achieve greater therapeutic gain and socially-economically better care for breast cancer patients.



**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.

Susan G. Komen for the Cure Tissue Bank at the IU Simon Cancer Center

Investigator(s): Anna Maria Storniolo, M.D.

Lead Organization: Indiana University

Grant Mechanism: Opportunity Grants

Grant ID: OGKTB1301

Public Abstract:

The Komen Tissue Bank (KTB) thanks those who have selflessly donated breast tissue or blood or given of their time to help find a cure for breast cancer. The KTB, the only repository in the world for normal breast tissue and matched serum, plasma, and DNA, continues its commitment to studying normal tissue with the ultimate goal of curing breast cancer.

The Komen Tissue Bank is the only repository in the world for normal breast tissue and matched serum, plasma and DNA. By studying normal tissue, we accelerate research for the causes and prevention of breast cancer. To more deeply understand the evolution of the disease, it is necessary to compare abnormal, cancerous tissue against normal, healthy tissue. We are committed to making a difference by acting as advocates for thinking, sharing and understanding NORMAL.



**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.

Translational Breast Cancer Research Consortium

Investigator(s): Antonio Wolff, M.D.

Lead Organization: Johns Hopkins University

Grant Mechanism: Opportunity Grants

Grant ID: LRTSTBCRC07

Public Abstract:

Extraordinary improvements in the treatment of breast cancer are within reach as new therapies become available. These therapies may involve novel agents designed to target specific molecules/pathways in cancer cells or existing drugs selected based on tumor characteristics. Tests that help understand how an individual cancer will behave and whether it will respond to specific treatments can give doctors and patients the information they need to increase the chances that each individual patient receives the most effective treatment. New laboratory discoveries must be confirmed in well-designed clinical trials. Insightful observations and findings from these trials and related clinical observations then inform the design of future laboratory studies. This seamless two-way flow of information, from the bench to the bedside and vice versa, requires a coordinated collection of previous information from blood samples, tumor tissue (research biopsies), and specialized imaging. These studies require unique skills that can only be assembled across a network of like-minded investigators from some of the most experienced breast cancer research programs.

In 2006, a group of leading investigators established the Translational Breast Cancer Research Consortium (TBCRC). Today, the TBCRC is a collaborative group of scientists from seventeen of the top US academic medical centers that conducts studies of new treatment approaches. Its clinical trials evaluate novel biomarkers using blood, tissue, and imaging to diagnose, stage, monitor, and treat all stages of breast cancer. The TBCRC conducts clinical trials before and after surgery in patients with early-stage or advanced disease. More than thirty trials have been designed, over twenty studies have been completed, and many have been reported or published in international meetings and journals. Some of these studies offered new insight in the biology and clinical behavior of diseases like triple-negative and ER-positive breast cancer, in women with early stage or advanced disease.

The TBCRC provides a forum where investigators from all disciplines, advocates, coordinators, scientists, and biostatisticians meet in person and via conference calls to share knowledge and plan new breast cancer trials. The TBCRC has also become a supportive and nurturing environment for some of the most creative young investigators to develop and test ideas working alongside more seasoned researchers, thereby ensuring the training and retention of a new generation of researchers to continue our march towards a brighter tomorrow with less suffering from breast cancer. Funding from organizations like Susan G. Komen and its supporters has proven critical for all these activities, especially at a time of diminishing federal funding for cancer research and for clinical trials.



**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.

Biospecimen bank for determinants of late relapse in operable breast cancer

Investigator(s): Joseph Sparano, M.D.

Lead Organization: ECOG Research and Education Foundation

Grant Mechanism: Opportunity Grants

Grant ID: OGECOG1201

Public Abstract:

Late relapse, defined as relapse occurring 5 or more years after breast cancer diagnosis, accounts for up to one-half of all breast cancer recurrences. There are no diagnostic tests available to identify which patients are at risk for late relapse. We propose to address this issue by collecting blood specimens from patients with operable breast cancer who have participated in two large clinical trials (E5103, TAILORx), received standard adjuvant therapy, and have not had a breast cancer recurrence (for between 4.5-7.5 years after their original diagnosis).

Subjects will be accrued into an ongoing perspective trial coordinated by the ECOG-ACRIN Research Group (EL1112), have blood samples drawn and stored in a biospecimen bank for future research, and be followed for up to 20 years after their original diagnosis for recurrence in accordance with standard clinical practice. After accrual has been completed and follow-up adequate, the samples may be used by researchers for evaluation of both tumor and host-related factors that may drive recurrence. Access to the samples will be granted to researchers who submit an application that will be peer reviewed by a scientific review committee.

The ultimate goal is to develop diagnostic tests that may identify which patients are at risk for late relapse, and may benefit from additional therapies (e.g., extended adjuvant endocrine therapy).



**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.

Carolina Breast Cancer Study 3

Investigator(s): H. Shelton Earp, M.D.

Lead Organization: University of North Carolina

Grant Mechanism: Opportunity Grants

Grant ID: OGUNC1202

Public Abstract:

The Carolina Breast Cancer Study (CBCS), which began in 1993, was at the time the largest population-based study of African American breast cancer. Phases I-II of the CBCS, which ran from 1993-2000, continue to generate publications, including several seminal findings that inform current research in breast cancer and disparities in outcome. These findings include the increased incidence of the poor-prognosis basal-like cancer in younger African-American women, description of a unique risk factor spectrum in basal-like compared with the more conventional luminal cancers (meaning that breast cancer epidemiology must take intrinsic subtypes into account), and the recent demonstration of profound disparity in African-American women regardless of subtype, in particular that the most marked difference in survival actually occurs in the best prognosis luminal cancers. These luminal cancers are those in whom several years of endocrine therapy is key to optimal treatment, so differential access to care and adherence may be particularly relevant.

The Carolina Breast Cancer Study (CBCS) Phase III is built upon findings from Phases I-II and on track to be the largest population-based studies of breast cancer in African-American (AA) and Caucasian women. Enrollment began in May 2008, and over 1800 women with breast cancer have been enrolled, with a goal of enrolling 3000 women. The study keeps the basic CBCS methodology, rapid case ascertainment through the state tumor registry, informed consent, a two-hour home visit with questionnaire, anthropomorphic data, germline DNA, and tissue blocks for intrinsic genetic subtyping. The major expansion is quite ambitious: obtaining clinical treatment and outcomes data from these population accrued cases, which involves working with health care providers across the state of North Carolina extracting the records for chemotherapy, hormonal therapy regimen completion, radiotherapy, and surgical approaches. Women will be followed yearly with phone interviews for at least 10 years. The comprehensive epidemiologic, tumor and germline genetic, breast cancer-specific treatment and health services and outcomes will yield generalizable findings not obtainable through hospital cohorts. Comprehensive, expanded follow-up of CBCS III patients would yield health outcomes information at an unprecedented level of detail for a diverse, at-risk population. The study would be the first to address how treatment decisions, access to care, and financial or geographic barriers impact breast cancer outcomes among African-American breast cancer patients in low income and rural areas. Furthermore, CBCS III combines health outcomes with breast cancer molecular subtype information to provide a systematic evaluation of breast cancer prognosis in younger African-American women.

This grant provides funds to obtain the clinical outcomes and treatment data for this large population-based study.



**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.

Evidence Based Consensus Conference on Margins in DCIS Treated With and Without Radiotherapy

Investigator(s): Monica Morrow, M.D.

Lead Organization: Society of Surgical Oncology

Grant Mechanism: Opportunity Grants

Grant ID: OG140012

Public Abstract:

Ductal Carcinoma In Situ (DCIS) accounts for approximately 25% of new breast cases diagnosed annually in countries where mammographic screening is employed. There are approximately 64,640 women diagnosed each year with DCIS in the United States. Breast conserving surgery (lumpectomy), with or without radiotherapy, is the most common treatment for DCIS. There is no agreement regarding the optimal amount of normal breast tissue (margin) which should be removed around the DCIS to minimize the risk of cancer recurring in the breast while still maintaining a good cosmetic appearance of the breast. Additionally, there is no agreement on whether the ideal margin width varies for women who will and will not receive radiation treatments to the breast. The Society of Surgical Oncology (SSO) in collaboration with the American Society of Therapeutic Radiation Oncology (ASTRO) proposes to convene a multidisciplinary group including surgeons, radiation oncologists, a pathologist, a medical oncologist, a patient advocate and a methodologist to critically review the scientific evidence regarding margin width and risk of cancer recurrence after breast conserving surgery for DCIS with and without radiation therapy and to develop an evidence based consensus guideline. As part of this evidence base, a systematic review and meta-analysis of the published literature on this subject will be performed. The completed consensus document will be submitted to the major professional organizations involved in the care of breast cancer patients for endorsement and widely disseminated through scientific publication, webinars, meeting presentations and the lay media. In patients currently undergoing excessively radical margin excisions, adoption of a evidenced based guideline has the potential to reduce the anxiety experienced by patients and families when re-excision is performed and to improve the cosmetic outcome of breast conserving surgery and reduce the use of unnecessary mastectomy for women who wish to preserve their breasts. In women currently undergoing inadequate margin resection, adoption of the guideline has the potential to decrease rates of cancer recurrence in the breast. Overall, an evidence based standard for margin width will optimize the extent of surgical resection, improve quality of life for patients, and decrease healthcare costs.



**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.

Targeting the stem cell niche in aggressive breast cancers

Investigator(s): Lisa Arendt, D.V.M., Ph.D.

Lead Organization: University of Wisconsin - Madison

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15332611

Public Abstract:

Obesity is one of the most important risk factors for postmenopausal women for the development of breast cancer. Women with a higher body mass index develop tumors that are larger at the time of diagnosis that are more clinically aggressive. Obese women also have an increased risk for the development of metastases and a shorter time before tumors can recur. Obesity also has been shown to enhance other risk factors for breast cancer. Understanding the differences in the breasts between obese and lean women could have a significant impact on our ability to treat obese women with breast cancer. One possibility for the difference in breast cancer development between lean and obese women is changes that occur in the fatty tissue surrounding the cells of the breast that are able to make milk during lactation. In this fat, a type of white blood cells, which are named macrophages, are increased. These macrophages are activated within the obese fat tissue to produce factors, which can increase the type of breast cells that may later form tumors in obese women. These activated macrophages also act in the early forming tumors to increase aggressive cells and change the environment of these growing tumors cells, to an environment that strongly promotes tumor growth. In this project, we will study how macrophages, activated by obese fat, change the populations of breast cells and identify the factors that are responsible for this change. We will examine how these same factors increase cells that are aggressive and resistant to treatment within the tumor and promote an environment that enhances tumor development. Many of the types of factors that macrophages produce are also involved in autoimmune diseases, such as rheumatoid arthritis. Because the factors that macrophages secrete have already been investigated for these other conditions, drugs which are used to treat these other illnesses may have substantial usefulness to either safely treat obese women at high risk for developing cancers early, such as women with a family history of breast cancer, or in conjunction with other clinically used treatments to increase the success for treating obese women with breast cancer.



**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.

Targeting the stem cell niche in aggressive breast cancers

Investigator(s): Jay Desgrosellier, Ph.D.

Lead Organization: University of California, San Diego

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15330839

Public Abstract:

There are still no effective therapies for patients with the most aggressive types of breast cancer. Increasingly, we are becoming aware that this is because breast cancers are complex. We now know that a single human breast tumor can consist of many different types of tumor cells, each with different jobs. Some of these cells are very similar to the normal stem cells present in adult breast tissue. These “stem-like” tumor cells are actually the most devious cells, causing tumors to recur after treatment or surgery and forming distant metastases that can often prove fatal. My project focuses on ways to specifically block these “stem-like” tumor cells. By targeting a molecular pathway that I recently discovered was important for normal breast stem cells, I hope to show that this strategy can eradicate “stem-like” tumor cells, offering a new treatment option for patients with the most aggressive breast cancers and reducing mortality due to recurrence and metastasis in breast cancer patients.

Clinical trials testing potential breast cancer drugs, including Src inhibitors, have had an alarmingly low rate of success, indicating a great need for new approaches to this problem. My proposed studies represent a change in how potential breast cancer therapies are identified and tested in the laboratory. Instead of focusing on the ability of Src inhibitors to shrink the tumor bulk, my project will assess how targeting “stem-like” tumor cells will reduce recurrence and metastasis, effects that are arguably more clinically relevant than tumor shrinkage. In fact, our preliminary data indicates that this approach will have no effect on tumor size. Importantly, we plan to use a Src inhibitor, dasatinib, already approved for use in patients, thereby accelerating the potential for translating successful outcomes from these studies into the clinic.

This research project represents a synthesis of many distinct areas of cancer biology, all brought together with the goal of “changing the game” with respect to how we think about and treat breast cancer. I believe this research may prove very important to the breast cancer patient and survivor community as it has the potential to offer new therapeutic possibilities for aggressive breast cancers that are currently untreatable, leading to a reduction in breast cancer mortality. Additionally, if successful these studies may lead to fundamental changes in breast cancer therapy in the clinic, with a focus on targeting the “stem-like” tumor cells to prevent recurrence and metastasis post-surgery or chemotherapy.



**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 therapeutic approach to triple-negative breast cancer: role of antioxidants

Investigator(s): Chiara Gorrini, Ph.D.

Lead Organization: University Health Network - Toronto

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15332575

Public Abstract:

Cells are constantly exposed to reactive forms of oxygen termed “ROS” that are generated by their physiological functions. If ROS levels become too high, they damage tissues and kill cells. Cells use antioxidant systems to neutralize and control ROS. Tumor cells have genetic and metabolic defects that produce very high ROS, which they handle by increasing the activity of their antioxidant systems. Tumor cells may die if these systems are blocked, offering a rationale for a form of new anticancer therapy. My proposal seeks to characterize antioxidant molecules crucial for the survival of breast cancers with mutations in one of four genes, namely BRCA1, BRCA2, ATM, PALB2 and BRIP1. Women with breast tissue cells carrying alterations in these genes have a greater chance of developing an aggressive form of breast cancer known as Triple-Negative Breast Cancer (TNBC). Tragically, these cancers develop at a young age, are very hard to treat, and currently lack the targeted therapies that have been effective in treating other breast cancer subtypes. Recent studies suggest that BRCA1, BRCA2, ATM, PALB2 and BRIP1 (“TNBC genes”) are normally important for controlling ROS levels inside the cell because they regulate the activities of antioxidant molecules. When a TNBC gene is mutated in a breast cancer cell, this cell has only a low level of antioxidant factors and consequently accumulates high ROS. I hypothesize that such cancer cells then activate alternative mechanisms to control ROS and ensure their survival, and that inactivation of these alternative mechanisms might be a new route to TNBC therapy. My research proposal aims to identify which antioxidant molecules are controlled by TNBC genes, and which alternative mechanisms are selected by tumor cells with mutations in TNBC genes. In addition, because research studies have theorized that administration of antioxidants to patients may interfere with their anticancer therapy, I will study whether the antioxidant vitamin E affects the response of TNBCs to two advanced chemotherapeutic drugs currently used for TNBC treatment: PARP inhibitors and PI3K inhibitors. The expected outcomes of my research are: 1) the identification of new factors that are essential for the survival of TNBC cells and thus may represent new potential drug targets for personalized cancer treatment, and 2) the clarification of whether antioxidants should be given to breast cancer patients. I envision that my research proposal will contribute to bridging the gap between basic science and clinical practice. Because my experimental approach includes human and mouse model systems of breast cancer that closely recapitulate the human disease, I believe my results will be readily translated into improved care for TNBC patients, bringing us closer to the ultimate goal of creating a world without breast cancer.



**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.

The role of RAGE-ligand signaling in breast cancer progression and metastasis

Investigator(s): Chunyan He, Sc.D.

Lead Organization: Indiana University (Indianapolis)

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15333233

Public Abstract:

“Epigenetics” is a study of the changes to gene activity without changing DNA sequences in the growth (or development) of an organism, in this case, breast cancer. In addition to research on how best to diagnose and treat all the various cancers, the moment that cancer begins (carcinogenesis) is an equally important area. This project pursues cancer by way of being able to identify epigenetic changes that indicate cancer will most likely begin. If science can fully understand what to look for, then effective therapies can be developed in response.

“DNA methylation” is a key epigenetic mechanism. The term describes the biochemical process where a methyl group attaches to specific DNA sequences called CpG sites or “islands.” (“CpG” stands for Cytosine-phosphate-Guanine: two of the four nucleotides that make up DNA, connected by a single phosphate.) DNA methylation is critical to cancer research because abnormalities in it can turn on oncogenes, the genes responsible for the uncontrolled growth of tumors. DNA methylation can also turn off, or “silence” tumor suppressor genes. When science is able to identify the how, why, and when of carcinogenesis, the battle will be won.

Such causal alterations in DNA methylation occur early in breast cancer development or even in normal breast long before tumor diagnosis. More importantly, alterations in DNA methylation, unlike alterations in DNA sequence, are reversible. Thus causal DNA methylation markers are attractive candidates for the development of early predictive biomarkers and new therapeutic targets. Identifying these casual DNA methylation markers remains a major challenge in breast cancer research. Most research in this area cannot distinguish the DNA methylation markers that cause breast cancer from those that are the consequences of the disease.

In this proposal, identifying the DNA methylation markers that cause breast cancer will be done using a novel, integrative genomic and epidemiological approach. The project will investigate how DNA methylation markers are altered in normal breast cells by genetic susceptibility factors (mutations in DNA sequence) versus environmental risk factors (reproductive history, lifestyle, and dietary factors). How are these changes linked to breast cancer initiation and progression? Answering these questions will help prevent cancer.

Because DNA methylation markers change in response to breast cancer-related environmental exposures, such as alcohol intake or hormone use, such DNA methylation markers can also be used as benchmarks to evaluate dietary and lifestyle interventions. The expected outcome of this project is identifying causal DNA methylation markers that drive breast cancer development. When science fully understands how oncogenes begin, it will pursue having them never turn on. That is cancer prevention. In this particular case, breast cancer, but it would apply to many, if not all, cancers.



**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.

The role of RAGE-ligand signaling in breast cancer progression and metastasis

Investigator(s): Barry Hudson, Ph.D.

Lead Organization: Miller School of Medicine of the University of Miami

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15331076

Public Abstract:

A major limit of the vast majority of breast cancer research conducted to-date is that it has focused primarily on what is wrong only with the cancer cell itself. This tumor cell centric approach has not until recently taken into account the role of normal cells of the breast, nor of immune cells circulating in the blood. We now know that other diseases and conditions that come with the aging process such as diabetes, obesity and other inflammatory states can influence the outcome of breast cancer. Whilst these conditions have nothing to do with the many genetic changes that occur in the cancer cells themselves, these inflammatory states can drive the cancer cells to be more aggressive and spread to other tissue more readily.

One of the ways that cancer cells and cells that surround the tumor can “talk” to each other and sense this state of inflammation is through a protein called “RAGE”. RAGE (Receptor for Advanced Glycation End-products) is a receptor present on the surface of normal cells which gets switched on by many of the inflammatory proteins produced in cancer. What is not clear in breast cancer, is how RAGE makes different cell types communicate, and if its importance is on cancerous or non-cancerous cells. We are especially interested how RAGE activates breast cancer cells, and how it makes cancer worse by recruiting a normal cell type from the blood known as myeloid derived suppressor cells (MDSCs). MDSCs have recently been shown to be major regulators of the amount of inflammation in a tumor and how aggressive breast cancer can become. Our preliminary data presented in this proposal, demonstrates clearly that RAGE makes breast cancer cells more aggressive, and ligands for RAGE (s100a8/9) are responsible for getting MDSCs into the tumor. Furthermore, we show that a new drug that specifically blocks RAGE makes breast cancer cells less invasive. We will test whether RAGE is important for the malignant function of breast cancer cells versus MDSCs in cell culture and in animal models. To show the human importance, we will perform analysis of RAGE protein levels in patient tissue samples to see if RAGE levels are predictive of invasiveness and metastasis. Finally, we will also test in mice if our RAGE drug inhibitor affects breast cancer progression and metastasis.

