FY19 Komen Funded Research Grants

This slate of research grants was approved for funding allocated from the FY19 budget. These grants will be funded upon the execution of grant agreements between Komen and the grantee institutions, and include the following research mechanisms:

Career Catalyst Research (CCR) Grants: CCR grants provide unique opportunities for scientists who have held faculty positions for no more than 5 years at the time of application to achieve research independence. The goal of the FY19 CCR grants is to support outstanding translational research focused on the understanding, detection, and treatment of metastatic breast cancer which will lead to a reduction in breast cancer deaths by 2026.

Global Research Grants: To help us achieve our goal of reducing breast cancer incidence and/or deaths around the world, our Global Research Grants seek to develop and implement innovative methods and programs aimed at addressing disparities and reducing barriers to breast cancer care worldwide.

Graduate Training in Disparities Research (GTDR):
GTDR grants provide funding to outstanding programs to establish and/or sustain innovative training programs for graduate students seeking careers dedicated to achieving health equity. The goal of the FY19 funding is to support programs for an additional year to maintain successful programs that are working towards achieving Komen's Bold Goal.

Leadership Grant (LG):
LGs provide support for hypothesis-driven research projects conducted by the distinguished breast cancer researchers and clinicians who served as Komen's scientific advisors and seek to discover and deliver the cures for breast cancer.

Opportunity Grants (OG)/ Scientific Partnerships and Programs (SPP):
OG and SPP grants support special research projects, programs, and collaborations that leverage research and community resources to facilitate the development of the infrastructure, tools, and other means to accelerate the translation of scientific discoveries from bench to bedside to curbside.

California

Discovering Novel Immunotherapy Strategies to Treat BRCA-Mutated Breast Cancer
Research Leadership Grant - Scientific Advisory Board Member
Principal Investigator: Alan Ashworth, Ph.D., F.R.S.
Institution: University of California, San Francisco
San Francisco Bay Area Affiliate

Snapshot: Komen Scientific Advisory Board Member Alan Ashworth, Ph.D., F.R.S., will improve treatment of BRCA-mutated breast cancers by exploring how BRCA1 and BRCA2 mutant breast cancer cells engage the immune system. Overall, these studies should identify new therapeutic targets that can be used to expand the toolbox of immune checkpoint inhibitors for BRCA1 and BRCA2 mutant breast cancer.

Abstract: Therapies that harness the host immune system have recently revolutionized the treatment of a subset of cancers. Because these treatments have led to long-lasting responses (possibly cures) and have proven to be far less toxic than conventional chemotherapies, scientists are racing to expand the use of these drugs to benefit more patients. Several clinical trials testing these therapies in breast cancer have been initiated, but so far, these drugs have showed limited success. Here we propose to investigate novel ways to improve the ability of immune cells to recognize and kill breast cancer cells.

California

Therapeutic Resistance in ER+ Breast Cancer
Research Leadership Grant - Chief Scientific Advisor
Principal Investigator: George Sledge, M.D.
Institution: Stanford University
San Francisco Bay Area Affiliate

Snapshot
Komen Chief Scientific Advisor George Sledge, M.D., will develop new therapeutic combinations that could be brought rapidly into the clinical trial setting for patients with estrogen receptor positive (ER+) breast cancer.

Project Summary
Recent years have seen the addition of multiple novel agents to existing therapies targeting the estrogen receptor. Despite these advances, metastatic estrogen receptor-positive breast cancer remains a major cause of morbidity and mortality. Drug resistance ultimately defeats our best efforts in the metastatic setting, as cancer cells undergo mutational events that render prior pathway blockade irrelevant. To date, attempts to overcome such resistance have largely relied on stepwise identification of resistance mechanisms and, where possible, targeting of those mechanisms using monotherapy. This approach, while biologically rational, is regularly thwarted by the large number of alternate pathways that can sustain growth and survival in human breast cancer. New technology developed at Stanford University in the Bassik lab uses the cutting-edge application of CRISPR to an age-old problem. In this approach, a CRISPR-based double knockout (CDKO) system improves the efficiency of combinatorial genetic screening using an effective strategy for cloning and sequencing paired single-guide RNA libraries and a robust statistical scoring method for calculating genetic interactions (GIs) from CRISPR-deleted gene pairs. This is an effective strategy to screen synergistic drug combinations in high throughput and is a broadly applicable means of repurposing old drugs. Given that cancer is a disease that is known to be highly evolvable and can adapt both mutationally and non-mutationally, it is likely that there will be many epigenome and gene expression changes between the drug naïve and drug resistant states. Therefore, to improve the targeting of CDKO libraries we will first map the chromatin state and gene expression changes that occur pre- and post-drug treatment to account for the non-mutational mechanisms of drug resistance that occur in estrogen-receptor positive breast cancer. We propose to apply this epigenetic and CRISPR-based double KO approach to the problem of drug resistance in ER-positive breast cancer, using established drug-resistant ER-positive cell lines, with the intention of developing novel therapeutic combinations with existing, off-the-shelf drugs that could be brought rapidly into the clinical trial setting in metastatic ER-positive breast cancer. Of note, this same approach could be applied in other metastatic breast cancer settings, e.g., HER2-positive and triple negative breast cancer.

Connecticut

Immunological Characterization of Primary Metastatic Breast Cancer (defining immune cell activity in metastatic breast cancer)

Research Leadership Grant - Komen Scholar
Principal Investigator: Lajos Pusztai, M.D.
Institution: Yale University
New England Affiliate

Snapshot

Komen Scholar Lajos Pusztai, M.D., D.Phil., will study how the immune system is regulated in breast cancer to improve tumor vaccination strategies and immunotherapy combinations. The study will also explore new therapeutic targets among abnormal metabolic proteins.

Abstract

Recent advances in cancer immunology suggest that some breast cancers do not elicit any immune response at all, while in others the anti-cancer immune response is attenuated by local immunosuppressive mechanisms. Consistent with this hypothesis, results from the first few immunotherapy trials in breast cancer suggest that 10-20% of patients benefit from this new treatment modality. An important challenge is to identify the minority of patients who respond to the treatment and to improve response rates for the others.