The potential clinical applications of our work is the rapid translation to clinical trials of our RAGE inhibitor in patients with invasive and metastatic breast cancer. Together with our experience in translating scientific findings to the clinic, and the resources at the University of Miami, these patient related outcomes could feasibly be accomplished in 5-10 years. The results of this study have great potential to impact clinical practice and treatment of breast cancer, and thus have the potential to make a significant difference in the lives of breast cancer patients.



**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

Investigator(s): Huiping Liu, M.D., Ph.D.

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.



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.

Mechanisms of normal-to-malignant transformation in the breast.

Investigator(s): Luke McCaffrey, Ph.D.

Lead Organization: McGill University

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15331358

Public Abstract:

Breast cancer remains a devastating disease with over 200,000 new cases and 40,000 deaths per year in the US. Women at high risk for developing breast cancer may be eligible for preventative therapy, however, existing treatments only prevent some breast cancers and the net benefit is limited by serious side effects. Identifying novel targeted therapies will reduce breast cancer incidence, but a major barrier to this is a limited understanding of the mechanisms underlying early stages of breast cancer development.

Breast cancer progresses step-wise, with normal mammary ducts made of tubes comprised of a single layer of cells, becoming multilayered and eventually a solid mass of cancer cells. The initial loss of organization is accompanied by increased cell proliferation, which drives cancer growth. Therefore, loss of organization is a key early event that may be essential for breast cancer initiation.

Fibroblasts are cells that surround mammary ducts play a supportive role in tissue maintenance. They become reprogrammed as breast cancer progresses, which further promotes the growth of breast cancer cells. Sometimes these reprogrammed fibroblasts are present in the normal margins of breast cancers that are removed surgically. We predict that cancer fibroblasts left behind may make it easier for cancer cells to develop again.

aPKC is an enzyme that regulates tissue organization and is over-expressed in breast cancer. Increasing its expression in normal cells causes disorganized growth, similar to cancer cells. Inhibiting aPKC in cancer cells, it blocks loss of tissue organization and overgrowth, restoring them to a more normal state. The precise mechanism by which normal cells transform into cancer cells, how aPKC regulates this, and whether the process is reversible is not understood.

Our hypothesis is that loss of cell organization initiates the earliest stage of breast cancer and that blocking it will prevent breast cancer development.

Aim 1 of our project will provide an indepth analysis of the expression of aPKC and other genes that regulate tissue organization by examining samples from breast biopsies. Since the patient outcome is known, we can identify if these genes predict whether an early lesion is likely to progress to breast cancer. Aim 2 of our project will examine how normal cells transform into cancer cells. Using a 3-dimensional (3D) culture system that closely recapitulates the normal organization of cells, we will induce the expression of cancer-causing genes and make videos of cells as they change. This will allow us to literally watch cancer cells form. We will then inhibit aPKC to learn its function in cancer initiation. We will establish a screen to identify other genes that interact with aPKC and are also involved in establishing a cancer state. In Aim 3 we will modify our 3D culture system to include fibroblasts and cancer-associated fibroblasts and determine how they affect the normal-to-cancer transformation.



**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.

Estrogen receptor reactivation for treatment of advanced breast cancer

Investigator(s): Todd Miller, Ph.D.

Lead Organization: Dartmouth College

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15330848

Public Abstract:

Estrogen hormones interact with estrogen receptor alpha (ER) inside breast cancer cells, which typically drives cancer growth. Approximately 70% of breast cancers have ER. Anti-estrogen drugs that block ER activation are used to prevent cancer growth and recurrence. While anti-estrogens are among the most effective anti-cancer drugs in history, ~20% of patients with breast-localized cancer removed by surgery and treated with anti-estrogens ultimately develop recurrent cancer that is metastatic or locally advanced (~180,000 new cases per year worldwide). In nearly all cases, metastatic breast cancer eventually becomes resistant to standard therapies and is fatal, making ER+ breast cancer responsible for more deaths than all other breast cancer subtypes combined.

Before anti-estrogens were developed, ESTROGENS were used to TREAT breast cancer. This may seem counterintuitive because estrogens and anti-estrogens have opposite effects on ER, but these therapies elicit similar degrees of response in patients with metastatic breast cancer. Estrogens are most effective against breast cancer following a period of estrogen suppression, suggesting that ER reactivation is toxic to cancers that adapted to estrogen-independent growth. Withdrawal of anti-estrogen therapy can also induce anti-cancer effects, further suggesting that ER reactivation can be therapeutic. Anti-estrogens were subsequently developed and have been a treatment standard for over 30 years, while estrogens were relegated to rare use. However, estrogen therapies are being resurrected through recent clinical trials in patients with anti-estrogen-resistant breast cancer, including our POLLY trial (clinicaltrials.gov identifier NCT02188745).

We postulate that adaptation to anti-estrogens induces changes in breast cancer cells that render ER reactivation toxic. We will test this concept through studies in breast cancer cells, mice bearing breast tumors derived from patients and cultured cells, and tumor samples from patients treated with estrogen therapy. These studies will reveal the mechanism and timing underlying the anti-cancer effects of ER reactivation, tumor-specific markers that predict subsequent tumor response, and ways to enhance the anti-cancer effects of ER reactivation. Such information is critical to the incorporation of estrogen therapy as a legitimate, inexpensive, widely available, relatively safe and tolerable treatment option for patients with anti-estrogen-resistant breast cancer, and to limit its use to patients with cancers likely to respond. Our early data suggest that inactivation of the protein EZH2 may be involved in the anti-cancer effects of ER reactivation. Anti-EZH2 drugs are undergoing initial testing in cancer patients.

Demonstrating that EZH2 inhibition blocks the growth of anti-estrogen-resistant breast cancer cells and tumors in mice would support testing of anti-EZH2 drugs in patients with anti-estrogen-resistant breast cancer.



**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

Investigator(s): Josh Neman, Ph.D.

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.



**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.

Targeting serine and glycine metabolism in breast cancer

Investigator(s): Richard Possemato, Ph.D.

Lead Organization: New York University School of Medicine

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15333441

Public Abstract:

Metabolic pathways are essential for maintaining a proper balance of small molecules within the cells, and in proliferative cells the demand to accumulate biomass requires substantial metabolic pathway alteration. Indeed, altered metabolism is a hallmark of cancer. To proliferate, a cell needs to synthesize or scavenge building blocks for creating another cell, such as membrane and protein components and DNA. Indeed, there is substantial evidence for upregulation of biosynthetic enzymes in cancer, often as a direct result of gene mutation. Indeed, several enzymes involved in biosynthesis are the targets of both well-established and emerging anti-cancer drugs. Recently and with the generous support of a Susan G. Komen Postdoctoral Grant, I devised a strategy to evaluate the impact of targeting hundreds of metabolic genes at once. I undertook this strategy directly in a growing ER-negative breast tumor in mice. Each cell in this growing tumor had a different metabolic gene inhibited, and they competed with other cells in the tumor to uncover which genes are most important for tumor formation and growth. This increased the number of genes that could be evaluated simultaneously and led to the discovery that the gene PHGDH is highly elevated in ER-negative breast cancer and important for the growth of such tumors. Here, I propose to engage in three pre-clinical experiments to evaluate the impact of targeting PHGDH on breast cancer prevention and treatment to impact breast cancer mortality within the next decade:

- (1) We will study a PHGDH inhibitor, which we identified from evaluating hundreds of thousands of molecules, and assess the impact of this inhibitor on breast tumors in mice. We will determine whether other commonly used drugs work better in combination with this PHGDH inhibitor, and whether cancer cells treated with this drug have new dependencies that can be exploited for therapy.
- (2) We will design a mouse that can model inhibition of PHGDH in the breast and assess the impact of PHGDH loss on normal breast tissue and the prevention of breast cancer.
- (3) We will use a powerful new genetic technique to uncover the underpinnings of ER-negative breast cancer's high demand for serine, a key nutrient produced by PHGDH.

Thus, the research objectives outlined here are important because they evaluate, in the most direct way possible in a pre-clinical setting, the effect of inhibiting a promising new breast cancer target.



**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.

Delineation and mutational analysis of open chromatin regions in breast cancer

Investigator(s): Trevor Pugh, Ph.D.

Lead Organization: University Health Network - Toronto

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15332792

Public Abstract:

The most common subtypes of breast cancer, estrogen receptor positive luminal A & B, are often treated with chemotherapy and few personalized treatments are available for these tumors. Expanded whole genome sequencing has yielded thousands of additional mutation cells in breast cancer, creating a major interpretive challenge as the relevance of mutations outside of well-studied protein coding genes remains unknown. We seek to build our knowledge of understudied mutations that dysregulate gene expression and may drive luminal subtype breast cancers. We will do this by examining what portion of the breast cancer genome is actively participating in gene regulation in 30 tumors, and then screening these regulatory regions for abnormal mutations in 150 breast tumors. We expect that these mutations will cluster in common regions across the tumors and that they will implicate specific genes not before implicated in luminal breast cancers. To test whether these mutations truly change gene regulation, we will then assess gene expression profiles across a subset of 120 tumors and look for altered expression levels between tumors that have functional mutations versus those that do not. This research will not only improve our understanding of genetic alterations underlying breast cancer but will also help scientists interpret similar regulatory mutations in other tumor types.



**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.

Dual immunotherapy plus a HER2 vaccine reverses anergy to eliminate breast cancer

Investigator(s): William Redmond, Ph.D.

Lead Organization: Providence Portland Medical Center

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15329664

Public Abstract:

Patients with early stage breast cancer have excellent survival rates, however the outlook for women with metastatic disease remains poor. Therefore, new treatments for metastatic breast cancer are urgently needed. One exciting approach to address this unmet need is immunotherapy, which is a class of cancer treatments that utilizes the patient's immune system to destroy malignant cells. Unfortunately, the induction of immune suppression by cancer cells can severely limit tumor-specific immunity. Regulatory proteins known as immune "checkpoints" including molecules such as CTLA-4, PD-1, and PD-L1 serve to inhibit immune cell activation. Checkpoint blockade with anti-CTLA-4, anti-PD-1, or anti-PD-L1 monoclonal antibodies (mAb) releases the "brakes" on white blood cells (T cells), thereby enhancing tumor immunotherapy. Alternatively, stimulation of T cells with an activating drug called anti-OX40 mAb provides the "gas" for the immune system to seek out and destroy breast cancer cells. Despite the clinical activity of agents such as anti-CTLA-4, anti-PD-1, and anti-PD-L1 in diseases such as renal and lung cancer and malignant melanoma, to date, similar efficacy has been lacking in women with breast cancer. Thus, there is a critical need to understand the mechanisms that hinder efficacy and develop new immunotherapeutic approaches to elicit robust tumor regression in women with metastatic breast cancer. In this proposal, we demonstrate that dual anti-OX40/anti-CTLA-4 therapy was not sufficient to eradicate mammary carcinoma due to immune suppression by the tumor. However, the inclusion of a breast cancer-specific vaccine synergized with anti-OX40/anti-CTLA-4 therapy to rescue the function of "killer" T cells and eliminate mammary carcinomas. We hypothesize that this combinatorial approach relieves immune suppression and elicits a unique immune profile in the "killer" T cells that is associated with their enhanced ability to locate and destroy breast cancer cells. Our specific aims are: 1) Test the hypothesis that anti-OX40/anti-CTLA-4 therapy plus anti-DEC-205/HER2 mAb vaccination rescues anergic CD8 T cells and mediates tumor regression through a CCL3 and CCL4-dependent mechanism in orthotopic models of mammary carcinoma; 2) Test the hypothesis that ICOS-mediated Th2 polarization and suppression by FoxP3+ CD4 T cells (Treg) following anti-OX40/anti-CTLA-4 immunotherapy plus breast cancer-specific vaccination impairs complete eradication of mammary carcinoma; and 3) Test the extent to which ICOS blockade can further boost the efficacy of anti-OX40/anti-CTLA-4/HER2 vaccine immunotherapy. Ultimately, our goal is to translate this approach to the clinic, as generating a more robust and targeted therapeutic immune response against breast cancer cells would represent a significant advance in treatment, thus putting us closer to our goal of eliminating the morbidity and mortality associated with metastatic breast cancer.



**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.

Targeting PI3K and CDK4/6 in breast cancer: integrative biomarkers of response

Investigator(s): Violeta Serra, Ph.D.

Lead Organization: Vall d'Hebron Institute of Oncology

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15330331

Public Abstract:

The PI3K/Akt/mTOR cell signalling pathway is inappropriately activated in 70% of breast cancer patients. Initially there was great excitement over the discovery of new drugs that can inhibit the PI3K pathway, which would have been able to treat this large group of patients. However, clinical results have not met these high expectations. We need to be able to predict which patients will benefit the most from PI3K-blockade, and understand why. In addition to the PI3K pathway, the cell cycle machinery, which are the molecules that drive cells to divide, also seems to be continuously “ON” in some tumors when it should normally be tightly controlled. Both the PI3K and the cell cycle pathways play central roles in cancer progression, by regulating processes such as cell growth and survival. Thus, new drugs that block these pathways have recently been developed, and there are currently numerous phase I/II/III clinical trials testing several different drugs and their combinations with chemotherapy or other so-called targeted therapies. However, predictive biomarkers other than mutation of PI3K for PI3K inhibitors or ER expression for CDK4/6 inhibitors, have not been identified. These biomarkers are insufficient to select the population of patients most likely to respond.

Our proposal seeks to identify predictive biomarkers of response to single agent and to combined PI3K and CDK4/6 inhibitors in breast cancer to improve their impact. To do this, we will use state-of-the-art patient-derived tumor xenografts (PDX) and patient-derived tumor cells (PDC). Our first aim is to develop a three-dimensional ex vivo assay that recapitulates the in vivo response of our PDX. This will allow us to perform pharmacogenomic screening of a “Discovery set” of PDC samples (N=40). Further, we will identify genetic factors in the tumor (mutations, copy-number alterations or epigenetic events) that correlate with the tumors responding to or being resistant to the PI3K and/or CDK4/6 inhibitors. Finally, we will develop an algorithm that will correlate the presence of these biomarkers with the likelihood that the tumor will respond to these drugs. To test the clinical validity of our findings, we will query a “Test set” comprising at least one hundred PDX, PDCs and tumor biopsies from patients being treated with these drugs in the clinic.

We anticipate that this proposal will identify patients that can be successfully treated with PI3K and/or CDK4/6 inhibitors, and, equally importantly, those who cannot. Subsequently, we foresee better stratification of patients into personalized treatments, improving treatment efficacy and reducing patient morbidity and mortality.



**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.

Improving MUC1-targeted immunotherapy to eliminate established breast cancer

Investigator(s): Adam Soloff, Ph.D.

Lead Organization: Medical University of South Carolina

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15329745

Public Abstract:

The protective effect of anti-tumor immunity has long been appreciated in the treatment of breast cancer. Patients with high level immune responses targeting the tumor-associated protein MUC1, present in over 90% of mammary tumors, have a favorable prognosis and increased survival. Yet, patient immunity against MUC1 is predominantly present at low frequencies and unable to prevent disease progression. Therapeutic vaccination provides a strategy to enhance the anti-tumor immune response and eliminate established mammary tumors. Regrettably, conventional vaccinations have failed to fulfill their potential due to two crucial factors; the inability to generate effective and long-lasting anti-tumor immunity, and the direct suppression of the immune response by the tumors themselves. Our proposal seeks to improve immune-based therapy for the treatment of breast cancer by 1) delivering a novel vaccine that induces unique, highly-specialized immune cells, termed T cells, capable of producing the inflammatory factor IL-17 to destroy tumors and, 2) combining vaccination with a new investigational drug, anti-PD-L1, which blocks the ability of cancer cells to hide from the immune system. We will test the ability of experimental vaccination to promote qualitatively superior immunity against the MUC1 target in mice which express MUC1 in a similar manner to humans. We will then compare our novel immunotherapy regimen with one using a conventional vaccination to treat disease in a clinically relevant mouse model which spontaneously develops breast cancer. We believe that our improved vaccination strategy will induce superior T cell-mediated immunity against MUC1 which will be capable of increased tumor killing and long-term persistence following treatment. We predict that a treatment regimen combining novel vaccination in the presence of anti-PD-L1 drug to render tumor cells susceptible to immune-mediated killing will completely eliminate both early and late stage mammary tumors and, importantly, prevent disease metastasis. Due to the high specificity of immune-based therapy, therapeutic vaccination will result in minimal toxicity, enhancing the quality of life of breast cancer patients. Notably, successful immunotherapy will establish long-lived immune memory capable of preventing disease recurrence in breast cancer Survivors. The present study represents the first demonstration that IL-17-mediated responses can be induced through vaccination and will provide an innovative method to improve immune-based therapy to eradicate breast cancer.



**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.

Breast cancer immunotherapy targeting sentinel lymph nodes

Investigator(s): Susan Thomas, Ph.D.

Lead Organization: Georgia Tech Research Corporation

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15330478

Public Abstract:

Immunotherapy has many advantages over conventional breast cancer therapy because it has the potential to treat not only a primary tumor but also metastasis. A patient's immune response to a breast tumor is controlled by the tumor-draining lymph nodes where breast cancers frequently metastasize. However, breast tumors actively suppress immunity within the tumor-draining lymph node and patients with inefficient immune responses typically have poor prognosis and survival. We therefore suggest that boosting immune reactions while simultaneously suppressing immune regulation within the tumor-draining lymph nodes may promote anti-tumor immunity and improve disease outcome.

We will investigate this hypothesis using nanoparticles as drug delivery vehicles that can target lymph nodes and deliver drugs that can stimulate immune activation status and inhibit immune suppression signaling pathways. We will perform these studies in immune-competent mice with implanted breast tumors and monitor the activation state of their immune cells within the lymph nodes and tumor. We will determine if suppressing mechanisms of immune regulation in the tumor-draining lymph node boosts anti-tumor immunity as well as slows tumor growth. This approach has the potential to benefit patients with disseminated breast cancer disease because the approach might be more effective in treating metastasis than conventional approaches. This work will potentially identify a new tissue target for drug delivery approaches in breast cancer immunotherapy that could be quickly translated into clinical practice.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Fibulin-3 as a novel biomarker and target in the breast tumor microenvironment

Investigator(s): Hongyu Tian, Ph.D.

Lead Organization: Duke University Medical Center

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15333124

Public Abstract:

Scientific Objective and Rationale: The dual tumor suppressor/tumor promoter role of the TGF- β signaling pathway suggests tight control and regulation of this pathway during breast cancer progression. However, this dual role makes targeting the TGF- β pathway difficult. Thus, it is important and necessary to investigate how the TGF- β pathway is regulated during breast cancer progression, especially by the microenvironment, which can be readily targeted. In addition, TGF- β also plays important roles in tumor associated-angiogenesis, the process which provides the tumor with oxygen and nutrients, and facilitates metastasis. However, angiogenesis only occurs during specific processes, including during development and breast cancer progression, suggesting that the microenvironment is also important for regulating breast cancer associated angiogenesis, potentially via TGF- β signaling. This proposed project is designed to investigate a fundamental and important question of how breast cancer and breast cancer associated angiogenesis are regulated by fibulin-3, a novel TGF- β regulator, in the breast cancer microenvironment. Thus, this project will yield novel insights into the how the dichotomous function of TGF- β signaling is regulated by the microenvironment during breast cancer progression. These studies will 1) aid in better understanding the impact of the breast cancer microenvironment on TGF- β signaling, breast cancer progression and tumor associated angiogenesis, 2) provide a novel mechanism by which fibulin-3 regulates TGF- β signaling and function in breast cancer and endothelial cells, and 3) define how fibulin-3 expression level in the microenvironment is changed and regulated during breast cancer progression.

Research Applicability: In the proposed work, we will investigate the roles of fibulin-3 in TGF- β signaling, breast cancer metastasis and breast cancer associated angiogenesis in vitro and in vivo. If successful, both the TGF- β signaling pathway and fibulin-3 could serve as potential anti-metastasis and anti-angiogenesis targets for the treatment of breast cancer patients. In addition, as fibulin-3 is a secreted protein, and serum fibulin-3 levels have already been proposed as a blood based biomarker for pleural mesothelioma, serum fibulin-3 levels could be used as a diagnostic, predictive or prognostic biomarker for breast cancer patients. Moreover, if fibulin-3 promotes breast cancer metastasis and tumor associated angiogenesis, as proposed in specific Aim 3C, recombinant fibulin-3 or agents based on fibulin-3 could potentially be used to treat breast cancer patients. Along those lines, we propose to assess the effects of fibulin-3 on tumor metastasis and angiogenesis directly in pre-clinical models of breast cancer. These pre-clinical studies could provide the rationale for the design and organization of phase I clinical trials of fibulin-3 based agents for patients with metastatic breast cancer (~4-5 years).



**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.

Receptor activator of nuclear factor-kB (RANK)-axis and mammographic density

Investigator(s): Adetunji Toriola, M.D., Ph.D.

Lead Organization: Washington University School of Medicine

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15332379

Public Abstract:

Background: Although a dense breast as seen on a mammogram is one of the strongest risk factors for breast cancer, there is very limited knowledge on how it can be modified to reduce a woman's risk of breast cancer. Increased breast density (heterogeneously or extremely dense breast) is common and is seen in >27 million women aged 40-79 years in the US. It is estimated that 28% of breast cancer cases are attributable to increased breast density. Importantly, a decrease in breast density over time is associated with reduced breast cancer risk; hence, strategies to reduce breast density could have great utility in the primary prevention of breast cancer. Further, as legislation that requires disclosure of breast density information directly to women becomes mandatory in many states in the US, women with increased breast density will be more sensitive to identifying ways to reduce their elevated risk of breast cancer. In this proposal, I will investigate for the first time the associations of the receptor activator of nuclear factor-kB (RANK) pathway with mammographic density. The RANK-axis was recently demonstrated to play an important role in the proliferation of breast parenchyma in pre-clinical studies. Hence, inhibiting the RANK-axis could be a novel strategy to reducing breast density and subsequently, breast cancer risk.

I hypothesize that RANK-axis will be associated with mammographic density.

Approach: I will evaluate my hypotheses in 365 women, recruited from among >25,000 women who undergo annual screening mammogram at the Joanne Knight Breast Health Center, Washington University School of Medicine, St. Louis, Missouri. Mammographic density will be evaluated by two radiologists with expertise in breast imaging using a Food and Drug Administration approved computer program that permits quantitative analysis of breast parenchymal density on a mammogram. In addition to mammogram, the women will provide a sample from a blood draw to assess the biomarkers of interest.

Innovation and Impact: This proposal is very innovative and has substantial public health importance. Findings from the study have the potential to greatly enhance scientific knowledge of breast density and could provide initial data that will allow for targeting RANK-axis in breast cancer prevention in millions of women. A RANKL inhibitor (denosumab) is already in clinical use, which will allow for a speedy translation of study findings and could provide a path to primary prevention of breast cancer in the very near future. As noted recently RANKL inhibition represents a "unique chance to potentially prevent breast cancer in millions of women - not in 20 years, but right now". My proposal has the unique opportunity to set that in motion.



**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.

Dissecting IRES mediated translation in breast cancer

Investigator(s): Christos Vaklavas, M.D.

Lead Organization: University of Alabama at Birmingham

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15331062

Public Abstract:

According to the central dogma of molecular biology, genetic information flows from DNA to RNA (transcription) and from mRNA to protein (translation) with mRNA serving as a template for the protein to be synthesized. While the mechanisms that regulate the first half (transcription) of the dogma have been intensively explored over the past 25 years, the mechanisms that regulate the other half, ie which mRNAs will be translated, how much or even what subtype of protein will be produced, are only now beginning to be investigated.

My research focuses on a special mechanism of protein synthesis that has a rescue or emergency role in breast cancer called IRES-mediated translation. This mechanism allows many mRNAs of oncogenes with unequivocal role in breast cancer to be preferentially translated into proteins under clinically relevant conditions of stress such as those induced by chemotherapy. A group of proteins called ITAFs are responsible for switching to this rescue translational mechanism.

With the proposed research, I intend to investigate how this IRES-mediated translation is involved in triple-negative breast cancer. By virtue of this mechanism serving as a rescue, I hypothesize that IRES-mediated translation will be responsible for the survival of triple-negative breast tumor cells when treated with chemotherapy. This research addresses a critical clinical problem as triple-negative breast cancer that persists after intensive chemotherapy is considerably more likely to come back.

With the first aim, I intend to investigate the role and clinical implications of a set of ITAFs. These ITAFs might ultimately be used for diagnostic purposes and guide treatment planning for individual patients with triple negative breast cancer. Triple negative breast tumors tend to be more primitive and therefore more likely to utilize IRES-mediated translation.

With the second aim, I am adapting a new technology (ribosomal profiling) that relies on next-generation sequencing to provide global views of translation across the entire genome in previously treated and untreated human breast tumor samples. Ribosomal profiling will provide “snapshots” of which mRNAs are being actively translated under each condition. With my adaptation of the ribosomal profiling protocol we can differentiate which mRNAs are preferentially translated by using the IRES mechanism. In doing so, we can gauge at the genomic level the degree to which IRES-mediated translation is responsible for unsatisfactory response to preoperative chemotherapy.

Lastly, using genetically engineered triple-negative breast cancer cells implanted in mice, we will visualize in vivo and real-time how IRES activity varies during tumor development and treatment. Our preliminary studies have indicated that the activation of IRES-mediated translation precedes the transition from a quiet indolent state to an aggressive proliferative cancer.



**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.

Diagnostic and therapeutic implications of extracellular HMGA1 in breast cancer

Investigator(s): Josep Villanueva, Ph.D.

Lead Organization: Vall d'Hebron Institute of Oncology

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15333737

Public Abstract:

Breast cancer is biologically and clinically diverse. A group of breast tumors, known as basal-like, afflict younger women and is refractory to endocrine and anti-HER2 therapies. These tumors tend to be particularly aggressive and have a higher metastasis incidence than other breast cancer subtypes. Unfortunately, the standard treatment for patients presenting basal-like tumors is limited to generic adjuvant chemotherapy and radiotherapy that has limited success and heterogeneous outcome. Recent research efforts aimed at characterizing the genomic portrait of breast cancer revealed that the somatic mutation catalog for BLBCs do not provide actionable drug targets. The limited results obtained through the genomics approach together with the evidence that BLBC have a strong involvement of its tumor microenvironment show that approaches different from genomics might be necessary to fight against BLBC. A study done in our laboratory and aimed at understanding how basal-like breast cancer cells (BLBC) communicate among them and with its microenvironment during tumor invasion, led us to study a protein called high mobility group A1 (HMGA1). HMGA1 is a protein that controls the transcriptional activity of several genes. HMGA1 has been causally related to tumorigenesis and its overexpression often correlates with the presence of metastasis and reduced patient survival. We discovered using proteomics and invasion-based functional assays that HMGA1 has an alternative extracellular function in tumor invasion and metastasis. Our hypothesis is that HMGA1 plays a key role in tumor invasion and metastasis, and both predicts the development of distant metastasis and is a promising drug target for BLBC. Based on preliminary data, the experimental focus of this proposal is to characterize the potential of HMGA1 as a biomarker and drug target in BLBC. This research program will lead to a significant advance in the characterization of the potential of HMGA1 as a biomarker and drug target in BLBC, and it will present a basis for new opportunities for cancer diagnostics and therapeutics. We envision that our work will allow stratifying patients who are more likely to develop metastasis to then give them a more aggressive treatment to reduce their metastasis incidence. Furthermore, if we could confirm that a drug against the extracellular form of HMGA1 blocks the establishment of both invasive tumors and metastasis, we would be in a better position to reduce the mortality rate of BLBC patients.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Identifying resistance mechanisms in ER+ breast cancer by translational genomics

Investigator(s): Nikhil Wagle, M.D.

Lead Organization: Dana-Farber Cancer Institute

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15333343

Public Abstract:

In spite of tremendous advances in the treatment of estrogen receptor-positive (ER+) breast cancer using hormonal therapy, patients frequently develop resistance to these therapies. These resistant tumors remain the most common cause of breast cancer death, yet mechanisms by which this resistance develops are poorly understood. Much more work is required to fully understand all of the clinically relevant resistance mechanisms in breast cancer patients treated with hormonal therapy. Moreover, there is an urgent need to develop new therapies for patients who no longer respond to hormonal therapy. The goal of this project is to improve our understanding of resistant ER+ breast cancer by using cutting-edge genomic technology to directly characterize tumor samples from patients who have developed resistant breast cancer, as well as systematic pre-clinical approaches in breast cancer cell lines. First, we will use next-generation sequencing technology to comprehensively characterize the genomes from breast tumor samples obtained from 100 patients who have developed resistance to hormonal therapy. At the same time, we will conduct a systematic pre-clinical study in breast cancer cell lines to identify genes that might contribute to resistance to anti-estrogen therapy. Once completed, this work should help us understand how ER+ breast cancers develop resistance to hormonal therapies, as well as identify new targets and therapeutic strategies in resistant breast cancer.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Control of mitochondrial function by Egln2 in breast cancer

Investigator(s): Qing Zhang, Ph.D.

Lead Organization: University of North Carolina at Chapel Hill

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR15331322

Public Abstract:

Among breast carcinomas, approximately 70% are estrogen receptor (ERa)-positive and estrogen-dependent. Tamoxifen is the single most effective drug for pre-menopausal patients, and targeting estrogen signaling is the core of therapeutics for metastatic disease in patients with ERa-positive tumors. The development of acquired resistance to ER-targeted therapies occurs in about 30-40% of women treated with tamoxifen for 5 years, which accounts for the greatest barrier to extended disease control in this cancer. In addition, the transition from tamoxifen sensitivity to tamoxifen resistance is associated with a rapid decline in survival time, essentially bringing about the beginning of the end for women with breast cancer. Therefore, it remains urgent to develop new therapeutic invention strategies to target breast cancer in addition to traditional tamoxifen treatment.

One of fundamental questions and challenges for cancer therapy is: What drives breast cancer cell growth and how we can stop it? In order for breast cancer cells to grow, they need to obtain necessary energy. The most important compartment in the cells for providing the energy is called the "mitochondrion". Mitochondria are essential for providing energy for cancer cells to grow. Therefore, if we can inhibit mitochondrial function in breast cancer cells, we may starve the cancer cells leading to cancer cell death. This strategy will benefit all cancer patients because it will help to solve the fundamental question for cancer therapy.

Our study aims to study how we can inhibit mitochondrial function in breast cancer. Our preliminary studies suggest that Egln2 is a master regulator controlling mitochondrial function. Our objectives are: (1) to validate and investigate the mechanism by which Egln2 regulates mitochondrial function in breast cancer; (2) to develop a small molecular screen to target Egln2 in breast cancer. Our ultimate goal from this study is to develop novel therapeutic interventions to target mitochondrial function and eliminate breast cancer growth. The outcome from this study will help identify new potential breast cancer therapies.



**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.

Genomic and functional circulating tumor cell analysis for personalized therapy

Investigator(s): Aditya Bardia, MBBS, MPH

Lead Organization: Massachusetts General Hospital

Grant Mechanism: CCR Clinical

Grant ID: CCR15224703

Public Abstract:

Despite major advances in genomics, real-time monitoring of breast cancer has been challenging because it is difficult to obtain tumor biopsies, particularly for hormone receptor positive breast cancer which is the predominant subtype involved in bone metastasis. Obtaining multiple serial biopsies would be required to evaluate dynamic change in tumor biology and discern the best therapy at a given time for an individual patient and is a challenge. In principle, molecular analyses of tumor cells in blood can serve as a “liquid biopsy” and rationally guide therapy selection based on tumor characteristics. While conceptually promising, detection of circulating tumor cells (CTCs) has been technically challenging beyond counting of cells, which has had limited value in guiding therapy decisions.

Recent advances have made it possible to isolate CTCs for sophisticated molecular analysis, and even culture them in the laboratory for drug testing, as recently demonstrated by a collaborative effort between myself and Cancer Center investigators. This is ground-breaking because it allows real-time monitoring of circulating breast cancer cells and individualized drug testing to potentially identify which therapy would work best for that individual at any given point of time. This clinical proposal builds on these exciting hypotheses and has been carefully developed with the input and advice of the mentorship committee and patient advocates including Ruth Fax, an experienced advocate who will serve on my mentoring committee. The study will evaluate the clinical application of CTCs for detecting tumor evolution and rational therapy selection, and will provide a foundation to build models for utilizing CTCs in clinic to personalize therapy selection for an individual with breast cancer.

Successful clinical application of CTC genotyping and functional analyses could have tremendous positive impact for patients with breast cancer. It will provide a more accurate snapshot of the current biological state of the cancer for identification of actionable targets and help select the right drug for the right patient. Furthermore, real-time close monitoring of the tumor could facilitate early identification of emerging resistant subclones and guide therapy switch that could overcome treatment resistance in breast cancer. This could allow us be one step ahead of tumors and potentially lead to a significant reduction in breast cancer morbidity and mortality. While the research is currently being proposed for hormone receptor positive breast cancer, if proved to be successful, the same principles could be applied for research in other subtypes including triple negative breast cancer. Thus, this study has the potential to lay clinical foundation of personalized therapy selection based on real-time monitoring of breast cancer biology, and sustain the quest to successfully treat and ultimately cure breast cancer.



**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.

Nail salon work and mammographic density in Vietnamese Americans

Investigator(s): Eunjung Lee, Ph.D.

Lead Organization: USC/University of Southern California

Grant Mechanism: CCR Clinical

Grant ID: CCR15333900

Public Abstract:

We aim to investigate the impact of nail salon work on breast cancer risk in Vietnamese American women. Nail salon workers are continuously exposed to the toxic fumes and chemicals from nail care products. Nail care products contain a variety of toxic chemicals and certain chemicals could have adverse effects on women's hormonal system such as in the production and/or elimination of various metabolites. Disruption in hormonal systems may have implications in women's breast cancer risk. However, there are no government regulations on pre-marketing safety testing of cosmetics and data are limited on human health effects of these products and ingredients. Human data on breast cancer risk in nail salon workers are almost nonexistent. One recent study conducted in California aimed to address this question, but had limitations in a number of areas including insufficient follow-up time (i.e. period of waiting for cancer outcomes to occur after carcinogenesis) for nail salon workers who have entered this workforce in recent decades. Two other epidemiological studies investigated specific chemical ingredients widely used in nail care products (called phthalates) and found associations with increased breast cancer risk.

We have designed this study to investigate whether nail salon workers are at an elevated risk of breast cancer by assessing mammographic density (MD). MD is a well-established strong predictor and early marker of breast cancer risk and is assessed from mammogram images. Women with denser breast have a ~4 fold higher breast cancer risk than women with non-denser breasts. In this study, we will focus on an underserved, minority ethnic group that comprises the majority of the nail salon workers: in California, it is estimated that up to 80% of nail salon workers are Vietnamese immigrants.

Our study will be one of the first to investigate the role of nail salon work in relation to breast cancer risk, using MD as our endpoint. Results from this study will inform the magnitude of effect; these results will help in designing larger epidemiological studies of nail salon workers and laboratory studies to identify risk-associated chemicals. Results from this study will be novel and should have relevance to a large underserved female workforce.



**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.

Molecular, treatment and behavioral factors in breast cancer race disparities

Investigator(s): Katherine Reeder-Hayes, M.D.

Lead Organization: University of North Carolina at Chapel Hill

Grant Mechanism: CCR Clinical

Grant ID: CCR15333140

Public Abstract:

Background: African American (AA) women with breast cancer have more recurrences and lower survival rates compared to their white counterparts. The racial survival gap is largest among women with hormone receptor-positive (HR+) breast cancer, meaning that their cancer expresses estrogen and progesterone receptors, but not HER2 receptors, and is responsive to estrogen-blocking medications as part of treatment. Hypothesized but understudied reasons for HR+ outcome disparities include: differences in obesity rates, biological difference between HR+ tumors in AA women and white women, and underuse of endocrine therapy (estrogen-blocking medications taken for 5-10 years after diagnosis) among AA women.

Methods: This study will use the broad and deep data resources of the Carolina Breast Cancer Study Phase III (CBCS III) to better understand the contributions of obesity, biological differences, and endocrine therapy (ET) underuse to racial disparities in HR+ breast cancer outcomes. The CBCS III study is a large prospective cohort study focused on understanding racial differences in breast cancer. CBCS III has already reached its enrollment target of 1500 white and 1500 AA women with newly diagnosed breast cancer, of whom approximately 1700 are expected to have ER or PR+/ HER2- disease and to be eligible for inclusion in the study proposed in this application. First, molecular subtyping data from previously collected tumor samples in women with ER+/PR+/HER2 negative receptor profile will be analyzed for racial differences in the patterns of gene expression in their tumors, commonly called the molecular subtype. Next, molecular subtype data along with detailed data regarding income and education, tumor characteristics, initial treatments, baseline obesity and ET use will be used in a series of statistical models to measure which factors have the most influence on outcome disparities. Finally, in depth case analysis using medical records and patient survey data will be conducted to identify ET non-initiators and early discontinuers, to identify racial differences in ET taking behavior, and to understand reasons for non-initiation and early discontinuation.

Expected results: This study is expected to identify the key drivers of racial variation in HR+ breast cancer outcomes, to improve our understanding of why women underutilize highly effective and non-toxic ET, and to prioritize targets for a future intervention study to improve outcomes for AA women.

Expected impact: This study will provide an unprecedented opportunity to comprehensively examine biologic, socio-demographic, and treatment contributions to racial disparities in HR+ breast cancer outcomes. The results are expected to lead within 3 years to the proposal of a rational, targeted intervention to reduce racial disparities in HR+ breast cancer.



**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.

Graduate Training in Breast Cancer Disparities at Lombardi Cancer Center

Investigator(s): Lucile Adams-Campbell, Ph.D.

Lead Organization: Georgetown University

Grant Mechanism: Graduate Training in Disparities Research Grants **Grant ID:** GTDR15330383

Public Abstract:

The primary goal of the Georgetown Lombardi Comprehensive Center Komen training grant is to increase the number of formally trained breast cancer disparities researchers and to increase the pipeline of minority scientists, particularly African-Americans and Hispanics, in this field. Georgetown University currently has an Interdisciplinary Program in Tumor Biology which has now included a new track in Health Disparities with a focus in Breast Cancer (BCHD). The purpose of this track is to provide master level and doctoral level students an opportunity to receive formal coursework training in breast cancer related disparities along with their proposed research interest.

We plan to identify and select three students (at any one time) who will receive training until they obtain a masters or doctoral degree from Georgetown University or the University of the District of Columbia (UDC). We have partnered with UDC, a Historical Black University for more than a decade which has resulted in a joint program in Tumor Biology at Georgetown and Cancer Biology, Prevention and Control at UDC which to date has been successful based on our graduates.

All students in this program will be mentored by Dr. Adams-Campbell, a population-based scientist, in collaboration with one other mentor from the BCHD mentoring team, such as a bench scientist or physician scientist. The mentoring approach represents a team science approach and a framework for the better understanding of the breast cancer disease process and the mechanism or causes of the various outcomes. This approach also helps students to understand how normal healthy cells are changed in human cancer and how breast cancer may be treated and prevented specifically in minority populations.