The goal of our research is to better understand the immune cell composition of breast cancer and to find out what cancer and patient genetic characteristics influence immune cell infiltration and anti-cancer immunity. We will use cancer biopsies collected during clinical trials to study the immune environment and to correlate the presence and activity status of immune cells with mutations in the cancer and with inherited genetic variations of the patient. We will also compare the immune cell composition of breast cancer before and after preoperative chemotherapy to learn how the immune environment changes during treatment. Most cancer immunology research focused on studying early stage breast cancer tissues and therefore it remains unknown if metastatic sites show similar immune environment as the primary cancer.

The breast oncology program at Yale, routinely collects metastatic breast cancer biopsies for molecular target profiling and these tissues represent a unique resource to study the immune composition of metastatic cancer. Using this resource, we will compare the immune environment of primary and metastatic breast cancers. This research is important because better understanding of what drives immune cell infiltration of breast cancer may lead to improved tumor vaccination strategies to render cancers that are immunologically inert to be more immunogenic. A clearer understanding of what regulates the immune cell activity in cancer tissues can also suggest rational combinations of immunotherapy drugs to increase the efficiency of an anti-cancer immune response. For example, if we knew the complete repertoire of immune suppressive mechanisms that operate in a particular cancer, we could design strategies to disable each of these inhibitory mechanisms and activate the immune system more efficiently than using just one drug blindly. This research will also generate a very rich data set that we will analyze beyond immune related parameters to identify new therapeutic targets for breast cancer including aberrantly expressed metabolic enzymes.

Florida

Analysis of the Immune Landscape in Breast Tumor Subtypes
Research Leadership Grant - Komen Scholar
Principal Investigator: Edith Perez, M.D.
Institution: Mayo Clinic Jacksonville
Florida Affiliate

Snapshot

Komen Scholar Edith Perez, M.D., will identify immune features/biomarkers present in patient breast tumors that influence their response to therapy. These markers could be used to guide decision making in the clinic and help develop new therapeutic options to treat breast cancer.

Abstract

We know broadly that immune cells are important in therapeutic response in triple negative and HER2+ breast cancer. This concept grew initially out of observations that clinical outcome, in many cases, was linked to not to genomic features within the tumor cells themselves, but to expression of genes in immune cells within the tumor environment. More recently, we have come to know that the presence or absence of immune cells within tumors has much to do with the success or failure of breast cancer treatment. However, the immune system is complex, made up of many different types of cells, some of which are beneficial and some deleterious to therapeutic outcome. We know little about the specific immune cells that account for good or bad outcome, how these cells are distributed within the tumor, or how the activity of such cells is linked to outcome. Understanding the principles that govern interaction between the immune system and tumor cells is essential to understanding the basic biology of breast cancer. Such an understanding, in turn, will provide new insight into why breast cancer therapy works or fails, will guide the development of new models to predict outcome, and will identify potential therapeutic targets that will guide the development of novel immune-based therapeutic strategies. Our goal in this Komen project is to take advantage of emerging technology that will, for the first time, enable us to measure expression of key immune function genes in a spatially defined manner within tumors. Using this novel technology we will be able to answer questions about the abundance of different types of immune cells, the activity of such cells, and the relationship between activity and proximity to tumor cells. Moreover, we will correlate these data with clinical response to neoadjuvant therapy in patients who have been diagnosed with either triple negative or HER2+ breast cancer. Our proposed work will help unravel components of the immune system, which in turn will follow the path of improving the biological understanding of breast cancer and how these changes affect patient's lives.

Florida

Scientific and Patient Advocate Programming at the 18th Congress of the Metastasis Research Society
Scientific Partnerships and Programs
Principal Investigator: Dihua Yu
Metastasis Research Society
Florida Affiliate

Snapshot
The Metastasis Research Society (MRS) will receive funding to support collaborative programming at MRS's 18th Biennial Congress. At this conference, researchers will discuss the latest experimental and clinical developments about cancer metastasis (spread) as well as new opportunities for more effective treatment strategies. The funding will also support travel to ensure participation of metastatic breast cancer patient advocates and early-career breast cancer researchers.

Georgia

Metastatic Breast Cancer Disparities: Identifying Multilevel Determinants in GA
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Lauren McCullough, Ph.D.
Institution: Emory University
Greater Atlanta Affiliate

Snapshot
Lauren McCullough, Ph.D., will study the different factors which can lead to racial differences in breast cancer metastasis mortality. From the factors identified in this study, Dr. McCullough hopes to identify innovative solutions to address racial disparities in metastatic breast cancer.

Project Summary
Breast cancer is the second leading cause of cancer-related mortality, with an estimated 40,610 deaths in 2017. The overall 5-year survival rate is over 90%. However, 6–10% of newly diagnosed women have metastases and another 30% will develop metastatic disease. Mortality in metastatic breast cancer has decreased, in part, due to the widespread availability of targeted therapies. Unfortunately, not all women have benefited equally—with persistent disparities by race/ethnicity, morbidity, and place of residence. Metastatic breast cancer almost always results in death, and about half of patients experience disease progression within 1-year of treatment. Given the mortality burden of metastatic breast cancer, documented disparities, and diversity of Georgia with respect to all major demographic characteristics, now is a pivotal time to characterize the pathways contributing to inequities in metastatic breast cancer prognosis.

The proposed study is based on the premise that reducing race/ethnic, Socio-economic status (SES), and urban/rural disparities in metastatic breast cancer requires that we (1) understand how they arise and (2) develop interventions to target the mechanisms that perpetuate them. We suggest that the development of future interventions that will reduce metastatic breast cancer disparities requires both robust multilevel analyses, including factors from the individual, neighborhood, and systems/policy levels, and a better understanding of how these factors can be targeted to reduce the disparity.