In addition to the formal training in the classroom, students will be able to select a topic of interest. Below are some potential areas of focus on breast cancer disparities that students will work on during their training:

Black Women's Health Study of Breast Cancer etiology; Diet and Physical Activity in African American Breast Cancer Survivors; Obesity, Metabolic Syndrome and Breast Cancer Prevention in Black and Latina women.

The role of environmental exposures to metals in the development of obesity and breast cancer in minority populations.

Understanding breast cancer initiating cells (BCIC) in basal breast cancer of African American women.

Adjuvant Chemotherapy and Adherence among Black Cancer Survivors; Exercise intervention in Black and Hispanic breast cancer survivors.

Role of the BP1 homeobox gene in triple negative breast cancer; The role of the BRCC2 tumor suppressor gene in early onset breast cancer in Latinas.

Developing novel anti-cancer therapies for African American women with triple negative breast cancer.



**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.

Boston University Mentoring and Training in Cancer Health Disparities (MATCH)

Investigator(s): Tracy Battaglia, M.D.

Lead Organization: Boston University, B U Medical Campus

Grant Mechanism: Graduate Training in Disparities Research Grants **Grant ID:** GTDR15331228

Public Abstract:

Background: At Boston Medical Center (BMC), the largest safety-net institution in New England, the breast cancer disparities observed nationally are acutely experienced where over 60% of the women seen for breast related concerns are racial/ethnic minorities and 60% are publically insured. Addressing these disparities is a principal concern across the Boston University Medical Campus and BMC, providing a rich opportunity to train college graduates in research methods. Tracy Battaglia and the Women's Health Unit have become national leaders in studying cancer care improvements designed to help women who have delays in their cancer care. As a National Center of Excellence in Women's Health, the Unit has clinical, research and education resources devoted to caring for women who are at risk for poor breast cancer outcomes.

Objectives: The goal of the Boston University Mentoring and Training in Cancer Health Disparities (MATCH) program is to train representative graduate public health students to become experts in breast cancer disparities research and make improvements to cancer care that target low-income women.

Methods: Three trainees from the Boston University School of Public Health graduate program will be selected each year for the MATCH program based on their eligibility, including motivation, as judged by the Breast Cancer Patient Advisory Group, academic qualifications as judged by the MATCH research team, and being reflective of the Boston Medical Center patient population, which is 66% racial/ethnic minority. Program components include:

(1) Classes toward a degree in research methods at the Boston University School of Public Health, (2) Career Mentorship to ensure future potential to work in breast cancer disparities research, (3) Hands-on experience in the conduct of team-based, patient-centered disparities research, and (4) Community engaged research methods training integrated with our Breast Cancer Patient Advisory Group. Trainees will engage with our Breast Cancer Patient Advisory Group to gain a patient perspective as they develop their research project, deal with problems that may come up during their research, and report their findings to the community.

Projected Outcomes: Graduates of the MATCH program will complete an independent research project for publication, such as a journal article, and develop the skills needed to pursue their research career to end breast cancer disparities.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Continuing an American Indian Breast Cancer Disparities Training Program

Investigator(s): Christine Daley, Ph.D.

Lead Organization: University of Kansas Medical Center Research Institute

Grant Mechanism: Graduate Training in Disparities Research Grants **Grant ID:** GTDR15333785

Public Abstract:

American Indians have the lowest educational attainment of any racial or ethnic group in the United States and suffer from some of the worst health outcomes. Though incidence of breast cancer has historically been low for American Indians, it is currently rising. In addition, mortality from breast cancer is disproportionately high in this population, with far more American Indian women diagnosed at later, less treatable stages of the disease. In 2010, the Center for American Indian Community Health (CAICH) at the University of Kansas Medical Center began a Master of Public Health (MPH) focus area of American Indian breast cancer disparities through a Susan G. Komen for the Cure grant. This application proposes the continuation of that program for an additional three American Indian students.

Students in our fully accredited MPH program complete 42 credit hours in one of four tracks in the program, including environmental health, epidemiology, public health management, and social-behavioral health. In addition, they complete 200 hours of an internship with a public health organization and 200 hours of research. Students in the Komen Scholars program through CAICH focus their coursework on breast cancer disparities, taking additional credits focusing specifically on American Indian breast cancer. They also complete both their internship and research on American Indian breast cancer disparities, working with CAICH partner organizations, including both reservation- and urban-based organizations. Previous scholars have created culturally tailored educational materials, examined atrazine levels and breast cancer incidence, and have helped in the creation of a scale that measures mammography satisfaction.

This proposal would continue the program and enhance it through the addition of a monthly lecture series given by potential mentors and advocates. By including both scientists and advocates in the lecture series, we ensure that our students are reminded of the importance of the research while they learn the scientific information. In addition, we bring an American Indian advocate into the program through direct mentorship of students. She will meet with students individually in each year of the program, with an additional meeting during the second year when students are deciding on their internship and research project. Students will have several potential projects on which to work, including (1) a weight loss program for breast cancer survivors, (2) a weight loss program developed for primary prevention of postmenopausal breast cancer, (3) mobile mammography and education programs on Kansas reservations, (4) a primary prevention project for high-risk women involving flaxseed, (5) quality of life issues in breast cancer survivors, (6) development of a patient navigator program for breast cancer screening in reservation-based populations, and (7) a computer touch screen program to increase mammography use.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Tufts Breast Cancer Training Program to Reduce Asian Health Disparities

Investigator(s): Karen Freund, M.D.; Susan Parsons, M.D.

Lead Organization: Tufts Medical Center

Grant Mechanism: Graduate Training in Disparities Research Grants

Grant ID: GTDR15333918

Public Abstract:

The Tufts Breast Cancer Training Program to Reduce Asian Health Disparities will train students to conduct breast cancer health disparities research, to ensure equity for all women with breast cancer. Our program will focus on breast cancer health disparities in Asian Americans, especially immigrant Chinese women. Asian Americans are the only racial/ethnic group in which cancer is the leading cause of death. Breast cancer is the most common type of cancer in Asian women. There is a lack of knowledge about breast cancer in Asian American women, and Chinese American women specifically. We know this group has delays and incomplete breast cancer treatment. This is in part due to language barriers, cultural barriers, and lack of trust in western medical care. It is also in part due to differing beliefs in what causes cancer and how it should be treated. We need to study the best methods to address these barriers. Tufts Medical Center sits within Boston's Chinatown and provides care for this vibrant community. We will train students to find ways to best support immigrant Chinese women through their breast cancer journey. We will identify interested students from the Tufts Cancer Center oncology fellowship training program, and students interested in the master's or doctoral program. We will select students with the background to complete the coursework. More importantly, we will choose students with the dedication to serve Asian American women with breast cancer. Tufts University will provide a rich set of resources to help trainees achieve their goals. Trainees will work with two breast cancer advocates, a consultant in traditional Chinese medicine, and a network of Chinese community based organizations already committed and engaged to participate in research and research training of our students. Each trainee will have a team of mentors to help their progress. They will have an overall mentor, a research project mentor, a mentor to help with data analysis, and an advocate to support their work. Our mentors are nationally known researchers in cancer disparities. Students will have their own research projects, drawn from the ongoing projects of the mentors. Students will complete a thesis, and present their work at local and national cancer meetings. They will prepare their research for scientific publication. The program will evaluate the progress of students and provide extra support for those who need it. Our training program will prepare students to perform research in Asian breast cancer disparities that meets important community needs. If successful, this research will have a major impact on the care to Asian women with breast cancer.



**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.

Training Program in Breast Cancer Survivorship Disparities Research

Investigator(s): Karen Meneses, Ph.D.; Wendy Demark-Wahnefried, Ph.D., R.D.

Lead Organization: University of Alabama at Birmingham

Grant Mechanism: Graduate Training in Disparities Research Grants

Grant ID: GTDR15329376

Public Abstract:

Eight years after the 2006 landmark report of the Institute of Medicine, “From cancer patient to cancer survivor: Lost in transition,” significant gaps in survivorship remain, particularly among the underserved. Female breast cancer survivors represent 22% of the 14.5 million cancer survivors in the U.S. Advances have occurred in testing interventions to reduce long term and late effects, improvement in healthy lifestyle behaviors, survivorship care planning, and the economic toxicity of cancer. Yet, these advancements have not been realized in underserved and minority populations particularly across the Deep South. The proposed BCSDR seeks to reduce survivorship disparities through training our next generation of independent investigators in breast cancer survivorship disparities research.

The overall objectives of the Training Program in Breast Cancer Survivorship Disparities Research (BCSDR) are to: (1) train predoctoral students from multiple disciplines to conduct research in breast cancer disparities; (2) increase the number of minority doctoral students engaged in breast cancer survivorship disparities research; (3) provide a specialized core curriculum of didactic and tailored research activities in breast cancer survivorship disparities; (4) foster the development of independent research careers in breast cancer survivorship disparities research; and (5) engage trainees to contribute to the reduction of disparities within their community of interest. In summary, our overall goal is to train the next generation of independent investigators in team science to reduce breast cancer survivorship disparities.

Several confluent trends support the BCSDR at UAB. First, a growing and robust group of senior research scientists have sustained research programs in breast cancer survivorship and disparities research. Second, UAB has a long-standing record of recruiting and retaining both qualified minority students and faculty; with sustained minority enrollment between 20-40%. Third, UAB has both outstanding institutional infrastructure and Comprehensive Cancer Center commitment directed toward the elimination of health disparities.

The Principal Investigator and co-PI have the requisite research and mentoring training experience. Drs. Meneses and Demark-Wahnefried have related yet distinct areas of breast cancer research in disparities examining quality of life and adherence outcomes, and behavioral nutritional and physical activity outcomes in breast cancer. Both scientists have sustained experience with a variety of behavioral intervention designs including randomized clinical trials, exploratory feasibility studies, and qualitative and economic evaluation outcomes.

The objectives, design and focus of the Training Program in BCSDR address critical elements in breast cancer disparities research and fill an urgent gap in training minority scientists in a region of the Deep South with little access to survivorship programs.



**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.

The Ohio State University Breast Cancer Disparities Research Training Program

Investigator(s): Electra Paskett, Ph.D.

Lead Organization: Ohio State University

Grant Mechanism: Graduate Training in Disparities Research Grants

Grant ID: GTDR15334082

Public Abstract:

Ensuring that the next generation of breast cancer researchers receive proper training with proper support from well-established researchers who have a wide array of training and experience is a vital step in the goal to end breast cancer forever. The Ohio State University (OSU) Breast Cancer Disparities Research Training Program will provide two master's and one doctoral trainee with opportunities to understand and eliminate disparities in breast cancer outcomes. Ohio provides a unique environment to pursue this area as breast cancer rates are high especially among underserved (rural, Appalachian, elderly) and minority populations in the state. The proposed training program will support the training of diverse individuals, including those from underrepresented groups through a combination of coursework and participation in mentored research focusing on breast cancer disparities. The program will provide full support to the trainees including tuition, stipend, mentoring, access to equipment, supplies, and pilot research support. The objectives of the training program are to:

1. Recruit two master's and one doctoral trainee to a transdisciplinary training program in breast cancer disparities research that includes mentored research and curriculum opportunities;
2. Provide hands on experience with research projects; and
3. Conduct evaluations of the training program and provide feedback to the Susan G. Komen Foundation.

Trainees will work with OSU researchers engaged in a wide range of breast cancer research. Some of the specific research projects (current and anticipated) that will be made available to trainees address risk factors including behavioral influences, causes of breast cancer, responses to breast cancer diagnosis, symptom intervention, survivorship, prevention and control communication with a concentration on minority and underserved populations, patient navigation and activation, drug development, biomarkers, and tissue biology.

The program will also provide training in a wide, yet unique array of areas related to breast cancer disparities, that focus on the strengths of our mentors and our environment. Trainees will be supervised by a primary mentor and up to two secondary mentors with strong track records in breast cancer and/or disparities research and successful mentoring of graduate-level students. Trainees are expected to present their breast cancer disparities research at scientific meetings as well as participate in professional development seminars.

This program will improve knowledge of the causes of health disparities and effective methods of preventing, diagnosing and treating disease and promoting health. The training program will also enhance trainee's research and professional development skills, increase trainee's knowledge of disparities in breast cancer outcomes, provide support in developing new research projects, and chances of securing future research funding and careers in breast cancer disparities.



**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.

Using Hsp90 inhibitors to treat triple negative breast cancer

Investigator(s): Abena Agyeman, Ph.D.; Suzanne Conzen, M.D. (Mentor); Rita Nanda, M.D. (Co-Mentor)

Lead Organization: University of Chicago

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15333330

Public Abstract:

This is an exciting time in breast cancer biology research, as we are beginning to identify targetable proteins that drive triple-negative breast cancer (TNBC) growth. For example, while TNBCs don't express estrogen, progesterone or HER2 receptor proteins, a subset of them do express significant glucocorticoid receptor (GR), androgen receptor (AR) and Janus Kinase (JAK) proteins. High GR-expressing TNBC is associated with earlier relapse after chemotherapy, while high AR expression promotes tumor cell proliferation. Janus Kinase (JAK) proteins play a role in both TNBC proliferation and chemo-resistance.

In addition to GR, AR and JAK proteins, TNBCs activate interconnected pro-cancer "signaling" pathways; therefore the need for simultaneous targeting of these pathways is of great importance. One approach for targeting multiple key proteins at once is to inactivate their common "chaperone" protein. These proteins associate with "client proteins" and shepherd them around the cell so that they fold properly and are functional. Hsp90 is an important chaperone protein that escorts cancer-promoting client proteins, thereby allowing tumor growth. When Hsp90 activity is blocked by a specific Hsp90 inhibitor, these cancer causing client proteins are misfolded and subsequently degraded. While previous Hsp90 inhibitors were quite toxic, new safer small molecule drugs are now available. In Phase 1 Hsp90 inhibitor clinical trials, there have been some dramatic responses of TNBC growth inhibition, but the specific characteristics of the responding tumors that allow them to be sensitized and shrink are not known. The goal of our studies is to discover which cancer-promoting client proteins are targeted by Hsp90 inhibitor treatment in TNBC, and use them to potentially identify which TNBCs are likely to respond.

We will study known TNBC oncogenic Hsp90 client proteins GR, AR and JAK, as well as examine "global" protein changes in the pre-clinical setting in response to Hsp90 inhibitors. Degraded Hsp90 client proteins will be present in significantly lower amounts after treatment with an Hsp90 inhibitor. This pre-clinical data will then be confirmed in TNBC patient biopsies taken before and after Hsp90 inhibitor neoadjuvant treatment. We will also perform global protein analysis in patient biopsies and compare to our pre-clinical results so that we can parse out a few biologically relevant client proteins. Our studies will provide new insights into TNBC biology while developing a much needed treatment for TNBC.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Loss of the lncRNA Malat1 impacts breast tumor progression and metastasis

Investigator(s): Gayatri Arun, Ph.D.; David Spector, Ph.D. (Mentor)

Lead Organization: Cold Spring Harbor Laboratory

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15332247

Public Abstract:

We have identified a long nuclear retained non-coding RNA, Malat1, whose knockdown with a highly specific therapeutic leads to differentiation of primary luminal B breast tumors to a less aggressive state and significantly impacts metastasis. Malat1 is one of the most abundant long non-coding RNAs whose expression is altered in many different cancers including breast cancer. Malat1 was originally identified as an RNA whose expression was increased in primary tumor that subsequently metastasized in non-small cell lung cancer patients. In collaboration with other groups we have shown that Malat1 loss using antisense oligonucleotides (ASOs) results in reduced metastasis in mice where lung cancer cell lines of human origin was transplanted. Studies have also shown that, Malat1 gene mutation occurs frequently in luminal breast tumor patients. Our preliminary data on matched primary and metastatic tumors from patients show that MALAT1 is highly abundant in metastatic lesions compared to the primary tumor. Thus Malat1 is an exciting target for understanding metastatic breast cancer and understanding its role in disease progression and metastasis is highly relevant for therapeutic and clinical implications.

Here, I propose to address the role of Malat1 in mammary breast tumor using antisense (ASOs) mediated knock down of Malat1 RNA in mouse models of breast tumors, such as MMTV- PyMT model that recapitulates human luminal B tumors and luminal PDX model. Additionally we will also employ a complimentary approach wherein, organoids, obtained from tumor mammary gland of the mouse models described above will be treated with the ASOs to study their property. We will also analyze the down stream effect of the loss of Malat1 in breast tumor tissue and the tumor organoid to understand the impact of the ASO medicated knock down and to study the mechanism of action. Anti-sense oligonucleotides are a short stretch of DNA that work by blocking the target RNA in the cell and direct them to degradation. Currently these are in clinical trials for many diseases such as spinal muscular atrophy and Duchenne Muscular Dystrophy. Malat1 knock out mice developed in our lab has no obvious phenotype and no changes in the physiology of the animal were observed. Thus it is believed that Malat1 has more specific role to play in tumors and thus its loss in tumors using the Malat1 specific ASOs will specifically impact tumors.

These studies proposed above will be the basis to extend our findings to subsequent clinical trials. The optimization of the use of Malat1 ASO in the organoids will also be useful in the future to evaluate the effect of Malat1 loss in tumor organoid derived from patients which requires very less biological material and study the patient tumor response to ASO which can be subsequently translated to a clinical treatment protocol. Overall this study has a very high impact in understanding the role of Malat1 in treatment against metastatic breast cancer.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Ubiquitin-dependent regulation of EMT in breast cancer metastasis

Investigator(s): Antoni Celia-Terrassa, Ph.D.; Yibin Kang, Ph.D. (Mentor)

Lead Organization: Princeton University

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15332075

Public Abstract:

Breast cancer is the most common female cancer and the second leading cause of cancer-related death in the United States. When breast cancer is detected early, patients have a five-year survival rate of 98.3%. However, after metastasis, where breast cancer spreads to distal organs, the five-year survival rate plummets to 24%, with most patients eventually die from the disease. Understanding what molecules regulate this process could provide a new therapeutic approach toward blocking metastasis and improving patient survival. There are specific molecular mechanisms, which trigger tumor cells to spread out from the primary tumor, and these gene alterations are orchestrated by a process called epithelial-mesenchymal transition (EMT). EMT is a highly-conserved embryonic development program that allow tumor cells to acquire migratory/invasive properties and escape from the primary tumor. Furthermore, EMT has been to cancer stem cell properties in breast cancer. Therefore, we want to better understand how the main EMT inducers are regulated and how best to generate targeted therapies to block this key step in metastasis.

The transcriptional factor SLUG has been well established as a strong driver of EMT, cancer stem cell function and metastasis in breast cancer. However, the molecular mechanism underlying the increased expression of SLUG protein in invasive breast tumors remains poorly understood. Most transcription factors are degraded rapidly in cells because of the E3 ubiquitin ligase-mediated proteasome degradation pathway, the main mechanism of protein degradation in cells. On the other hand, there are enzymes that ubiquitin marks from proteins, which prevents their degradation by the proteasome. These enzymes are called deubiquitinases (DUBs). We performed genome-wide E3 ligase and deubiquitinase screens and identified candidate E3 ligase and deubiquitinase regulating SLUG through the ubiquitin/proteasome pathway. We hypothesize that these E3 ubiquitin ligase and deubiquitinase regulates EMT and breast cancer metastasis by modulating the SLUG protein expression level by degradation or stabilization of the protein, respectively.

In our proposed study, we will use a series of biochemical analyses, in vitro and in vivo metastasis assays, and clinical correlation studies to investigate the role of this E3 ubiquitin ligase and deubiquitinase in SLUG protein degradation, EMT, and metastasis. Discovery of a novel E3 ubiquitin ligase targeting the SLUG protein, and especially a deubiquitinase stabilizing SLUG, has significant translational value in providing a new therapeutic approach to block cancer metastasis. Small inhibitors to specifically block the interaction between DUB with SLUG would decrease its stability and promote degradation. This could block EMT, breast cancer stem cell activity and metastasis, and thereby, potentially improve cancer patient survival.



**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.

A novel function for ALK4 in suppressing breast cancer progression

Investigator(s): Jian Chen, Ph.D.; Gerard Blobel, M.D., Ph.D. (Mentor); Donald McDonnell, Ph.D. (Co-Mentor)

Lead Organization: Duke University Medical Center

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15336023

Public Abstract:

Most breast cancer patients die because of a process called metastasis in which the breast cancer cells spread to distant vital organs. Once breast cancer advances to the metastatic stage, current therapeutic strategies are largely ineffective. Therefore, identification of novel therapeutic targets for metastatic breast cancer are urgently needed. Metastatic breast cancer develops from localized lesions where the cancer cells are restricted by the basement membrane. The cancer cells acquire mutations that allow them to invade through the basement membrane, leading to disease progression. Breast cancer metastasis involves multiple steps, including cell migration and invasion that allows cancer cells to enter blood vessels, survive in the circulation, and colonize the second organ. In addition, the cancer cells undergo a process termed epithelial to mesenchymal transition (EMT) by which the cancer cells lose epithelial cell features and gain connective tissue cell features. The cancer cells that have undergone EMT have enhanced migration and invasion capabilities and increased survival. Here, we aim to identify the changes that increase the ability of breast cancer cells to spread, and aim to develop novel therapeutics for treating breast cancer metastasis. We recently uncovered that activin receptor-like kinase 4 (ALK4), a transforming growth factor-beta (TGF- β) superfamily receptor, is mutated in some breast cancers, with decreased ALK4 expression correlating with high grade breast cancer, advanced stage, and a poorer prognosis. TGF- β is a family of related proteins that binds cell membrane receptors and sends signals into the nucleus to regulate gene expression. We utilized a genetic approach to decrease ALK4 protein levels in cultured human mammary epithelial cells and breast cancer cells and demonstrated that loss of ALK4 results in enhanced migration, invasion and EMT, which is often induced by TGF- β . Conversely, restoring ALK4 expression in ALK4 silenced highly metastatic cells and suppressed breast cancer metastasis in a mouse model of breast cancer. In the absence of ALK4, TGF- β signaling was increased in these breast cancer cells. Interestingly, we also found that decreased ALK4 increases TGF- β levels at the cell surface. Therefore, we hypothesize that loss of ALK4 increases TGF- β receptors and their signaling to promote breast cancer progression and metastasis by increasing cell invasion and EMT. In our proposed study, we will investigate how ALK4 expression is decreased during breast cancer progression. We will also assess how loss of ALK4 enhances TGF- β receptors and their signaling, and test whether inhibition of TGF- β signaling can block breast cancer metastasis induced by ALK4 loss in a murine model. The scientific findings of this proposed work could identify ALK4 as a novel biomarker to predict breast cancer progression and a therapeutic target in the treatment of metastatic breast cancer.



**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.

Clinical identification and regulation of cancer stem cells in TNBC

Investigator(s): Yuanzhang Fang, Ph.D.; Yi Li, Ph.D. (Mentor); Michael Lewis, Ph.D. (Co-Mentor)

Lead Organization: Baylor College of Medicine

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15330612

Public Abstract:

Approximately 15% of human breast cancer cases are triple negative (TNBC), which is associated with high tumor grade, increased risk of visceral or cerebral metastasis, and poor survival after recurrence. TNBC has a strikingly higher rate of mortality and distant recurrence within the first 5 years of diagnosis compared with non-TNBC. Breast cancers may be driven by a small population of cancer stem cells (CSCs), and these cells are particularly abundant in triple-negative disease. CSCs are a subpopulation of tumor cells with the ability to undergo self-renewal and recapitulate the entire tumor population *in vitro* and *in vivo*, and they are responsible for tumor growth and recurrence as well as treatment failure. Therefore, examining CSCs in human breast cancer may help guide patient treatment and may lead to better drugs to subsequently target them.

While breast CSCs can be identified using sophisticated assays in a laboratory setting, until now CSCs cannot be easily assessed in a clinical setting on frozen or paraffin embedded tissues. Consequently, the value of CSC theory has not been fully harnessed to benefit breast cancer patients. Our preliminary data using both mouse models and human TNBC cell lines suggest that cytokeratin 6 is a novel marker of breast CSCs. Cytokeratin 6 is highly stable protein, and I have already developed an assay that is suitable for detecting cytokeratin 6 in frozen or paraffin embedded human breast cancer samples. Therefore, in this proposal I will validate cytokeratin 6 as a marker of CSCs in human TNBC samples. If successful, our data could have direct and immediate clinical implications.

We have found that these cytokeratin 6-positive CSCs produce a soluble protein, interleukin 1, that can maintain self-renewing potential of CSCs. This is novel because this type of protein was previously found to be made only by immune cells that infiltrate cancer, but not cancer cells themselves. I will test whether this interleukin 1 protein indeed regulates CSCs in human breast cancer tissues that are grafted in mice. In addition, I will test whether targeting interleukin 1 and the signaling pathway that it controls can suppress CSCs and halt TNBC progression.

Scientific Impact: My work may lead to the identification of a new CSC marker for human breast cancer, and may implicate an interleukin-mediated signaling pathway as a key factor in controlling CSCs and TNBC progression.

Clinical impact: My work on K6a a CSC marker may lead to a new clinical assay for assessing CSCs in human breast cancer patients. My mechanistic studies on key factors regulating CSCs may implicate IL-1 signaling as a novel molecular target for treating TNBC patients. Moreover, my work may provide an efficacious adjuvant chemotherapy for preventing TNBC progression and relapse.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Overcoming resistance to treatment of brain metastases from HER2 positive breast

Investigator(s): Gino Ferraro, Ph.D.; Rakesh Jain, Ph.D. (Mentor)

Lead Organization: Massachusetts General Hospital

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15331878

Public Abstract:

Scientific rationale: Patients with metastatic breast cancer have a median survival of two years, and account for 40,000 deaths, annually, in the US alone. Human Epidermal Growth Factor 2 (HER2)-positive breast cancer represents about 20-25% of all breast cancer, and is a particularly aggressive subtype that is associated with a poor prognosis. Up to 50% of patients with metastatic HER2-positive breast cancer will eventually develop brain metastasis. Unlike HER2-amplified breast cancers in extra-cranial locations, brain metastases do not respond to HER2-targeted therapies. The standard treatment option for patients with brain metastases, whole-brain irradiation, provides only a limited survival benefit at the cost of high morbidity. The mechanisms behind the differential response of brain metastases from HER2-expressing breast cancer to these agents, compared with extra-cranial disease, remain unknown. My project is dedicated to identifying the resistance mechanisms of breast cancer brain metastases, and then developing clinically translatable strategies to overcome this resistance – ultimately to prolong survival and increase the quality of life of breast cancer patients with brain metastases.

My objective is to design and undertake clinically relevant experiments to reveal and block the mechanisms of metastatic progression and resistance to current therapies. The training plan I propose here will allow me to develop an in depth understanding of clinically relevant research and expose me to new cutting edge experimental techniques. The research proposal I describe here has been designed to remain as clinically relevant as possible throughout the study. This is an invaluable opportunity to me, as a basic scientist, not to stray too far from clinical relevance while performing basic research. Together, my proposed fellowship plan will allow me to strengthen my chances of becoming an independent scientist performing clinically relevant research to improve treatment of metastatic breast cancer patients.

Impact of research: My project focuses on HER2 positive breast cancers, which often metastasize to the brain. There are limited treatment options for patients with these metastatic lesions. I plan to use our pre-clinical animal model to develop a combinatorial therapeutic approach to block resistance in the brain, while selectively targeting HER2 positive tumor cells with currently approved therapies. We have gathered preliminary data demonstrating that a protein related to HER2, HER3, is present in brain metastases and that inhibiting its function could improve HER2 targeted therapies. We have collaborations with breast oncologists who are eager to begin clinical trials studying the therapeutic outcome of these combinatorial treatment approaches.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Cellular and molecular mechanisms of breast cancer invasion

Investigator(s): Dan Hossamov Georgess, Ph.D.; Andrew Ewald, Ph.D. (Mentor)

Lead Organization: Johns Hopkins University-School of Medicine

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15332336

Public Abstract:

For breast cancer patients, the dissemination of the tumor through the body, a process called metastasis, marks the transition away from curable disease. Unfortunately, the biological mechanisms that initiate tumor metastasis are poorly understood, and most cancer therapies do not target metastasis. My objective is to identify which tumor cells initiate breast cancer metastasis, which of these cells' genes drive them to metastasize, and what novel drugs we can use to specifically target these genes. I have strong advocate/survivor support for the high potential impact of my research aims on breast cancer patient.

The gene Twist1 is frequently active in several types of breast cancers, and its presence is associated with increased tumor invasion and poorer survival for patients. In the breast tumor, Twist1 is known for initiating the dissemination of tumor cells. However, as tumors are composed of different types of cells but not all of which metastasize, my first aim is to use identify the cell type that is the most 'corruptible' into disseminating by Twist1. Starting from a controllable genetically engineered mouse model, I will culture breast tissue, switch on Twist1 in the different cell types, and use the microscope to observe which cells disseminate. I will then validate the dissemination of these cell types in cultured human tumors sampled from patients. The presence of such disseminative cells in human tumors could ultimately be applied to predict if a certain type of cancer will metastasize and how overall survival of the patient will be affected.

My second aim is to develop new therapies against Twist1-driven metastasis. Despite the fact that there are no drugs that can directly target Twist1, we know that Twist1 functions inside tumor cells by activating a multitude their genes. By combining mouse tissue culture, genetic engineering and methods for monitoring gene activation in the presence of Twist1, our lab has recently identified these Twist1-activated genes in the tissue from which breast cancers arise. I since found that the targeting of at least three of these genes with specific chemical compounds can block dissemination of cultured mouse tissue. We have also developed state-of-the-art techniques that allow us to culture individual patient-derived breast tumors and capture their invasion as it occurs in real time. As there are different types of breast cancers, I will validate chemical compounds successful in stopping tumor invasion for each major cancer type. By finding the tumor type which is most susceptible to a certain drug, we will be able to design more accurate and efficient preclinical and clinical studies to develop therapies with maximal potential benefit to patients diagnosed with that same tumor type.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Dynamics of cell fate decisions after breast cancer radiotherapy

Investigator(s): Adrian Granada, Ph.D.; Galit Lahav, Ph.D. (Mentor); Joan Brugge, Ph.D. (Co-Mentor)

Lead Organization: Harvard Medical School

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15331988

Public Abstract:

Most breast cancer patients receive adjuvant radiation therapy. Despite its success, still many patients gain little or no benefit from this treatment, as evidenced from the elevated rates of locoregional recurrence, distant metastatic spread, and breast cancer deaths. Unfortunately, those patients will nevertheless suffer the short and long-term side effects of the inefficient radiation therapy. Currently there are no reliable tools to predict how different patients will respond to radiotherapy. In addition, breast cancers are known to be extremely heterogeneous; cells react differently and some are insensitive in response to a specific treatment, which might account for the diverse outcomes among patients. Our aim is to develop patient-specific strategies that maximize the damage in tumor cells while minimizing the damage to normal cells. Recent studies in breast cancer have shown that classical breast cancer subtypes have different sensitivity to radiation. Many efforts are directed to improve the classification of breast cancer subtypes by characterizing the genetic make-up of the particular tumor. However, current therapies do not incorporate these differences, and instead follow a standardized protocol that consists of daily doses of radiation, over several weeks. The radiation beam induces DNA damage in both tumorous and nearby non-tumorous cells. Cells then initiate diverse cellular programs ranging from DNA repair and transient cell cycle arrest to terminal fates such as cell death and permanent cell cycle arrest. Despite its importance, the connection between breast cancer subtype and a specific cellular outcome remains largely unknown.

To address this challenge we have designed an experimental project at the single-cell level to quantitatively investigate the temporal response and fate of a collection of modified breast cell lines upon radiation. Most breast cancer studies are performed by averaging the behavior of a population of cancer cells. Such approaches cannot detect variation between cells and sometimes even mask the true behavior of single-cells. We will use a collection of breast cells carrying single genetic modification frequently found in breast cancer in combination with live cell imaging reporting on the state of each cell and test cells survival in response to a variety of fractionated DNA damages. We will develop computational tools for image processing and statistical analysis of single-cell data, and develop simple mathematical models connecting cellular states with cell-fate in response to various frequencies of radiation. This will be an interdisciplinary study integrating knowledge and skills from diverse disciplines including molecular biology, live-cell microscopy, radio-oncology, engineering and computational biology.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Hippo pathway activation in chemo-sensitive and -insensitive breast cancer

Investigator(s): Sara Hanna, Ph.D.; Gary Johnson, Ph.D. (Mentor)

Lead Organization: University of North Carolina at Chapel Hill

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15331014

Public Abstract:

Breast cancers are generally divided into subtypes based on the presence, or lack, of receptors found within the tumor: estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2). The most successful treatments for breast cancer are hormonal and targeted therapies for these receptors. Unfortunately, none of these receptors are found in women with the triple negative breast cancer (TNBC) subtype and patients are treated with nonspecific chemotherapies. While 20-30% of TNBC patients respond to chemotherapy treatment, TNBC patients with residual disease post-therapy have low overall survival rates. Even patients who do respond to chemotherapy treatment are likely to have recurrence and metastasis years after the initial treatment. It is therefore necessary to develop novel and improved therapies for patients with TNBC. We propose to interrogate the difference between Hippo pathway activation in chemo-sensitive and -insensitive TNBC cell lines and patient samples using our novel MIB/MS (multiplexed inhibitor beads and mass spectrometry) technology. Kinases themselves are highly tractable molecular targets that have been shown to be dysregulated in many cancers, and cancer cells have been shown to respond to targeted kinase inhibitor therapies. The Hippo pathway is an evolutionary conserved regulator of tissue growth and cell fate that has been shown to be dysregulated in many cancers, including breast cancer. Therefore, determining kinase activation states within the Hippo pathway in response to chemotherapy in TNBC should enable understanding of why some tumors respond to chemotherapy and others remain insensitive. Our studies will define kinase dynamics within the Hippo pathway that can be used to target specific kinases with small molecule inhibitors to enhance the sensitivity of chemo-resistant tumors to combination therapies. Using these methods, we hope to find better treatment options for patients with TNBC.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Targeting urokinase receptor for diagnosis & therapy of aggressive breast cancers

Investigator(s): Efrat Harel, Ph.D.; Charles Craik, Ph.D. (Mentor); Laura van't Veer, Ph.D. (Co-Mentor)

Lead Organization: University of California, San Francisco

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15330246

Public Abstract:

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer representing 15-20% of the invasive breast cancer cases of women. These women have a high rate of recurrence with a poor prognosis. Cancer cells from the breast can leave the confines of the gland and spread or metastasize to other parts of the body making their new environments cancerous. TNBC most commonly spreads to visceral organs including lung, liver, brain and bone leading to the formation of cancer metastases. Once a primary TNBC tumor has metastasized, death generally occurs within two to three years.

The ability to monitor the disappearance or reappearance of metastases would be beneficial to physicians selecting the best treatment for a specific patient. Accurate and reliable diagnostic methods for TNBC are urgently needed and could be achieved by identifying cellular markers (proteins) that are expressed at higher levels in metastatic cancer. Antibodies (Abs), proteins of the immune system that naturally recognize other proteins with high selectivity and specificity, will be developed to recognize the cancer markers. Abs that recognize the cancer cells marker, uPAR, will serve as a diagnostic tool to stratify breast cancer subpopulations according to their marker's expression levels. That will be done using human breast cancer tissue from biopsies with known outcomes and classification. In addition, we will combine two or more antibodies against uPAR into a modular platform that will result in a specific tool for non-invasive detection of uPAR, predicting early metastases of TNBC. Our preclinical antibody platform will be evaluated also as a therapeutic monotherapy that could, if successful, be offered to patients at the earliest stage of metastasis, inhibiting tumor aggressiveness and growth, and leading to better patient outcomes.

My academic training has provided me with an excellent background for the project in multiple biological disciplines. The current research plan is designed to develop tools that will provide a better understanding of breast cancer aggressiveness as well as in targeting both primary tumors and their subsequent metastases. This research proposal presents interdisciplinary research and required expertise in antibody engineering, and breast cancer oncology and immunology which will be supported by the mentor committee that includes a patient advocate and collaborators that are experts in these respective areas and who are committed to providing training for the proposed research.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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A role for PDK1 in acquired resistance to CDK4/6 inhibitors

Investigator(s): Valerie Jansen, M.D., Ph.D.; Carlos Arteaga, M.D. (Mentor)

Lead Organization: Vanderbilt University Medical Center

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15329319

Public Abstract:

Breast cancer is the most common cancer diagnosed in American women and is the second leading cause of female cancer-related deaths. More than two-thirds of breast cancers express the estrogen receptor (ER) and thus depend on estrogen for growth. Treatment for ER-positive breast cancer is aimed at blocking ER function using antiestrogens such as tamoxifen, fulvestrant and aromatase inhibitors (letrozole, anastrozole). However, after an initial response to treatment many ER-positive tumors develop resistance and then progress, resulting in more women dying from ER-positive breast cancer than all other breast cancer types combined. Thus, it is absolutely critical to understand the mechanism of de novo and acquired resistance and to find better ways to target this major subtype of breast cancer in order to prevent deaths from this disease. One of the most promising new therapies for breast cancer is the development of cyclin-dependent kinase (CDK) 4/6 inhibitors. CDK4 and CDK6 are proteins involved in the regulation of the cell cycle pathway. Inhibition of CDK4 and CDK6 results in cell cycle arrest thus preventing the proliferation of cancer cells. Early clinical trials have shown that CDK4/6 inhibitors are active against ER-positive breast cancers and are likely to be approved for the treatment of patients with this cancer subtype. However, as for other targeted therapies, development of resistance to CDK4/6 inhibitors is expected. Our long-term goal is to identify novel therapeutic strategies capable of preventing and reversing clinical resistance to CDK4/6 inhibitors in ER-positive breast cancer. Based on preliminary data, we propose that 3-phosphoinositide dependent protein kinase 1 (PDK1) is important for the acquired resistance to CDK4/6 inhibitors, thus providing a rationale for therapeutic targeting of PDK1 and CDK4/6 in combination as a novel treatment strategy for ER-positive breast cancer. In this proposal we will investigate the mechanisms by which PDK1 signaling is involved in the growth of breast cancer cells resistant to CDK4/6 inhibition. We will determine if the combination of PDK1 and CDK4/6 inhibition will result in superior antitumor activity in human ER-positive breast tumors that we will establish in experimental mice. In summary, this investigation should meaningfully contribute to the understanding of how ER-positive breast cancers acquire resistance to CDK4/6 inhibitors, and in turn contribute to the eradication of ER-positive breast cancer.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Targeting basal-like breast cancer via CRISPR-mediated multiplex gene knockout

Investigator(s): Xin Jin, Ph.D.; Todd Golub, M.D. (Mentor); Kwanghun Chung, Ph.D. (Co-Mentor)

Lead Organization: Broad Institute

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15331102

Public Abstract:

Basal-like breast cancer (BLBC) is the most malignant form of breast cancer. An effective targeted therapy for this breast cancer subtype remains unavailable to date. Combination therapy that co-targets multiple oncogenic signaling has emerged as an appealing therapeutic approach. However, an integral approach for comprehensive investigation of combination therapies is still lacking. Identifying optimal combination options has become a pressing need in medical oncology to reduce the mortality rate of BLBC. Inspired by this clinical challenge, this proposal intends to take a rational approach and establish a systematic platform for developing combinatory strategies. The project aims to develop a multiplexed CRISPR-based gene perturbation system to investigate and model combination therapies for BLBC. CRISPR is a cutting-edge technology that allows us to abolish gene functions by editing DNA sequences of specific genes. It is more accurate and versatile than previous tools. The novel multiplex design here allows this approach to screen gene combinations faster than current one-by-one methods. From a defined set of genes that are functionally relevant to BLBC malignancy, the project aims to identify optimal gene targeting combinations against BLBCs in clinical relevant experimental models. Based on the identified genetic combinations, the project will move forward to find whether small molecule inhibition of the target genes can achieve the same effects as CRISPR editing. In-depth mechanism investigation and detailed characterization of the cancer lesions undergoing the combination treatment will be performed to reveal the molecular underpinnings of its therapeutic efficacy as well as potential toxicities. Collectively, these efforts aim to establish a pipeline of mechanism-based combination therapy for BLBC that is translatable to the clinic, from uncovering cancer vulnerabilities to developing novel therapeutics.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Targeting CDK8 to overcome resistance to targeted therapies in breast cancer

Investigator(s): Steve Lee, Ph.D.; Stephen Kron, M.D., Ph.D. (Mentor); Ralph Weichselbaum, M.D. (Co-Mentor)

Lead Organization: University of Chicago

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15333618

Public Abstract:

Metastases are the cause of most human breast cancer deaths. The overall 5-year survival rate for breast cancer has improved to 89% today, whereas the 5-year survival rate for patients with distant metastatic breast cancer is still lower than 25%. Although conventional treatments such as surgery, chemotherapy, and radiotherapy can generally control primary tumor growth, recurrent and metastatic breast tumors are often inaccessible or resistant to these treatments.