Our study, for the first time, will examine multi-level contributors to race/ethnic, SES, and urban/rural disparities in both distant breast cancer recurrence (among women diagnosed with early stage breast cancer, Aim 1) and morality (among women with metastatic breast cancer, Aim 2) using multiple data sources (e.g., cancer registry, discharge, administrative claims, hospital and census data) to identify the factors, from the individual to policy-level, influencing recurrence and mortality. Our innovative modeling approach will move the field beyond simply describing the existing disparities, to understanding why they exist; informing future therapeutic, behavioral, and policy interventions to improve outcomes in marginalized populations—achieving a reduction in metastatic breast cancer deaths by 2026.

Illinois

Developing New Treatments for Drug-resistant ER+ Metastatic Breast Cancer
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Sean Fanning, Ph.D.
Institution: University of Chicago
Chicago Affiliate

Snapshot

Sean Fanning, Ph.D., will develop new drugs to overcome estrogen resistance in metastatic breast cancer. By modifying an existing drug to better bind to the estrogen receptor, similar to a lock and key, Dr. Fanning plans to better block estrogen and stop tumor growth while also improving patient drug tolerance (i.e. low side-effects).

Project Summary

Breast cancer is the second leading cause of cancer-associated death in women. Most breast cancers depend on the female sex hormone estrogen to spread. Estrogen binds to the estrogen receptor alpha (ERα). If ERα is a lock then estrogen is the key that opens the door for the disease. Drugs that block the action of estrogen, like tamoxifen, are often effective treatments to prevent the spread of breast cancer following chemotherapy/radiation. Tamoxifen is known as a selective estrogen receptor modulators (SERMs) and can be given for long periods of time but unfortunately, often the cancer will become resistant to this treatment. Another class of drugs, called selective estrogen receptor degraders (SERDs) can be used in patients who fail on tamoxifen or develop resistance. Rather than just blocking estrogen, SERDs make the cells destroy ERα thereby removing the lock that the keys open. However, SERDs, which include fulvestrant, have limitations in the clinic due to toxicity. As a result, there is a need to develop new molecules to treat ER+ breast cancer. SERMs are better tolerated by the patient but not as effective in blocking estrogen and thus our goal was to find or develop a drug that is both effective and well-tolerated. Using models of drug-resistant breast cancers, we recently found that the SERM lasofoxifene (laso) is more potent than fulvestrant in drug resistant pre-clinical models. Laso can be taken orally and is better tolerated than fulvestrant. Using minimal modifications to laso, we will make it behave as a SERD (laso-SERD) to increase its effectiveness, while keeping its low-toxicity. We will compare this drug to unmodified laso in models of tamoxifen-resistant breast cancer. If our laso-SERDs are better, then we will have new drugs ready for clinical evaluation. If our laso-SERDs do not show improved potencies then laso and other SERMs with improved properties over tamoxifen should be further developed., Regardless of our result we will know the best route to develop critically needed therapies for many women who do not respond to tamoxifen. This work will assist in developing new treatments that are better tolerated by patients, more effective at removing estrogen in breast cancer treatment, and less likely to lead to developing hormone treatment resistance. By overcoming this resistance, we will hopefully prevent recurrence and thus help reach Komen's goal of reducing breast cancer deaths by 50% by 2026.

Illinois

A Learning Healthcare System to Improve Adherence and Persistence to Adjuvant Hormone Therapy
Research Leadership Grant - Komen Scholar
Principal Investigator: Mia Levy, M.D.
Institution: Rush University Medical Center
Chicago Affiliate

Snapshot

Komen Scholar Mia Levy, M.D., Ph.D., will develop new documentation and reporting strategies to improve healthcare delivery for breast cancer patients. This strategy, called Learning HealthCare System (LHS), will use the patient electronic health record to collect and report outcomes related to adjuvant endocrine therapy. The LHS could improve healthcare delivery for patients with breast cancer, decreasing rates of recurrence and death from breast cancer.

Abstract

Adjuvant endocrine therapy (AET) significantly improves long-term survival of breast cancer patients with hormone receptor-positive disease. Despite the proven benefit of tamoxifen and aromatase inhibitors, many breast cancer survivors either fail to take the correct dosage at the prescribed frequency (adherence) or discontinue therapy early (persistence). Non-adherence and non-persistence to AET increases the risk of death from recurrent breast cancer. Despite awareness of the magnitude of the problem and the implications for avoiding death from breast cancer, few studies have been performed evaluating strategies to improve adherence and persistence to AET. A learning healthcare system offers the opportunity to learn from the experiences of all patients by purposely collecting data during routine clinical care that enables continuous evaluation of novel interventions to improve outcomes. The learning healthcare system presents an opportunity to reconceptualize the management of patients on AET at a population level and to systematically evaluate interventions designed to improve adherence and persistence to AET. We hypothesize that a learning healthcare system with the goal of improving patient adherence and persistence to AET will decrease rates of recurrence and death from breast cancer. Towards this goal, we propose to develop novel documentation and reporting strategies within the electronic health record that allow for collection and reporting of outcomes related to the management of AET. We further propose to develop novel clinical interventions including clinical decision support systems that notify providers of patients at risk for nonadherence or non-persistence to AET, and clinical practice guidelines for management of patients on AET with the goal of improving outcomes. The successful implementation of an end-to-end learning healthcare system could dramatically change the paradigm of healthcare delivery for patients with breast cancer, transforming it into an evidence generating system that drives the process of discovery, continuous innovation, and quality improvement.

Indiana

Susan G. Komen Tissue Bank at the IU Simon Cancer Center
Research Opportunity Grant
Principal Investigator: Anna Storniolo, M.D.
Institution: Indiana University
Central Indiana Affiliate

Snapshot
Indiana University (IU) will receive funding to continue to support the Susan G. Komen Tissue Bank (KTB) at the IU Simon Cancer Center, the world's only biorepository, or "bank", of normal breast tissue. The KTB collects and stores whole blood, DNA, serum, plasma and healthy breast tissue from women not known to have breast cancer. It then makes the samples available for researchers to use worldwide. The availability of normal tissue has the potential to revolutionize the understanding of changes that happen in a normal breast as breast cancer develops and spreads to other organs.

Maryland

Catalyzing Personalized Treatment for Metastatic Breast Cancer Using Circulating Tumor Cells
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Soojung Hur, Ph.D.
Institution: Johns Hopkins University
Maryland Affiliate

Snapshot
Soojung Claire Hur, Ph.D., will develop a new system aimed at improving personalized therapy for people living with metastatic breast cancer. She will collect patient blood samples containing metastatic circulating tumor cells and test the effectiveness of drug combinations on those tumor cells. This goal is to create a system that will help doctors, quickly and non-invasively, find the best treatments for their patients.

Project Summary
Despite the improvement in screening, prevention, and treatment for breast cancer, metastatic breast cancer remains to be the second leading cause of cancer deaths among women because there are still no clear answers to why metastatic breast cancer occurs, relapses, and stops responding to certain therapy.

This problem has led to the development of personalized medicine approaches to select ideal therapies for individual patients at the right time. Fast, sensitive, and non-invasive tests performed directly on breast cancer patients' cells will enable accurate personalized risk assessments to screen large cohorts, identify a suitable patient population for available treatments, and predict the corresponding therapeutic outcomes. Circulating tumor cells, known as CTCs, found in cancer patients' blood are good substitute markers to perform tests on because the blood can be routinely extracted for CTC collection, and CTCs reflect real-time, suggestive information of cancer status. Accurate and reliable tests performed on CTCs from individual patients will shed light on the causes of individual variation in treatment response, which will better arm clinicians. Unfortunately, the current CTC assessments preclude further testing as the collection of extremely rare CTCs from blood is difficult, and the majority of the extracted CTCs do not grow in the laboratory.

The proposed study plans to develop a simple and highly efficient gene delivery system that can purify CTCs from patients' blood and create the replica tumor outside of the body from CTCs. The simple workflows of the proposed CTC analytical procedures will enable the developed protocol to be used in conjunction with other established or newly developed diagnostic and prognostic clinical modalities. Upon successful completion of the study, the proposed system will provide a simple means for routinely testing CTCs to select the most effective treatment to cure metastatic breast cancer patients who were once incurable.

Maryland

Overcoming Resistance to Immunotherapy in Metastatic TNBC
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Debangshu Samanta, Ph.D.
Institution: Johns Hopkins University
Maryland Affiliate

Snapshot

Debangshu Samanta, Ph.D., will study how a protein called BIRC2 protects breast cancer from immunotherapy and promotes metastasis of breast cancer. He will explore if targeting BIRC2 can provide new treatments for metastatic breast cancer that will both improve immunotherapy and stop metastasis.

Project Summary

Triple-negative breast cancer (TNBC) is a subtype of breast cancer which lacks the expression of estrogen, progesterone, and HER2 receptor. Since TNBC does not express the receptors, targeted therapy is lacking in this subtype of breast cancer. Even though TNBC patients lack the targetable receptors, they have a high percentage of tumor-infiltrating leucocytes, which kill the cancer cells and high mutation rates, which makes the cancer cells recognized by the leucocytes, making TNBC suitable for anti-PD1 therapy. Anti-PD1 therapy usually works best in which there is a high percentage of tumor-infiltrating leucocytes and high mutation rates. However, only 18% of the TNBC patients treated with anti-PD1 benefit from the therapy. Thus, it is essential to determine why the majority of the patients do not benefit from anti-PD1 treatment.

Recently, it has been shown that hypoxia (less oxygen concentration in tissue) and epithelial to mesenchymal transition (EMT) (a process which makes nonmetastatic cancer cells become metastatic cancer cells) influence non-response to anti-PD1 therapy. However, the causative role of hypoxia in resistance to anti-PD1 treatment is not known. It has also been demonstrated that cancer cells expressing high levels of a protein called BIRC2 are resistant to cancer-killing T-cells. But how the BIRC2 makes cancer cells resistant to T cell-mediated killing is not known. When cancer cells undergo EMT, they turn into cancer stem cells (CSC). CSC are also resistant to immunotherapies and gives rise to metastasis. My project will serve to determine how hypoxia induces the expression of BIRC2 and thus plays a causative role in resisting T cell-mediated killing. I will also examine whether inhibiting BIRC2 and hypoxia would improve the efficacy of antiPD1 therapy. Additionally, I will determine whether BIRC2 expression causes metastasis by regulating CSC survival. The achievement of the project will lead to the discovery of more effective drugs which can be used in combination with anti-PD1 therapy, and to the identification of a new target to arrest metastasis.

Maryland

Susan G. Komen Breast Cancer Challenge at Obesity Week 2018
Scientific Partnerships and Programs
Principal Investigator: Laura Tester Meyer
The Obesity Society
National Capital Field Office

Snapshot
The Obesity Society received funding to support six Susan G. Komen® Breast Cancer Challenge Awards during the Obesity Week conference in 2018 and 2019. Early career researchers were invited to submit short proposals for research that would shed light on how obesity is connected to poorer outcomes for people living with metastatic breast cancer or the role obesity plays in breast cancer disparities.

Maryland

Susan G. Komen Breast Cancer Challenge at Obesity Week 2019
Scientific Partnerships and Programs
Principal Investigator: Laura Tester Meyer
The Obesity Society
National Capital Field Office

Snapshot
The Obesity Society received funding to support six Susan G. Komen® Breast Cancer Challenge Awards during the Obesity Week conference in 2018 and 2019. Early career researchers were invited to submit short proposals for research that would shed light on how obesity is connected to poorer outcomes for people living with metastatic breast cancer or the role obesity plays in breast cancer disparities.