To overcome this challenge, cancer immunotherapy using the adaptive immune system has been extensively studied. With advances in cancer immunology and development of antibodies, various immunotherapeutic antibodies are currently used to systemically treat metastatic breast cancers. Although the antibody treatment can shrink tumors and slow cancer growth, tumor recurrence and metastasis persist in most patients despite the treatment. The therapeutic limitations of the antibodies for metastatic breast cancer are mainly attributed to low tumor-targeted delivery efficacy and insufficient anti-cancer immune response. Moreover, “off-target” effects of the antibody can cause severe side effects, such as autoimmune disorders. To improve current antibody immunotherapy, a clinically-viable approach for efficiently guiding the antibody to targeted tumors and inducing anti-cancer immunity is necessary.

In this proposed research, radiation will be utilized not only as a guide for delivering antibodies to the targeted tumor but also as an immune modulator for enhancing immunotherapy against breast tumor metastasis. Our research will open new opportunities for treating recurrent and metastatic breast cancer by the combination of antibody immunotherapy with radiation therapy. Our research will also provide new knowledge about the mechanism of inducing adaptive anti-tumor immunity, which will be useful for development of novel immunotherapeutic interventions. Furthermore, using FDA-approved immunotherapeutic antibodies and current radiation therapy systems, our method will be directly applied to advanced breast cancer patients through a clinical trial program at the University of Chicago. Success in the clinical trials will reduce mortality due to breast cancer recurrence and metastasis.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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Targeting CDK8 to overcome resistance to targeted therapies in breast cancer

Investigator(s): Martina McDermott, Ph.D.; Igor Roninson, Ph.D. (Mentor)

Lead Organization: University of South Carolina - USC

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15329865

Public Abstract:

Scientific objective and rationale:

Therapies such as letrozole or tamoxifen which target breast cancers (BC) expressing estrogen receptor (ER) and trastuzumab which targets BC expressing HER2 have significantly improved the outcome for BC patients and opened up an era of cancer treatment known as targeted therapy. Unfortunately, many patients either fail to respond to targeted therapies despite the presence of the target receptor in their tumors, or respond initially but go on to develop resistant disease. The treatment options for these highly aggressive and ultimately lethal tumors are extremely limited. The purpose of this study is to utilize a dual treatment strategy combining ER or HER2 targeted therapies with an inhibitor developed by our team that targets a protein called CDK8, expression of which is associated with poor response to treatment in BC patients. Our preliminary results show that combining either ER or HER2 targeted therapies with CDK8 inhibition strongly inhibits BC growth, even in cancer cells that exhibit resistance to a targeted therapy. We found that inhibition of CDK8 with our drug is preventing a specific signaling event (phosphorylation of STAT1) within the cancer cells that may prime such cells to be killed by the targeted drugs.

Therefore we are proposing to test whether CDK8 provides a new target to improve the treatment and survival of patients with ER and/or HER2 positive BC. We will do this by treating multiple cancer cell lines, some of which are sensitive to ER/HER2 targeted therapies and others which exhibit resistance, with combinations of the CDK8/ER inhibitors to investigate the anti-BC efficacy of such drug combinations in cell culture and in animal studies. We will also determine if CDK8 inhibition will prevent BC cells from becoming resistant to ER- and HER2-targeting drugs. We will also analyze CDK8 expression and STAT1 phosphorylation in samples from normal and cancerous human breast tissue, to confirm the clinical relevance of our laboratory studies.

Ultimate applicability of the research:

Successful completion of this project will provide a very strong rationale for clinical trials combining CDK8 inhibitors with ER inhibitors in ER-positive BC and with HER2 inhibitors in HER2-positive BC. The overall goal of the research that we propose is to provide a new treatment strategy for those breast cancer patients who at present have no viable treatment options available to them. We hope that this project will contribute to changing the lives of the millions of women who will develop breast cancer within and beyond our lifetimes.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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The role of breast cancer exosomes in organotropic metastasis

Investigator(s): Ayuko Nitadori, Ph.D.; David Lyden, M.D., Ph.D. (Mentor); Jacqueline Bromberg, M.D., Ph.D. (Co-Mentor)

Lead Organization: Joan & Sanford I. Weill Medical College of Cornell University

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15331556

Public Abstract:

Cancer spread, or metastasis to distant vital organs such as bone, lung and brain is the most devastating feature of breast cancer, accounting for over 40,000 deaths in the United States each year. Over the past decade, we have gained a better understanding of how cells in the body other than breast cancer aid in the growth and spread of cancer. It is crucial now to investigate the cancer cell-host cell interactions that drive malignant behaviors of susceptible epithelial cells in the breast as well as their secondary homes. In 1889, Stephen Paget first proposed that cancer spread is a non-random event, yet why cancer in general and breast cancer in particular spreads to specific organs remains one of the greatest mysteries in cancer biology. There are growing number of studies demonstrating tumor-derived microvesicles, referred to as exosomes, may alter the environment in target organs in which cancer will develop. However, what mechanisms drive this process occurs, and the specific role of exosomes in tumor progression remains unknown. In this study, I will be using a well-characterized human breast cancer cell line model to investigate the role of exosomes in breast cancer progression. My preliminary data shows that the breast cancer organ-specific cell line derived exosomes home to the future metastatic sites where the cancer cells of origin are known to spread. Furthermore, pre-treatment with lung-homing breast cancer exosomes can instruct cancer cells that lack the capacity to colonize the lung to now spread to the lung. In this study I am investigating which molecules packaged in organ-specific exosomes are responsible for exosome homing to organ specific sites of cancer spread. I will identify which cells in each future metastatic organ are responsible for uptaking breast cancer exosomes and also what changes are induced in these cells by cancer exosomes. The ultimate goal of this novel and unique proposal is to establish the clinical, biological and functional relevance of breast cancer-derived exosomes in organ specific cancer spread, and to establish whether exosomes that home to future metastatic niches contain unique cargos that are therapeutically targetable or can be used as biomarkers for early diagnosis of cancer spread.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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The consequences of centrosome amplification in breast cancer

Investigator(s): Remigio Picone, Ph.D.; David Pellman, M.D. (Mentor); Kornelia Polyak, M.D., Ph.D. (Co-Mentor)

Lead Organization: Dana-Farber Cancer Institute

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15333560

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.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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β 1-integrin hyperactivation as a novel anti-breast cancer therapy

Investigator(s): Laila Ritsma, Ph.D.; Sridha Ramaswamy, M.D. (Mentor)

Lead Organization: Massachusetts General Hospital

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15329694

Public Abstract:

One of the major problems in breast cancer is the regrowth of a tumor after a patient was thought to be cured. This can happen even years later. Traditionally, breast cancer is treated with chemotherapy. This therapy is very effective because it kills fast dividing cells, like cancer cells. However, a downside of chemotherapy is that some cancer cells are not dividing fast at all; they divide rather slowly and seem to sleep (or be dormant). Once the chemotherapy is stopped, these cells can “wake up” at any time, and regrow to form a new tumor (sometimes in another organ).

To prevent regrowth of the tumor, all cancer cells including the dormant cells must be killed. To do so, a combination of chemotherapy and a drug that kills dormant cells is needed. In this way, the chemotherapy can kill dividing cells, and the other drug can kill the non-dividing dormant cells.

To find such a drug that kills dormant cells we need to understand how dormant cells are created. By studying dormant cells, our lab has found a molecule called β 1-integrin that, when not active, causes the breast cancer cell to become dormant. We then designed a new drug (TS2/16) that activates β 1-integrin and awakens all of the sleeping cells. When we gave this new drug to mice after treatment with chemotherapy, all of the dormant cells disappeared, and regrowth of the tumors was greatly prevented. However, we do not know exactly how TS2/16 is having its effect. In this grant we propose a set of experiments to further explore this. This is important, because this information will help improve our understanding of the new drug. This new understanding could provide new therapeutic option such as combining it with other drugs and forms of therapy to strengthen and improve treatment of breast cancer.



**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.

Therapy of triple negative breast cancers by targeting the TPX2 mitotic regulator

Investigator(s): Julia Rohrberg, Ph.D.; Andrei Goga, M.D., Ph.D. (Mentor); Zena Werb, Ph.D. (Co-Mentor)

Lead Organization: University of California, San Francisco

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15331114

Public Abstract:

The aim of my study is to find novel targeted therapies against triple negative breast cancer (TNBC), the subtype with the poorest patient outcome for which no therapeutic strategies are currently available. As it is the most difficult-to-treat form, there is an urgent need to deepen our understanding of this aggressive breast cancer and to identify clinically relevant targets for therapeutic intervention. Our lab recently found an oncoprotein called MYC that is highly elevated in TNBC and associated with poor prognosis. We seek to take advantage of this distinctive molecular feature to identify effective treatment strategies. Unfortunately, no small molecule inhibitor for MYC is available for clinical use. An alternative approach to selectively kill MYC-driven tumors is to inhibit those proteins that are indispensable for the viability of such tumors but are not essential in non-tumorigenic cells. We were successful in identifying such a protein, called CDK1, and in translating this concept into a clinical trial at UCSF. However, CDK1 is also an important engine for normal cells to divide. Thus, its inhibition could potentially lead to toxicity and limit the usefulness in the clinic. In my proposal, I seek to find a novel, non-toxic, efficacious targeted therapy based on our lab's success of CDK1 inhibition.

I analyzed patient data to find CDK1 substrates that are specifically elevated in TN tumors. I discovered the CDK1 substrate TPX2 to be required for the TNBC tumor cell to survive. Using bioinformatics analyses of several clinical cohorts, we found that patients with elevated TPX2 have a dramatically worse prognosis than those with low TPX2 expression.

In my proposal, I will study how the tumor cells die after depletion of TPX2 and why TPX2 is indispensable for MYC overexpressing TNBC tumors. I will further evaluate the preclinical efficacy of targeting TPX2 function and its influence on the metastatic process.

I will use various cell based assays and the best pre-clinical mouse model of TNBC to date to address these proposed aims. I will screen drugs that are currently being evaluated in clinical trials, thus my proposal harbors a high potential to translate into clinic. The understanding of the underlying biology will help to identify the patient population with the strongest response, which will make an existing drug much more powerful and efficacious (while limiting toxicity) in personalized therapy. My study aims to identify a compound that can readily go into early phase clinical trials here at UCSF to evaluate its effectiveness against a selected patient population with breast cancers that have elevated MYC and TPX2 expression.



**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.

Chromosomal enhancer/architectural misregulation in breast cancer

Investigator(s): Jia Shen, Ph.D.; Michael Rosenfeld, M.D. (Mentor)

Lead Organization: University of California, San Diego

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15333267

Public Abstract:

Of the 180,000 cases of invasive breast cancer diagnosed each year in the United States, more than 70% express estrogen receptor a (ERa), and are subjected to endocrine therapies. However, approximately 30% of ERa-positive (ER+) breast cancers exhibit de novo resistance, whereas 40% acquire resistance to these therapies. Endocrine-resistant ER+ disease accounts for approximately one in four breast cancers, similarly to the triple-negative phenotype that does not express ERa, progesterone receptor (PR) nor ERBB2 amplification, and it is not well served by current targeted therapies. Two major challenges for the successful treatment of breast cancer are the development of more specific biomarkers that predict therapeutic response to endocrine therapies and the identification of new therapeutic targets for endocrine-resistant disease. A prerequisite towards this goal would be a better understanding of ERa-mediated transcriptional network, exhibiting estrogen-dependent activation in the initial but later developing ligand-independent “autonomy” during cancer progression and/or following endocrine therapies. Recently, genomic sequencing of ER+ breast tumors before and after hormone deprivation revealed condensed recurrent mutations in ESR1, a gene coding for ERa. Of note, mutations in ESR1 are rare in treatment-naive primary ER+ breast cancer samples, indicating that ESR1 mutants are selected by hormone deprivation therapy, possibly as a result of the reduced estrogen state caused by aromatase inhibitors. However, the mechanistic nature of these selected ERa mutants, specifically their genome-wide transcriptional targets and the key underlying molecular events required for ligand-independent transcription activation, remains poorly understood. As advanced technologies have begun to uncover previously-unknown aspects of ERa- and/or the hormone-refractory mutant ERa-mediated transcriptional networks at the full chromosomal level, it is now, for the first time, possible to link the emerging discoveries, from clinical and basic research, to the mechanisms of ERa regulatory transcriptional programs important in breast cancer etiology. This proposed study will begin to address this important question and provide critical insights into the regulation of ERa-mediated gene transcriptional programs. This will uncover novel and previously-unsuspected key steps in ERa regulation of gene transcription that are likely to serve as new, potential targetable candidates for ER+ breast cancer patients who are refractory to hormone therapies. This proposed research would significantly advance our understanding of how ERa mutants succeed in evading hormone deprivation to activate cancer gene transcriptional programs, and will also facilitate the translation from bench to bedside by examining a novel combination strategy that would likely achieve a synergistic antitumor effect by simultaneously targeting estrogen/ERa and its regulatory programs required for the breast cancer progression.



**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.

Targeting breast to bone metastases via bone seeking metalloproteinase inhibitors

Investigator(s): Marilena Tauro, Ph.D.; Conor Lynch, Ph.D. (Mentor); Srikumar Chellappan, Ph.D. (Co-Mentor)

Lead Organization: H. Lee Moffitt Cancer Center & Research Institute

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15332812

Public Abstract:

In 2014, the American Cancer Society predicts that approximately 40,000 women will succumb to breast cancer. The primary cause of death is due to metastasis, that is the spreading of cancer cells from the breast to other part of the body. Studies have shown that the skeleton is one of the most prominent sites of metastasis for breast cancer. In bone, metastatic breast cancers induce extensive bone destruction by manipulating normal bone building cells known as osteoblasts and bone destroying cells known as osteoclasts. Excessive bone destruction causes a great deal of pain to women with bone metastasis and can lead to bone fracture. This in turn greatly impacts the patient's quality of life. Despite medical advances, the treatments available to women with bone metastases remain limited and geared toward pain management rather than actually curing the lesions. By understanding the factors through which metastatic breast cancer cells interact with the normal cells of the bone, we can develop new therapies to prevent that interaction. The Lynch Lab has demonstrated that an enzyme, matrix metalloproteinase-2 (MMP-2), is expressed by both breast cancer cells and bone cells. Importantly, we have found that MMP-2 is a key regulator of cell-cell communication and in allowing the cancer cells to grow in the bone environment. We therefore think that targeted inhibition of MMP-2 would be a valuable therapy in preventing the growth of metastatic breast cancer in bone.

To specifically target MMP-2, I have built a novel inhibitor that specifically prevents MMP-2 enzymatic activity. I have built this inhibitor on a bisphosphonate foundation. Bisphosphonates are chemicals that can specifically stick to areas of bone undergoing remodeling and they prevent bone destruction by killing the bone destroying osteoclasts. Therefore, by integrating MMP-2 inhibition into bisphosphonate structures, I have generated a powerful inhibitor of MMP-2 that can specifically target breast cancer cells growing in bone. This is important because the MMP inhibitor targets the skeleton where the breast cancer is growing (thus reducing whole body side effects). In my preliminary studies using a mouse model of bone metastasis, I have shown that bone seeking MMP-2 inhibitors (BMMPis) are very effective in preventing the growth of breast cancer in bone. In my Susan G. Komen fellowship, I propose to expand upon these preliminary findings in this grant application. Importantly however, I believe that these studies will be critical for the development of the BMMPis and their rapid translation to the clinic for the treatment of women with bone metastatic breast cancer. I expect that at the end of the study period I will have built up a body of data that will allow me to generate very competitive future grant applications so that I can transition to an independent investigator dedicated to finding cures for breast cancer.



**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.

Characterizing the anti-tumorigenicity, structure, and biochemistry of proBMPs

Investigator(s): Yuan Tian, Ph.D.; Timothy Springer, Ph.D. (Mentor); Judy Lieberman, Ph.D. (Co-Mentor)

Lead Organization: Children's Hospital Boston

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15334161

Public Abstract:

Breast cancer is the most common invasive cancer and the leading cause of cancer-related death among women. Despite significant progress in early diagnosis techniques like mammography and effective therapies like chemo-, radio- and immuno-therapies, treatments to prevent cancer cells from spreading and initiating new tumor growth in other tissues, a process called metastasis, are still lacking. A current concept is that metastasis is mainly due to a small population of cells in breast tumors called cancer stems cells (CSCs). These cells can break away from breast tumors, migrate to a distant site through the bloodstream, and start new tumor growth at a new location. Unfortunately, these breast CSCs are generally resistant to conventional chemo- and radio-therapies, making new therapies that specifically target these cells the most desirable to treat breast cancer patients. Previous research showed that a group of proteins called bone morphogenetic proteins (BMPs) markedly reduced the population of breast CSCs and hindered bone metastasis, making BMPs promising candidates for preventing breast cancer metastasis. BMPs are messenger molecules. They are secreted from some cells and bind to receptors on other cells. In this way, cells communicate with each other to coordinate proper development of different tissues and organs. There are other proteins in the body known as BMP antagonists, which can interact with BMPs and intercept the message delivered by BMPs. BMPs exist in two forms: mature BMPs and pro-form BMPs (proBMPs). In proBMP, a larger molecule known as prodomain connects to mature BMP. It has been established that prodomains help BMPs form properly, but whether they affect the anti-tumorigenic activity of BMPs has never been studied. We hypothesize that prodomains may change how BMPs bind to receptors or protect BMPs from antagonists, both of which could make proBMPs more effective anti-metastatic reagents than mature BMPs. –In this study, we will compare the abilities of proBMPs and BMPs to specifically reduce the number of breast CSCs and prevent their migratory behavior. To better comprehend differences between proBMPs and BMPs, we will also study how prodomains affect the way in which BMPs bind to receptors and antagonists. We will determine the atomic and molecular structure of proBMPs to fully understand how the prodomain interacts with BMPs. These studies will enable profound understanding of how prodomains impact BMP binding to receptors and antagonists, and hence influence the anti-tumorigenic activity of BMPs. The results from this proposed work will be used to identify the most anti-tumorigenic BMP or proBMP and translate them into potent anti-metastatic therapies to improve the lives of breast cancer patients.