Maryland

The Translational Breast Cancer Research Consortium (supporting breast cancer clinical trials at multiple institutions)
Research Opportunity Grant
Principal Investigator: Antonio Wolff, M.D.
Institution: Johns Hopkins University
Maryland Affiliate

Snapshot

The Translational Breast Cancer Research Consortium (TBCRC), a collaboration of 19 of the top U.S. academic medical centers run through Johns Hopkins University. TBCRC develops and conducts innovative, high-impact, research projects and supports clinical trials that investigate new treatments for breast cancer. Led by Komen Scholar, Antonio Wolff, M.D., the TBCRC has developed 50 clinical trials with more than 5,000 patients enrolled. About half of these trials have focused focus on metastatic breast cancer, drug resistance and/or recurrence (return of cancer).

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.

Massachusetts

Eliminating Metastasis by Harnessing the Immune System to Attack Dormant Disseminated Cancer Cells
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Judith Agudo Cantero, Ph.D.
Institution: Dana-Farber Cancer Institute
New England Affiliate

Snapshot

Judith Agudo Cantero, Ph.D., will investigate ways to use the immune system to attack breast cancer cells that have spread to the lungs. The goal of this study is to develop an immune therapy to target and eliminate breast metastases.

Project Summary

The spread of breast cancer to vital organs such as the brain, lungs and liver is the cause of death for the vast majority of breast cancer patients. This process of spreading is called metastasis and is caused by cancer cells that leave the breast and travel (disseminate) to these vital organs. Once these breast cancer cells reach the new organ, they can wait for some time before they grow into a new tumor, in a state that resembles hibernation called dormancy (like sleeping). This hibernation can explain why metastasis can occur some months to even some years after initial diagnosis, and it is a major cause of resistance to therapy. Chemotherapy drugs are compounds that selectively kill cells that are growing in an abnormally fast pace, and this is how they discern between healthy and cancerous cells. Thus, hibernating or dormant breast cancer cells are by nature resistant to chemotherapy. This explains how breast cancer can re-appear after treatment and grow new tumors in distant places like the lung or the brain. Hence, it is of the utmost importance to eradicate these dormant disseminated cancer cells before they have the chance to grow into new and life-threatening tumors. Since chemotherapy is not effective to target these dormant cancer cells, we aim to use the patients' own immune system to eradicate them. Our immune systems have evolved to be able to distinguish good from bad, and can keep memory of a successful battle, killing every time they see the same danger once it was able to do it the first time. Our goal is to develop strategies to train the patients' immune cells to find all these dormant disseminated breast cancer cells, wherever they are, before they can give rise to new tumors in vital organs and establish a protective anti-metastasis immune response. Thus, our approach aims to prevent metastasis and its devastating effects in breast cancer patients.

Massachusetts

Personalized Risk Assessment with Deep Learning (assessing breast cancer risk using artificial intelligence)
Research Leadership Grant - Komen Scholar
Principal Investigator: Regina Barzilay, Ph.D.
Institution: Massachusetts Institute of Technology
New England Affiliate

Snapshot

Komen Scholar Regina Barzilay, Ph.D., will develop an accurate risk assessment model to improve early detection of breast cancer. The model will enable personalized screening programs to predict patients at high risk of developing breast cancer. Overall, this project should improve outcomes by identifying high-risk populations and improving early detection of the disease.

Abstract

The goal of the proposed research is to develop personalized risk models that fully utilize the richness of information available in mammograms. Today, these images are primarily used to diagnose existing malignancy, and, in a very limited way, are used to assess risk. We hypothesize that mammograms reflect important information about the future trajectory of the patient, and thus can be used directly to predict the risk.

Our goal is to build deep learning models that are trained to read mammograms and predict patient risk. This deep learning technology has become a staple in many object recognition applications and is mature enough to be applied to predicting risk. In our prior work, supported by Susan G. Komen, we have already demonstrated that these techniques significantly outperform traditional models. The empirical performance of our image-based risk model has justified their clinical implementation in Massachusetts General Hospital Breast Imaging Clinic. The goal of this proposal is to further improve the predictive power of these models. We will achieve this advancement by analyzing sequences of consecutive patient's mammograms to model temporal change in their tissue and incorporating additional patient information, such as BRACA status or family history, into the image-based models. In addition, we will work on making models' predictions more interpretable and transparent to physicians and patients.

Making risk models more accurate and personalized can be transformative. Risk models used in clinical practice today are not precise enough at the individual level, and most patients do not know their risk until they have been diagnosed. We believe that the high predictive ability of image-based models would support early diagnosis via personalized screening programs. This personalization will diminish unnecessary tests for the low-risk population and provide access to a more comprehensive screening for the high-risk population. This work has the potential to reduce the number of patients diagnosed at the late stages of the disease and could ultimately decrease breast cancer mortality.

Massachusetts

Identifying Novel Synthetic Lethal Vulnerabilities to Overcome Endocrine Resistance in Breast Cancer (develop new ways to overcome endocrine resistance)
Research Leadership Grant - Scientific Advisory Board Member
Principal Investigator: Myles Brown, M.D.
Institution: Dana-Farber Cancer Institute
New England Affiliate

Snapshot

Komen Scientific Advisory Board Member Myles Brown, M.D., will study how patients with metastatic breast cancer become resistant to endocrine therapies and develop methods to test new combinations of targeted treatments that can overcome drug resistance.

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 metastatic 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.

Both clinical and pre-clinical data 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.

Massachusetts

Tufts Breast Cancer Training Program to Reduce Asian Health Disparities (training program for young scientists)
Graduate Training in Disparities Research
Principal Investigator: Karen Freund, M.D.
Institution: Tufts Medical Center, Inc
New England Affiliate

Snapshot

Karen Freund, M.D., will lead the Tufts Breast Cancer Training Program to train students in breast cancer disparities research aimed at reducing disparities among Asian-American women. This program will focus on the best methods to address language and cultural barriers, which include a lack of trust in Western medical care by Asian-American women.

Project Summary

We plan to train master's and doctoral students to conduct cancer disparities research to address the needs of underserved women with breast cancer, with a focus on Chinese American breast cancer patients and survivors.

To meet these goals, we have to date identified five candidates, 3 in the master's program and 2 in the doctoral program and have provided all with the financial and mentoring support to develop the skills to conduct health disparities research. All trainees are within the Clinical Translational Science graduate program within the Sackler School of Graduate Biomedical Sciences at Tufts University School of Medicine. We plan to recruit and train two additional candidates. We have already selected the first trainee, Dr. Maria Rodriguez ND, who has a strong interest on cancer disparities research.

The program is directed and coordinated by Drs. Freund and Parsons. They serve as the primary mentors for all of the trainees, overseeing their specific research projects and their overall experience. They also serve as faculty in the Clinical Translational Science graduate program and also serve on the Advisory Board of the program that reviews and approves the progress of each student, approves their thesis proposal, and their final thesis. This allows them to jointly monitor both the coursework and overall progress in the graduate program, and specifically the progress of the specific research thesis project.

In addition to the support of Drs. Freund and Parsons, the trainees benefit from the exposure to the broad group of mentors, including those with expertise in biostatistics, epidemiology, predictive modeling and heterogeneity of treatment effects, health economics, stakeholder engagement, and qualitative methods. They also benefit from the interactions with students in diverse fields and expertise. For example, current students come from a range of medical specialties, veterinary medicine, basic sciences, biomedical engineering, and speech pathology. This ensures both a deep understanding of breast cancer health disparities research and a broad context of clinical research. It also teaches students to discuss their science broadly with other scientists and advocates.

Massachusetts

Elucidating Mechanisms of Resistance and Drivers of Metastatic TNBC
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Ana Garrido-Castro, M.D.
Institution: Dana-Farber Cancer Institute
New England Affiliate

Snapshot
Ana Garrido-Castro, M.D., will study how genetics and immune cells can contribute to drug resistance and metastasis by using data from patients with triple-negative breast cancer (TNBC). The results of this study could lead to new drug targets for TNBC or to new ways to identify TNBC patients at risk for developing drug resistance and metastasis.

Project Summary
Triple-negative breast cancer (TNBC) is a type of breast cancer that lacks expression of hormone receptors, which include the estrogen receptor and the progesterone receptor, and of HER2. Metastatic TNBC, where the cancer has spread to other parts of the body, is highly aggressive and has a shorter average survival compared to patients with other subtypes of metastatic breast cancer. In early-stage or localized TNBC, there are certain clinical features that can help identify patients in whom the cancer is more likely to return, also known as recurrence. However, not all TNBC patients with these features will experience a recurrence. To date, we do not fully understand the mechanisms that drive TNBC to metastasize. Distinguishing between signs of resistance to treatment and drivers of metastasis is key to developing tailored treatments to prevent recurrences and reduce overtreatment for patients for whom additional therapy may be unnecessary.

One method to identify signs of resistance to treatment or drivers of metastasis is to sequence and analyze the DNA of the tumor. New methods of evaluating cancers include sequencing technologies, which provide large amounts of data on tumor DNA. Additionally, current research also suggests that the immune system, the body's natural defense system against disease, also plays a critical role in shaping outcomes for TNBC patients. Combining information about the DNA, RNA and proteins in the tumor and surrounding immune cells will help improve our knowledge of the behavior of TNBC and develop strategies for treatment.

We hypothesize that there are genomic and immune features that result in the development of metastatic TNBC. To test this, we will sequence and evaluate genomic and immune profiles in: 1) patients with metastatic TNBC at diagnosis who have paired breast and metastatic biopsies, and 2) patients with early-stage TNBC at diagnosis, comparing those who do versus do not recur. To identify mechanisms of resistance to treatment in patients with early stage TNBC who receive preoperative chemotherapy, we will compare these profiles before treatment (biopsy at diagnosis), at surgery and at time of recurrence, should that occur.

Altogether, this project will improve our understanding of changes in the biology of TNBC over time, identify factors that drive metastasis in TNBC, and evaluate new targeted therapies based on genomic and immune profiles in high-risk patients, and improve survival in TNBC.

Massachusetts

Elucidating (finding) Novel Mechanisms of Resistance to HER2-directed Therapy

Research Leadership Grant - Komen Scholar
Principal Investigator: Ian Krop, M.D., Ph.D.
Institution: Dana-Farber Cancer Institute
New England Affiliate

Snapshot

Komen Scholar Ian Krop, M.D., Ph.D., will identify mutations in blood and metastatic breast cancer tissues that are associated with resistance to the latest HER2- targeted therapies currently in clinical trials. Overall, this project should identify how metastatic breast cancers develop resistance to HER2-targeted therapies so that it can be stopped, thereby improving survival.

Abstract

Approximately 20% of breast cancers are characterized by abnormally high levels of a cell surface signaling protein called HER2. These HER2 positive cancers typically have an aggressive behavior and poor outcome when treated with conventional therapies. The introduction of drugs specifically targeted against HER2, including trastuzumab (Herceptin), lapatinib, pertuzumab, and trastuzumab emtansine (T-DM1) has significantly improved outcomes for patients with HER2+ breast cancer. However, despite these new therapies, resistance to HER2-directed therapies, particularly in the metastatic setting, is an important clinical problem. Because of the development of resistance, metastatic HER2+ breast cancer remains largely incurable. It is thus critical that we identify the molecular mechanisms that cause resistance to these agents so that approaches to overcome these mechanisms can be developed. While a number of potential resistance mechanisms have been proposed based largely on laboratory-based studies, none of these have been validated in metastatic tumor tissue from patients. We hypothesize, that based on work by our laboratory and that of our collaborators, that there are at least several potential mechanisms through which tumors can become resistant to HER2-targeted therapy. One mechanism is the development of mutations in HER2 itself which may make the protein resistant to the effects of the HER2-targeted therapy. Our initial results from this Research Plan suggest that such mutations do occur in a subset of cancers. A second potential mechanism is through the cancer's ability to suppress the body's immune response to the tumor. A third mechanism may arise because cancers are heterogeneous; even in HER2+ cancers some cells within the cancer may have little or no expression of HER2, making these cells resistant to HER2-targeted agents. To validate these potential mechanisms in human cancers, and begin to develop approaches to overcome them, we propose the following Aims. 1) To determine, using analysis of tumor DNA in blood samples from patients with HER2+ breast cancer on clinical trials, the rate at which HER2 and other mutations occur in HER2+ cancers after treatment with HER2 therapies. 2) To identify tumor DNA mutations that are observed in tumors that are resistant to immunotherapy. 3) To conduct a preoperative trial of T-DM1 in patients with HER2+ cancers and determine if cancers that do have a subpopulation of HER2 negative cells are less likely to completely respond to T-DM1. Through these Aims, we will improve our understanding of the actual molecular mechanisms of resistance that occur in patients with trastuzumab-resistant cancers, leading to approaches to overcome these mechanisms.