**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.

NLK inhibitor as new targeted agent for endocrine resistant breast cancers

Investigator(s): Xian Wang, Ph.D.; Xiaosong Wang, M.D., Ph.D. (Mentor); Rachel Schiff, Ph.D. (Co-Mentor)

Lead Organization: Baylor College of Medicine

Grant Mechanism: P01 Basic and Translational

Grant ID: PDF15333523

Public Abstract:

About half of the breast cancer patients treated with endocrine therapy will relapse eventually. There is no effective treatment to overcome endocrine resistance due to the lack of mechanistic insights and viable targets. Our lab has identified a new therapeutic target for endocrine resistant breast cancer called nemo-like kinase (NLK). NLK is a serine-threonine kinase overexpressed in ~30% of breast tumors. Prognostic analyses suggest that NLK overexpression significantly and specifically correlates with worse outcome in tamoxifen-treated patients.

My previous studies show that NLK may promote tamoxifen-resistance via phosphorylating ER and its key coactivator SRC-3. Most importantly, I have identified a selective NLK inhibitor that has been proven safe in phase I/II clinical trial for inflammatory diseases. In vitro studies suggest that this drug potentially sensitizes endocrine-resistant breast cancer cells to tamoxifen treatment. Combination of NLK and mTOR inhibition showed promising therapeutic effect in a xenograft tumor with acquired tamoxifen resistance. The objectives of this study are to further assess the therapeutic value of the NLK inhibitor in combination with other targeted agents such as mTOR inhibitors in endocrine resistant breast cancer, and identify the biomarkers that may predict the tumor response to the targeted therapy cocktails.

This study will have substantial basic and clinical impacts. Co-targeting ER and alternative survival pathways may be the most effective means to combat endocrine resistance; such strategies have shown promising results in clinical trials. Here we have identified a new survival mechanism associated with endocrine resistance, and this project will develop the cocktails of NLK targeted therapy in combination with other targeted agents to manage endocrine-resistant breast cancers, as well as identify the potential biomarkers to predict tumor response and optimize the regimen of the targeted therapy cocktails. The outcome of this study could quickly move into clinical development, leading to a new line of targeted therapy as well as predictive assays for precision treatment, which would benefit a substantial population of incurable breast cancer patients. This project will greatly enhance my career goals to apply multidiscipline approaches including genomics, cancer biology, preclinical and translational researches to better understand the breast cancer biology and translate the laboratory advancements into improved patient care.



**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.

Epigenetic coding of EMT regulators as diagnostic targets for breast cancer

Investigator(s): Yun Zhang, Ph.D; Robert Weinberg, Ph.D. (Mentor)

Lead Organization: Whitehead Institute for Biomedical Research

Grant Mechanism: P01 Basic and Translational

Grant ID: PDF15301255

Public Abstract:

Despite extensive research on breast cancer in the past few decades, breast cancer patients and oncologists are still facing two major problems: First, although there are over 230,000 women diagnosed in this country annually with breast cancer, only about 39,000 die from it. The difference between these numbers indicates the fact that many women are diagnosed with a form of breast cancer that would not progress to a life-threatening state even if left untreated. However, lack of information about the molecular network that governs the transition from a benign status of breast cancer cells to an aggressive one significantly limits the development of diagnostic methods to distinguish such patients. Second, for breast cancer patients with metastasis or recurrence, there are limited therapeutic options, largely due to the resistance of such diseases to currently available antitumor therapies. Accumulating studies conducted in various laboratories have confirmed the existence of cancer stem cells (CSCs) in breast cancer. CSCs are referred to as a subpopulation of neoplastic cells within a tumor that exhibit elevated abilities to seed new tumors and increased resistance to various types of chemotherapy. These abilities of CSCs naturally link it with tumor recurrence and metastasis - two problems accounting for more than 90% of breast cancer patient deaths. In a recent study performed in our lab, others found that non-CSC population within basal breast cancer cell lines, but not those within luminal cell lines, were responsive to certain microenvironmental stimuli, notably TGF- β of stromal origin, to undergo an epithelial-mesenchymal transition (EMT) and generate CSCs de novo, raising the intriguing possibility that the aggressiveness of breast cancer is determined not by its existing content of CSCs but by its responsiveness to contextual signals of generating new CSCs. The differing abilities of non-CSC-to-CSC conversion between luminal vs. basal cells are correlated with different histone modifications within the promoter region of ZEB1 gene, a master transcription factor regulating the EMT program. Therefore, the differing clinical behaviors of luminal vs. basal breast cancer cells can be explained, at least in part, by the differences in the configuration of the ZEB1 promoter in the respective non-CSCs. Based on these results, I plan to further our understanding on the epigenetic control of the non-CSC-to-CSC conversion in this proposal by identifying additional epigenetically regulated genes that control this process and characterizing the molecular mechanisms of these epigenetic modulations by the tumor microenvironment, which may eventually lead to the development of effective therapies that prevent non-CSC-to-CSC conversions. Importantly, I will also examine the potential of using epigenetic coding of the already-documented ZEB1 gene in diagnosing breast cancer patients with higher likelihood to progress into an aggressive stage.



**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.

PARP inhibition in homologous recombination-deficient breast cancer

Investigator(s): Anosheh Afghahi, M.D.; James Ford, M.D. (Mentor); Melinda Telli, M.D. (Co-Mentor)

Lead Organization: Stanford University

Grant Mechanism: PDF Clinical

Grant ID: PDF15331052

Public Abstract:

Poly ADP ribose polymerases (PARPs) play an important role in DNA repair in the human body. Inhibitors of PARP have been shown to lead to disease improvement in breast cancer patients, who carry an inherited BRCA mutation. The theory is that tumors arising in BRCA mutation carriers have damaged DNA repair mechanisms making them susceptible to additional DNA damage by PARP inhibitors. It has been hypothesized that PARP inhibitors may also have a role in the treatment of triple-negative (estrogen receptor-, progesterone receptor-negative and HER2 receptor normal) breast cancer patients, who do not have an inherited risk, but whose tumors have similar DNA repair defects and thus act "BRCA-like." Furthermore, there has been increased awareness of other hereditary breast cancer syndromes, such as PALB2, that are also implicated in the same DNA repair pathway as BRCA. In addition, as researchers conduct more testing on the tumor tissue itself, we are identifying patients with similar gene mutations, who may also benefit from PARP inhibitor therapy. The role of PARP inhibitors in these breast cancer patient populations remains undefined. The question is important as treatment in the advanced setting is often limited to chemotherapy, which can be associated with toxic side effects and short-term tumor responses.

In this clinical trial, we aim to evaluate if an oral PARP inhibitor can shrink tumors in patients with advanced breast cancer, who carry faulty DNA repair mechanisms, either due to a triple-negative "BRCA-like" breast cancer or due to a hereditary or tumor-tissue breast cancer gene mutation in the same pathway as BRCA. Patients with triple-negative breast cancer, whose tumors are "BRCA-like" based on a novel assay by Myriad Genetics, will be enrolled in Cohort A of our trial. Patients with a hereditary breast cancer similar in its origin to BRCA, or whose tumors have been evaluated and found to have a mutation in the same DNA repair pathway, will be eligible to enroll in Cohort B. All patients will be given daily BMN 673, a potent, oral PARP inhibitor. We will assess for tumor response every 8 weeks with imaging. Our hypothesis is that this powerful class of drugs, which is often better tolerated compared to standard chemotherapy, can lead to sustained anti-cancer activity in breast cancer patients beyond those who carry a harmful BRCA mutation. Notably only about 5-10% of breast cancer patients carry a BRCA mutation, and those patients, who do not have this inherited risk, are not eligible for current PARP inhibitor trials.

This work is important because women with advanced breast cancer are often left with chemotherapy as the only drug option. If our hypothesis is true, and our trial shows clinical activity in these high-risk breast cancer patients, it will provide an effective, targeted drug option. Furthermore, this trial will accelerate research in early-stage breast cancer, where it has the greatest potential to impact mortality.



**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.

Uncovering mechanisms responsible for shoulder morbidity following radiotherapy

Investigator(s): David Lipps, Ph.D.; Jonathan Strauss, M.D. (Mentor); Eric Perreault, Ph.D. (Co-Mentor)

Lead Organization: Northwestern University

Grant Mechanism: PDF Clinical

Grant ID: PDF15329262

Public Abstract:

As advances in treatment seek to end breast cancer, a new focus is needed on the functional abilities of those who benefit from these treatments to ensure that breast cancer survivors can maintain a high quality of life. The inclusion of radiotherapy in breast cancer treatment has successfully improved survival rates of patients diagnosed with early-stage breast cancer. Yet these same patients can experience shoulder disease in the months and years after radiotherapy, including pain, weakness, and restricted movement. These limitations affect a patient's daily living, including their ability to lift and carry objects or maintain employment. There is a poor understanding of why shoulder disease develops following radiotherapy, which has prevented the development of a standard of rehabilitative care for survivors. Therefore, the objective of this proposal is to understand how different radiotherapy treatments impact the prevalence of shoulder disease in breast cancer patients. We suspect that the build-up of scar tissue in the skin, fat, and muscle tissues exposed to radiation can predispose some breast cancer patients to shoulder disease. Since multiple muscles control the shoulder, scar tissue from radiation in one or more muscles may alter a patient's ability to use their affected shoulder. Identifying these affected muscles is key to optimize radiotherapy protocols for future patients. In order to isolate the mechanisms of shoulder disease in breast cancer patients, we will introduce new clinical methods that can robustly assess shoulder stiffness, which is a quantitative measure of the shoulder's functional capacity to move and generate force. These shoulder stiffness measurements will be directly compared to ultrasound images of the muscles exposed to radiation, which can help identify if radiation-induced scar tissue precedes shoulder disease following radiotherapy. Our specific aims are 1) to determine the longitudinal effect of radiotherapy on shoulder stiffness and 2) to quantify the physiological causes contributing to shoulder stiffness. We will investigate these specific aims in 20 women undergoing radiotherapy of the breast and 20 women undergoing radiotherapy of the breast and draining lymphatics. The inclusion of different treatment plans will allow us to determine if increasing the area exposed to radiation produces worse shoulder outcomes. Patients in both aims will be examined at four time points during their first year of recovery. The proposed research will assist in the prevention, screening, and rehabilitation of women undergoing radiotherapy, including using the clinical tools developed here to adjust radiotherapy treatments to maximize disease free survival and shoulder function. I will gain key training in radiation oncology to clinically translate these findings in my own independent laboratory.



**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.

Elucidating ER transcriptional network associated with endocrine resistance

Investigator(s): Myles Brown, M.D.

Lead Organization: Dana-Farber Cancer Institute

Grant Mechanism: SAB Grants

Grant ID: SAB1000008

Public Abstract:

Over 200,000 women in the US will be diagnosed with breast cancer this year, and close to 40,000 will die of it. Most (75%) breast cancers in developed countries are estrogen receptor positive and endocrine treatments are the mainstay therapy for breast cancer. The most common endocrine treatments include either targeting the ER for inhibition using the antagonist tamoxifen, or reducing ER activation by suppressing endogenous estrogen production using aromatase inhibitors in postmenopausal women. These endocrine treatments in the adjuvant setting reduce the risk of disease recurrence by up to 60%. However, women treated with adjuvant endocrine treatment still have a 1-2 % annual risk of recurrence, and in the metastatic setting, such endocrine treatments achieve response rates of only 20%-40%, underscoring the need for new effective therapies. Unfortunately, nearly all women with advanced ER+ breast cancer will eventually progress through all endocrine treatments and chemotherapy options, and ultimately die of their disease. Such loss of responsiveness to endocrine therapies represents acquired resistance, and determining its mechanisms is a major challenge in the field and the goal of the proposed research.

Clinical and pre-clinical data both suggest that acquired resistance is not associated with ER mutations or loss of ER expression and targeting the estrogen receptor and associated factors remains a key therapeutic approach capable of improving outcomes and reducing mortality. Therefore, in the proposed research we will investigate the key changes that occur in the ER transcriptional network in acquired endocrine resistance by studying both breast cancer cell lines as well as primary metastatic breast cancer cells. We will also develop new assays, which will facilitate the study of human metastatic tissue specimens both in culture system and xenograft models, which has been limited because of the paucity of such tissue specimens. Finally, these assays will be employed to study novel treatment targets in acquired endocrine resistance that will arise from our studies of the ER transcriptional network.



**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.

Identification of phosphatases for the treatment of ER-negative breast cancer

Investigator(s): Powel Brown, M.D., Ph.D.

Lead Organization: UT M.D. Anderson Cancer Center

Grant Mechanism: SAB Grants

Grant ID: SAB1300006

Public Abstract:

Breast cancer is the leading cause of cancer-related death in women. For this reason, there is an urgent need to identify effective therapeutic treatments for breast cancer. Approximately 60-70% of breast cancers express ER and respond to current therapies. However, the remaining 30-40% of breast cancers do not express this receptor and do not respond effectively to these therapies. There is a critical need to develop new, more effective therapies for the treatment and prevention of these ER-negative breast cancers. The results from the research outlined in this study have the potential to significantly impact the diagnosis and therapeutic treatment of ER-negative breast cancer patients. We have identified a set of phosphatases significantly over-expressed in ER-negative breast cancer which may play a critical role in the progression of these tumors. In this study, we aim to identify those phosphatases that play a critical role in the development and progression of ER-negative breast cancer. This would provide the basis necessary for the development of targeted, effective treatments for patients with ER-negative breast cancer, thereby improving the therapeutic prognoses of these women in the future.



**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.

Rx for better breast health

Investigator(s): Amelie Ramirez, Dr. PH

Lead Organization: UT Health Science Center at San Antonio

Grant Mechanism: SAB Grants

Grant ID: SAB0800005

Public Abstract:

U.S. breast cancer survivors are expected to rise in number from 3 million today to about 4 million by 2022, but the risk of cancer recurrence in this group is high, especially in obese survivors. Nutritional anti-inflammatory diets, if successfully planned and implemented, could reduce the risk of cancer recurrence and potentially increase survival rates even further. This 2-year research study will randomly assign 200 breast cancer survivors to one of two groups, intervention or control. The intervention group will acquire knowledge, skills and motivation to use an anti-inflammatory dietary prescription that may reduce their risk of cancer recurrence. The dietary plan includes six monthly anti-inflammatory food workshops (culinary demonstrations, recipes and meal planning) and a variety of assistance and services from a patient navigator to help stimulate beneficial dietary changes. The intervention group will be compared to a control group, which will get minimal nutritional information at baseline, monthly American Cancer Society survivorship brochures, and two telephone calls prior to assessment appointments. Both groups will be evaluated for dietary behavior changes and levels of certain biological markers at the beginning of the study and at 6 and 12 months post-treatment. Study findings will shed new light on how culinary-based anti-inflammatory dietary prescription can alter dietary intake and reduce inflammatory biomarkers in cancer survivors.



**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.

Measuring circulating tumor cells in vivo for breast cancer metastasis detection

Investigator(s): George Sledge, Jr., M.D.

Lead Organization: Stanford University

Grant Mechanism: SAB Grants

Grant ID: SAB1500003

Public Abstract:

Measuring circulating tumor cells (CTCs) in patients with advanced breast cancer is a currently available clinical test, but the potential of this test to affect patient outcome has been limited. While we do a good job of counting CTCs with the existing technology, and while CTC Counts provide some information regarding the treatment response and ultimate prognosis, this information alone does not “move the needle” with regard to breast cancer treatment and outcome. New approaches are needed to fulfill the full potential of CTC evaluation. We are evaluating two novel, locally created technologies to evaluate CTCs. The first technology has the potential to measure CTCs noninvasively with great precision. The second technology has the potential to be used to measure the effects of targeted therapies on breast cancer cells, providing an early read-out on benefit and appropriate dosing of new-targeted agents.



**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.

Improving treatment approaches for women with HER2+ metastatic breast cancer

Investigator(s): Eric Winer, M.D.

Lead Organization: Dana-Farber Cancer Institute

Grant Mechanism: SAB Grants

Grant ID: SAB0800001

Public Abstract:

Our research seeks to develop improved treatment strategies, particularly for HER2+ breast cancer patients with disease that is refractory to standard therapy and for patients with brain metastases. New treatment approaches will be tested in prospective clinical trials. Specifically, we will test a novel approach using two antibodies (trastuzumab and pertuzumab) and a PI3kinase inhibitor in patients with refractory metastatic disease. We will also test an entirely novel anti-HER2 specific tyrosine kinase inhibitor in combination with trastuzumab in patients with HER2+ brain metastases. If successful, these studies, as well as others, will lead to new potential treatment approaches for women with HER2+ metastatic disease. Our proposed work is of particular importance because the currently available treatment options, while highly effective, are still incapable of providing long-term disease control in a subset of patients. For this subset of patients, the outcome remains very poor. Ultimately, using our proposed novel treatment approach, we hope our research will also lead to improvements in the treatment of HER2+ early stage disease. Importantly, support from the Komen leadership grant will provide overall programmatic support that will allow the Dana-Farber team to pursue a breadth of studies in the treatment of HER2+ disease.



**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.

2015 Accelerating Anticancer Agent Development and Validation Workshop

Investigator(s): H. Kim Lyerly, M.D.

Lead Organization: Duke University

Grant Mechanism: SPP

Grant ID: SPP150010

Public Abstract:

The overall purpose of the 2015 Accelerating Anticancer Agent Development and Validation workshop is to provide, for early- and mid-career clinical investigators, intensive education and real life examples of how high quality data enable effective interaction with the US FDA. Through effective and collaborative interaction, as well as mutual understanding of research and regulatory processes, strategies can be developed for the design and conduct of translational research and cancer clinical trials - in a way that enables expeditious delivery of new agents to consumers.

The Workshop's three instructional objectives are to: 1. Instruct both academic and industry researchers, individuals with experience in clinical and translational research in all oncology subspecialties, in the planning and design skills necessary to effectively interact with the FDA to develop new anticancer and cancer prevention agents. The workshop gives participants the tools they need to design and conduct trials that will yield definitive answers to hypotheses. 2. Expose early- and mid-career translational/clinical scientists to the full spectrum of challenges in clinical cancer research and drug development. It is expected that participants will become motivated to devote all or a portion of their future careers to some area of translational and clinical research. 3. Develop a cadre of well-trained researchers who interact effectively with the FDA.

Over time, the research activities of this cadre will improve clinical trial design in general, thereby hastening the introduction of improved agents for cancer therapy and prevention into everyday clinical practice.



**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.

AACR Programming - 2014-2015 --Prevention, Disparities, SABCS, Rally for Med Research, SPP, Awards, SITAs

Investigator(s): Michael Stewart

Lead Organization: American Association for Cancer Research (AACR)

Grant Mechanism: SPP

Grant ID: SPP150002

Public Abstract:

This grant provided funds to support the AACR scientific conferences, advocate training programs and scientific awards listed below:

- 2014 AACR Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved (Lead Sponsor). The program features all levels of basic, population, clinical and transdisciplinary research related to cancer and brought together physicians, scientists, health professionals and health care leaders working in a variety of disciplines to discuss the latest findings in their fields, to foster collaborative interdisciplinary interactions and partnerships, and to stimulate the development of new research in cancer health disparities.
- 2014 Distinguished Lectureship on the Science of Cancer Health Disparities, funded by Susan G Komen
- AACR Scientist↔Survivor Program (Disparities). The AACR Scientist↔Survivor Program is designed to build enduring partnerships among the leaders of the scientific and cancer survivor and patient advocacy communities worldwide. The Scientist↔Survivor Program offered during the Science of Cancer Health Disparities Conference will expose advocates to the latest discoveries in cancer detection, treatment, and prevention in racial/ethnic minorities and the medically underserved. Special lay-language lectures, small group discussions, and other interactions will provide participants a solid background in cancer research to stimulate collaborative interdisciplinary interactions and partnerships.
- 2014 AACR International Conference on Frontiers in Cancer Prevention Research (Lead Sponsor). This conference promotes public, academic, government and industry awareness of the vital importance of cancer prevention science in reducing cancer incidence and mortality. It also catalyzes coordinated, focused research in basic, clinical, epidemiologic and behavioral science that promises to accelerate cancer prevention.
- 2014 CTCR-AACR San Antonio Breast Cancer Symposium (SABCS). SABCS is presented by the Cancer Therapy & Research Center at UT Health Science Center San Antonio, the American Association for Cancer Research, and Baylor College of Medicine. The driving force behind this collaboration is the shared mission of the organizations to advance progress against breast cancer. As exciting strides are made in the field of breast cancer research and treatment our program continues to present essential up-to-the minute information combined with engrossing discussion for basic, translational and clinical cancer research professionals.
- 2014 AACR Outstanding Investigator Award for Breast Cancer Research, funded by Susan G Komen.
- Scholar In Training Awards (Disparities, Prevention, SABCS). Like AACR, Susan G. Komen for the Cure recognizes the importance of preparing the next generation of researchers for successful careers in cancer research. Providing the resources that allow early-career researchers to travel to scholarly meetings is central to this goal. With Komen's support, AACR will facilitate the travel of young researchers to its Cancer Prevention Research, and Science of Cancer Health Disparities meetings; and to the San Antonio Breast Cancer Symposium. These funds are important because of the increasing need for support of bringing together young investigators with senior researchers.



**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.

2015 AACR Annual Meeting

Investigator(s): Michael Stewart

Lead Organization: American Association for Cancer Research (AACR)

Grant Mechanism: SPP

Grant ID: SPP150018

Public Abstract:

This grant provided funds to support the 2015 AACR Annual Meeting and associated advocate training programs, scientific awards and events listed below:

- Five breast-cancer related scientific sessions
- AACR Scientist - Survivor Program
- Scholar In Training Awards



**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.

24th Annual AACR Workshop Molecular Biology in Clinical Oncology, July 19-26, 2015

Investigator(s): Michael Stewart

Lead Organization: American Association for Cancer Research (AACR)

Grant Mechanism: SPP

Grant ID: SPP150021

Public Abstract:

Launched by the AACR in July 1992, this intensive one-week summer workshop, entitled Molecular Biology in Clinical Oncology, provides a blend of lectures and laboratories designed to highlight major investigational areas and methodological approaches in basic and translational cancer research across cancer types and to address the translational gap faced by physicians who aspire to build an academic career as physician-scientists. Unfortunately, this gap is growing.

Two significant barriers exist within the lifecycle of a physician-scientist: the “Fellow to Faculty” transition and the transition to independent research funding (e.g., “K to R” transition). In laboratory-based oncology research, these transitions are tethered to one another in that both are contingent upon the ability to formulate clear, hypothesis-driven specific aims and to develop a cohesive experimental plan to pursue these aims that will withstand peer review. Therefore, equipping oncologists with (1) knowledge of the range of investigative approaches that might be tapped to pursue cutting-edge research; and (2) the ability to develop an incisive research plan to address key unanswered medical questions based on this knowledge represent vital aspects in terms of maximizing their likelihood of traversing these obstacles early in their careers.

Now in its 24th year, the AACR Molecular Biology in Clinical Oncology workshop provides a substantive overview of key areas in molecular biology and translational cancer research for the aspiring physician-scientist and provides trainees with the opportunity to meet and receive training from successful physician-scientists in an environment that promotes formal and informal interactions at a critical juncture in their career development: the transition from clinical training to laboratory-based training. Through these interactions, the workshop faculty members convey the “secrets” behind their success, the exhilaration of the scientific discovery process, and the rewards of a professional life as a physician-scientist. In parallel, workshop trainees receive intensive instruction from the faculty regarding the principles and practice of designing effective scientific experiments and writing a laboratory-oriented research grant such as a K08 or other major career development award.



**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.

SSO 2015 Annual Cancer Symposium - March 25-28, 2015 in Houston, TX and the SSO 2015 Susan G. Komen Breast Cancer Research Award

Investigator(s): Eileen Widmer

Lead Organization: Society of Surgical Oncology

Grant Mechanism: SPP

Grant ID: SPP150012

Public Abstract:

The Society for Surgical Oncology's 66th Annual Cancer Symposium is a scientific conference for all surgeons and other healthcare professionals who are involved in the treatment of patients with cancer to discuss recent updates and current controversies in the multidisciplinary management of patients with breast cancer and other types of cancer and learn about advances and innovations in basic and translational sciences and targeted therapies. The meeting includes a special Komen Symposium that this year will provide a comprehensive look at Triple Negative Breast Cancer.



**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.

Friends of Cancer Research: 2014 Clinical Cancer Research Workshop - Nov mtg

Investigator(s): Jeff Allen

Lead Organization: Friends of Cancer Research

Grant Mechanism: SPP

Grant ID: SPP150004

Public Abstract:

Each year, Friends of Cancer Research convenes the Conference on Clinical Cancer Research to address critical issues in new drug development and approval. This event brings together leaders from federal health and regulatory agencies, academic research centers, patient advocacy organizations and the private sector to identify challenges, propose consensus solutions and develop a clear path forward on critical issues surrounding the development and regulation of drugs and therapies.

This year's conference will highlight the following three topics, potential strategies for non-randomized evaluation of new drugs, considerations for summary review of supplemental NDA/BLA submissions, and post-marketing evaluation of off-label oncology use. Anticipated attendance is 200 patient advocates, researchers, federal officials and industry representatives. The conference will highlight the three consensus-driven issue briefs developed on the topics above.

This project will help fulfill Komen's mission by providing attendees with the knowledge of the opportunities and challenges we face in developing innovative cancer research. The event will be publicized through mass media, invitations, websites and registration database. Each attendee will receive an evaluation allowing them to provide feedback on the conference and to provide suggestions on ways to improve the conference.



**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.

8th International Symposium on the Breast

Investigator(s): Heather Ortner

Lead Organization: Dr. Susan Love Research Foundation

Grant Mechanism: SPP

Grant ID: SPP150008

Public Abstract:

The key to identifying the cause of breast cancer and determining methods to prevent it lies in understanding the normal human breast and how it develops malignancy. To accelerate progress, it is critical to transition the study of the breast from animal models to humans. New technologies for DNA/RNA analysis and procedures to obtain samples or observe human breasts in situ are opening up promising new avenues for exploration.

The 8th International Symposium on the Breast (the “Symposium”) brings together a multidisciplinary and international group of iconoclastic researchers, clinical scientists, and advocates in an intimate think-tank environment to stimulate ideation, collaboration, and ultimately, breakthroughs that will end breast cancer. Komen is supporting the Pilot Grant Program occurring at the Symposium, which will challenge attendees to form multidisciplinary consortiums of basic scientists, advocates and clinicians to address the following key issues: the anatomy and physiology of the human breast; early changes of cancer: microenvironment/duct; microbiome of the human breast; and applying next generation technology to studying the breast and how it develops cancer. Teams form at the Symposium, where they develop and present research proposals. An expert panel evaluates the proposals and grants are announced at the Award Dinner on the final evening of the three-day program.



**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.

Advanced Breast Cancer Third International Consensus Conference (ABC3)

Investigator(s): Alberto Costa

Lead Organization: European School of Oncology

Grant Mechanism: SPP

Grant ID: SPP150013

Public Abstract:

The Advanced Breast Cancer Consensus Guidelines were developed thanks to the success and commitment of the European School of Oncology (ESO) Task Force Members and the Panel Members that contributed to the 1st International Consensus Conference for Advanced Breast Cancer (ABC1), which took place in Lisbon, Portugal, in November 2011 and brought together 800 participants. These guidelines were further developed at ABC2 in 2013 (over 1000 participants) by ESO and the European Society of Medical Oncology and were published simultaneously in *Annals of Oncology* and *The Breast*.

The Advanced Breast Cancer Third International Consensus Conference (ABC3) will take place in Lisbon, Portugal, on 5-7 November 2015. At ABC3 all topics will be presented from the perspective of a multidisciplinary and multi-professional approach, from basic research to clinical implementation. Patient advocacy sessions will take place in conjunction with the conference, with a report from the Patient Advocate Committee to be given during an ABC3 session. The conference will close with a Consensus Session where discussion will focus on updating the aforementioned guidelines.



**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.

Mammary Gland Biology (GRS) Finding Your Pathway: Breast Development and Breast Cancer

Investigator(s): Nancy Ryan Gray

Lead Organization: Gordon Research Conferences

Grant Mechanism: SPP

Grant ID: SPP150014

Public Abstract:

The Mammary Gland Biology Gordon Research Seminar (GRS)/Gordon Research Conference (GRC) conference aims to disseminate the latest unpublished data and stimulate discussion among leading investigators and trainees on the most recent findings and future research regarding the cellular and molecular mechanisms of mammary gland development, breast cancer risk, prevention, and progression to metastasis.

The Gordon Research Seminar on Mammary Gland Biology is held in conjunction with the GRC and is a unique forum for graduate students, postdocs, and other scientists with comparable levels of experience and education to present and exchange new data and cutting edge ideas. The goal of this seminar is provide young scientists with a forum to present their current research, develop a network to establish future collaborations, and exchange mentorship advice in preparation for the next steps in their career paths. GRS participants also attend the Mammary Gland Biology Gordon Research Conference, which brings together a fascinating blend of scientists interested in the molecular and cellular mechanisms governing normal mammary gland development, physiology and cancer. This meeting provides unique opportunities to engage with experts and learn about breaking concepts and specialized techniques in these research areas.



**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.

14th St. Gallen International Breast Cancer Conference: Primary Therapy in Early Breast Cancer, Vienna, Austria March 18-21, 2015

Investigator(s): Hans-Joerg Senn

Lead Organization: St. Gallen Oncology Conferences

Grant Mechanism: SPP

Grant ID: SPP150019

Public Abstract:

This important biannual international conference, drawing regularly some 3000-4000 breast cancer treatment oriented delegates from 90-100 countries worldwide, started in 1978, when the first (divergent) results of adjuvant post-surgical chemotherapy in patients with breast cancer from trials in the USA (by NSABP-Group) and from Europe (Milano-Trial; St.Gallen-Trial in Eastern Switzerland, early IBCSG-trials) were generated, and needed to be periodically compared and discussed. This is the only larger repeated conference worldwide that centers exclusively on primary curative therapy of early breast cancer, and regularly closes with an international consensus panel on the presently optimal curative treatment approach in early breast cancer, since 1988, regularly and prominently published (in JNCI, then JCO, and since 2005 in Annals of Oncology).



**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.

Travel scholarship sponsorship; Obesity Week – November 2-7, 2015 – Los Angeles, CA

Investigator(s): Francesca Dea

Lead Organization: The Obesity Society

Grant Mechanism: SPP

Grant ID: SPP150020

Public Abstract:

Obesity Week 2015 is the major international conference dedicated to increasing understanding of obesity, its consequences and co-morbidities. The conference goal is to reduce morbidity and mortality, including obesity-driven breast cancer. In 2014, 5,266 investigators, clinicians, trainees and other people attended the conference in Boston. There were 909 international attendees from 73 countries, 604 integrated health professionals, 1,586 abstract submissions, 29 sponsors/education grant providers and 265 exhibit booths. This meeting represents an important opportunity for junior and senior investigators in the field of obesity medicine to meet and exchange scientific and medical information. In particular, new insights into the mechanisms of chronic inflammation and abnormal metabolism in insulin-resistant obesity are thought to drive breast cancer progression. Innovative and significant new research is being conducted in this area, as well as investigating why some obese women seem to be protected from obesity-driven breast cancer, in part because of their more 'normal' metabolism and reduced inflammation. These insights point the way to new preventive strategies and potential therapies for the large number of women affected. The Komen travel awards invested critical support in their early career development. In 2015, Komen will support three peer-reviewed travel awards for junior investigators.



**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.

HGEI-Lancet Commission on Global Access to Pain Control and Palliative Care

Investigator(s): Felicia Knaul, Ph.D.

Lead Organization: Harvard Global Equity Initiative

Grant Mechanism: SPP

Grant ID: SPP150011

Public Abstract:

The Harvard Global Equity Initiative-Lancet Commission on Global Access to Pain Control and Palliative Care (GAPCPC) is the timely result of recent and path-breaking efforts calling for national and global action to address the lack of access to pain control experienced by millions of patients, especially those in low and middle income countries (LMICs). The GAPCPC comes at a pivotal moment, providing an opportunity to redefine universal health coverage (UHC) by including pain control and palliative care as an essential component of effective UHC. This will help to bring alleviation of human suffering from the margins of medicine back to its center and core.

GAPCPC aims to conduct novel analysis on the links between health systems strengthening and access to pain control and palliative care, using the diagonal approach as a guiding framework. The objectives of the Commission are multi-fold: 1. Contribute to global discussions on universal health coverage (UHC) and the sustainable development goals (SDGs) as well as the momentum at the country level in various LMICs; 2. Identify opportunities for incorporating pain control and palliative care within health reforms to strengthen health systems and achieve effective universal health coverage; 3. Develop core instruments for expanding priority setting to include human dignity and freedom from unnecessary pain and suffering and thus enable policy makers to incorporate palliative care into priority setting; 4. Contribute health system strengthening and program proposals to meet disease specific and overall needs for pain control and palliative care; and 5. Provide recommendations for innovative health strategies that harness national and global platforms.

GAPCPC will produce, within 24 months, a report for publication in The Lancet including recommendations and enabling actions to promote universal access to pain relief and palliative care. Valuable inputs towards and complementing the Commission's report include: a) country case studies analyzing challenges, opportunities, and best practices in expanding access to pain control and palliative care, b) a guide on developing national pain control and palliative care plans, and c) a projected demand and tracer-illness analysis based the case of metastatic and late-stage breast cancer.

The GAPCPC is a Lancet Commission. This provides a huge platform for creative and applied knowledge-building and outreach to policy makers. Lancet Commissions have a track record of being instrumental in advancing the global health agenda, with reports that bridge cutting edge research and analysis with innovative policy recommendations. The Commission was conceived at a Harvard University Radcliffe Institute workshop, "Closing the Pain Divide: A diagonal approach to harness health systems," held in April 2014. GAPCPC was officially launched at The Lancet offices in NYC in September of 2014. The Commission includes more than 30 members from 19 countries representing all major regions of the world– all leaders in the fields of public health, global health, health systems, pain control and palliative care, and health economics among others.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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AIS Program at 2015 ASCO Breast Cancer Symposium

Investigator(s): Elda Railey

Lead Organization: Research Advocacy Network

Grant Mechanism: SPP

Grant ID: SPP150015

Public Abstract:

The Advocates in Science (AIS) Program at the 2015 ASCO Breast Cancer Symposium offers the opportunity for selected AIS members to participate in a class that will prepare them for attendance at the 2015 ASCO Breast Cancer Symposium (<http://breastcasym.org/>) and to disseminate the research results back to Komen Affiliates and the breast cancer community. The Symposium offers a world-class multi-disciplinary faculty and an accessible setting. Past AIS participants have found this to be an excellent learning opportunity and the perfect venue to learn more about breast cancer research and treatment and interact with scientists and clinicians that are working to incorporate the latest science into clinical practice.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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A2SPIRE Grant

Investigator(s): Kathryn Martinez

Lead Organization: Tyler Affiliate of Susan G. Komen

Grant Mechanism: SPP

Grant ID: SPP150024

Public Abstract:

This grant will leverage the expertise and connections of Advocate Komen Scholars to enable Affiliates to begin or enhance research-related programs that engage Komen's Scientific Advisory Board members, Komen Scholars or Komen grantees (hereafter called Komen Scientists) in an Affiliate-managed research-focused program/event. The program will enhance the partnership between Komen Advocates, Affiliates and Scientists and enhance community awareness, understanding, and support of breast cancer research.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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A2SPIRE Grant

Investigator(s): Kirsten Bruce

Lead Organization: Kansas Affiliate of Susan G. Komen

Grant Mechanism: SPP

Grant ID: SPP150025

Public Abstract:

This grant will leverage the expertise and connections of Advocate Komen Scholars to enable Affiliates to begin or enhance research-related programs that engage Komen's Scientific Advisory Board members, Komen Scholars or Komen grantees (hereafter called Komen Scientists) in an Affiliate-managed research-focused program/event. The program will enhance the partnership between Komen Advocates, Affiliates and Scientists and enhance community awareness, understanding, and support of breast cancer research.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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A2SPIRE Grant

Investigator(s): Carli Howard

Lead Organization: Greater Kansas City Affiliate of Susan G. Komen

Grant Mechanism: SPP

Grant ID: SPP150026

Public Abstract:

This grant will leverage the expertise and connections of Advocate Komen Scholars to enable Affiliates to begin or enhance research-related programs that engage Komen's Scientific Advisory Board members, Komen Scholars or Komen grantees (hereafter called Komen Scientists) in an Affiliate-managed research-focused program/event. The program will enhance the partnership between Komen Advocates, Affiliates and Scientists and enhance community awareness, understanding, and support of breast cancer research.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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A2SPIRE Grant

Investigator(s): Lisa Wolter

Lead Organization: Orange County Affiliate of Susan G. Komen

Grant Mechanism: SPP

Grant ID: SPP150027

Public Abstract:

This grant will leverage the expertise and connections of Advocate Komen Scholars to enable Affiliates to begin or enhance research-related programs that engage Komen's Scientific Advisory Board members, Komen Scholars or Komen grantees (hereafter called Komen Scientists) in an Affiliate-managed research-focused program/event. The program will enhance the partnership between Komen Advocates, Affiliates and Scientists and enhance community awareness, understanding, and support of breast cancer research.



**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.

A2SPIRE Grant

Investigator(s): Kelly Kesler

Lead Organization: Maryland Affiliate of Susan G. Komen

Grant Mechanism: SPP

Grant ID: 150028

Public Abstract:

This grant will leverage the expertise and connections of Advocate Komen Scholars to enable Affiliates to begin or enhance research-related programs that engage Komen's Scientific Advisory Board members, Komen Scholars or Komen grantees (hereafter called Komen Scientists) in an Affiliate-managed research-focused program/event. The program will enhance the partnership between Komen Advocates, Affiliates and Scientists and enhance community awareness, understanding, and support of breast cancer research.



**Susan G. Komen
Research Grants – Fiscal Year 2015**

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A2SPIRE Grant

Investigator(s): Pam Kohl

Lead Organization: North Carolina Triangle to the Coast Affiliate of Susan G. Komen

Grant Mechanism: SPP

Grant ID: 150029

Public Abstract:

This grant will leverage the expertise and connections of Advocate Komen Scholars to enable Affiliates to begin or enhance research-related programs that engage Komen's Scientific Advisory Board members, Komen Scholars or Komen grantees (hereafter called Komen Scientists) in an Affiliate-managed research-focused program/event. The program will enhance the partnership between Komen Advocates, Affiliates and Scientists and enhance community awareness, understanding, and support of breast cancer research.



**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.

IMPAKT Breast Cancer Conference, May 7-9, 2015

Investigator(s): Keith McGregor

Lead Organization: European School of Medical Oncology

Grant Mechanism: SPP

Grant ID: SPP150030

Public Abstract:

The IMPAKT Breast Cancer Conference focuses specifically on translational research and new drug development, in an era where there is potential to provide tailored treatment to biologically homogeneous groups of patients. The Conference provides an ideal environment to foster dialogue between laboratory and clinical scientists as well as representatives of the pharmaceutical industry, and for physicians to gain the knowledge and skills to use new technologies and integrate translational research components into clinical trials.