Massachusetts

Improving Treatment Strategies for Breast Cancer Brain Metastases
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Jose Leone, M.D.
Institution: Dana-Farber Cancer Institute
New England Affiliate

Snapshot

José Pablo Leone, M.D., will test two new treatment combinations for patients with breast cancer that has spread to the brain. His work aims to determine if these treatment combinations can eliminate brain metastases and improve patient survival.

Project Summary

Breast cancer can sometimes spread, or metastasize, throughout the body to form other tumors, called metastases. One of the places where breast cancer metastasizes is the brain, where it can form metastases which disrupt normal brain functions and sometimes lead to death. Breast cancer brain metastases (BCBM) are a common and difficult condition to treat, particularly among patients with metastatic HER2+ breast cancer. Unfortunately, there are few treatments available for these patients with limited benefit. Finding a treatment is an unmet need for patients with BCBM.

We have data which suggest that there are two separate pathways that are very important for BCBM to grow in the brain. We hypothesize that by blocking these pathways, we will be able to treat BCBM. To do this, we will conduct two clinical trials testing two different drug combinations for their impact in treating BCBM. The first pathway is called the PI3K/PTEN/mTOR pathway, which we will block with the combination of the drug GDC-0084 and trastuzumab on a phase II clinical trial. The second pathway is the cyclin D1/CDK4 pathway, which we will block with the combination of abemaciclib, tucatinib, and trastuzumab, on a phase 1b trial. In addition, we suspect that we can use a blood sample to identify the genetic alterations present in the brain metastases. This could help provide genetic and treatment information about a tumor without surgery. To test this, we will analyze blood and cerebrospinal fluid from patients enrolled in both trials. If these clinical trials are successful, they would help reduce the number of breast cancer deaths in the US by 2026 by providing better treatment options for our patients with brain metastases.

Massachusetts

Breast Cancer Weight Loss (BWEL) Study
Research Leadership Grant - Komen Scholar
Principal Investigator: Jennifer Ligibel, M.D.
Institution: Dana-Farber Cancer Institute
New England Affiliate

Snapshot
Komen Scholar Jennifer Ligibel, M.D., will conduct a clinical trial to test whether weight loss can reduce the risk of breast cancer recurrence in overweight or obese women with stage II-III breast cancer. By understanding the effect of weight loss on breast cancer outcomes, this study has the potential to determine whether weight loss programs should become a standard part of breast cancer care.

Abstract
Obesity is a growing health problem in the Unites States and around the world. Studies have shown that obese women are at higher risk of developing breast cancer, and recent studies also suggest that obesity may be a risk factor for cancer recurrence in women who are diagnosed with early breast cancer. More than 100 studies have looked at the connection between a woman's weight at the time that she is diagnosed with breast cancer and her risk of developing a cancer recurrence and dying from the disease. These studies show that women who are obese when they are diagnosed with breast cancer have a 35% higher risk of dying from breast cancer as compared to women who are of normal weight when they are diagnosed. Some studies have suggested that women who are overweight when they are diagnosed with breast cancer may also be at higher risk of recurrence compared to normal weight women. These findings are concerning, given that approximately 35% of breast cancer survivors in the United States are obese and an additional 30% are overweight. Although evidence clearly suggests that there is a link between obesity and an increased risk of breast cancer recurrence, we do not know whether losing weight after breast cancer diagnosis could help lower this risk and improve survival rates in women with early breast cancer. Studies are needed to test the effect of losing weight on the risk of breast cancer recurrence. The Breast cancer Weight Loss (BWEL) study is a randomized trial that will test the impact of a supervised weight loss program on the risk of breast cancer recurrence in overweight and obese women with stage II-III breast cancer. The primary hypothesis of this study is that weight loss will reduce the risk of breast cancer recurrence in women with early-stage breast cancer. This hypothesis will be tested by randomly assigning overweight and obese women with breast cancer to a group that takes part in a weight loss program and a group who does not and determining if the women who take part in the weight loss program have a lower risk of breast cancer recurrence or death. The study will enroll 3136 women with Stage II-III breast cancer. Patients will be randomly assigned to a 2-year weight loss program or to a group that does not receive the weight loss program. The weight loss program will be delivered through telephone calls, supplemented with a print or on-line workbook. The goal of the weight loss program will be to help patients to lose 10% of their body weight, achieved through reducing calories and increasing physical activity. Patients assigned to the other group will receive general health mailings and be invited to Webinars and teleconferences that provide updates about breast cancer. The study will compare rates of breast cancer recurrence and mortality in the patients assigned to the weight loss group compared to the control group. The study will have the ability to determine whether the weight program reduces the risk of breast cancer recurrence by at least 20%, which is similar to improvements seen with many of the drugs commonly used to treat breast cancer. This study will be the first trial testing the impact of losing weight after breast cancer diagnosis upon the risk of breast cancer recurrence and death. If this study

shows that losing weight improves survival rates in breast cancer, this could lead to weight loss programs becoming a standard part of the treatment for millions of breast cancer patients around the world.

Massachusetts

Breast Cancer in Young Women: Understanding Factors Affecting Outcomes
Research Leadership Grant - Komen Scholar
Principal Investigator: Ann Partridge, M.D., MPH
Institution: Dana-Farber Cancer Institute
New England Affiliate

Snapshot

Komen Scholar Ann Partridge, M.D., M.P.H., will study breast cancer in young women, including disease, treatment and psycho-social characteristics at diagnosis and in follow-up visits, compared to older women. Her goal is to identify potential interventions that could lead to reduced morbidity (health degradation, poor quality of life) and mortality (death) in young patients.

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 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 1,300 women in our 13th 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. Now that the cohort is maturing, we will be able to evaluate later outcomes including how issues such as weight gain and physical activity, local recurrence, and fertility and pregnancy uniquely affect disease outcomes in this large cohort of young women. The proposed research will study questions that are of upmost importance to this population. Specifically, we will test the following hypotheses (assumptions) in young survivors: a) weight gain and inactivity are common and associated with worsened disease outcomes, b) local therapy impacts on local recurrence but not overall survival in young survivors, and c) pregnancy after breast cancer is not associated with increased risk of recurrence or death after breast cancer. The specifics aims of the proposed research are: 1) To describe weight and physical activity changes over time and factors associated with changes, and explore how weight change and physical activity change impacts on disease outcomes; 2) To determine how local therapy, including bilateral mastectomy, impact on risk of local and distant recurrence, and how local recurrence impacts survival in particular in this unique cohort; and 3) To evaluate how interest in pregnancy, fertility, and pregnancy itself, uniquely affect disease outcomes in this large cohort of young women. Successful completion of the proposed work should uniquely advance our understanding of breast cancer in young women and potentially inform the decisions and care of young survivors to improve not only how they feel but how they do from a cancer standpoint in the long run. 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 young women with breast cancer, a vulnerable population.

Massachusetts

Mammary Epithelial Progenitors as Targets for Breast Cancer Prevention
Research Leadership Grant - Komen Scholar
Principal Investigator: Kornelia Polyak, M.D., Ph.D.
Institution: Dana-Farber Cancer Institute
New England Affiliate

Snapshot

Komen Scholar Kornelia Polyak, M.D., Ph.D., will study how a population of normal breast cells, called epithelial cells, act as precursors to breast tumors. Outcomes from this project should form the basis of future prevention studies to help women at high risk for breast cancer.

Abstract

As the incidence of breast cancer continues to rise in densely populated developing countries, the global impact of the disease continues to increase. We believe that breast cancer can be eradicated only by instituting strong preventive measures. The highest impact on breast cancer associated morbidity and mortality will be achieved with two tools. The first is a test that accurately predicts an individual's risk of developing breast cancer allowing us to identify who needs the preventive action and who does not. Second, is to discover the best agent for prevention that will be universally effective. We know that inheriting mutated BRCA1 and BRCA2 genes confer a high risk of breast cancer and the most effective prevention strategy currently available is prophylactic oophorectomy and mastectomy. Other significant determinants of breast cancer risk are reproductive history and mammographic density. Epidemiological data suggest that pregnancy induces long-lasting effects in the normal breast, except in BRCA1 and BRCA2 mutation carriers, where pregnancy does not decrease breast cancer risk. A number of studies have shown that breast epithelial progenitor cells are the likely the "cell-of origin" of breast cancer. It stands to reason then, that eliminating them will abolish tumor development. In recent work we analyzed and characterized multiple cell types from normal breast tissues of nulliparous and parous women, including BRCA1 and BRCA2 mutation carriers. We detected the most significant differences in breast epithelial progenitors and found that the frequency of these cells is higher in women with higher risk of breast cancer. We have also identified key signaling pathways important for their proliferation and showed that by modulating the activity of these pathways we can decrease the frequency of the progenitor cells, thus, potentially reducing breast cancer risk. We performed similar studies in mice and rats and could replicate what we saw in human breast, suggesting that rodent models can be used for our proposed preclinical studies. Lastly, we analyzed normal breast tissues of women in the Nurses' Health Studies and found that premenopausal women with thigh Ki67+/low p27+ cell frequencies had a 5-fold higher risk of breast cancer compared to women with low Ki67+/low p27+ cell frequencies.

The goals of this study are (1) characterize how TGFβ and ovarian hormones regulate p27+ mammary epithelial progenitors and the perturbations of these in BRCA1/2 mutation carriers. and (2) to test our hypothesis that elimination of the breast progenitors we identified will decrease breast cancer risk. Second, we will test if depleting mammary epithelial progenitors will prevent breast cancer in animal models. We will use inhibitors of the transforming growth factor beta receptor signaling pathway that will induce their proliferation mimicking the effects of pregnancy. Our goal is to generate strong preclinical data on which we can build future prevention studies for women of all ages with a high risk of breast cancer.

Massachusetts

New Patient-Derived Cell Models to Develop Treatments for Metastatic Inflammatory Breast Cancer
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Jennifer Rosenbluth, M.D., Ph.D.
Institution: Harvard Medical School
New England Affiliate

Snapshot
Jennifer Rosenbluth, M.D., Ph.D., will study new treatments for inflammatory breast cancer (IBC), an especially aggressive cancer type that is prone to become metastatic. She will identify drugs that enhance the effectiveness of chemotherapy for metastatic IBC with the goal of moving these drug combinations to clinical testing.

Project Summary
Inflammatory Breast Cancer (IBC) is an aggressive type of breast cancer that is characterized by the rapid onset of swelling and redness of the breast. This is caused by clusters of cancer cells that escape from the local tumor and block the lymph vessels in the skin of the breast. In addition, IBC has an increased likelihood of early metastasis, and is associated with a worse outcome. Research into IBC is hampered by a lack of sufficient preclinical models to study IBC in the research setting. This Komen funded project focuses on using a new technique for growing tumors in the lab from tissue samples collected from IBC patients called patient-derived organoids. We have found that this method preserves key features of the original tumor to a greater extent for better modeling in the research setting. By culturing the organoids with cells that line blood and lymph vessels, we can investigate methods by which the cells become metastatic and spread to other parts of the body. Because a single tumor can be comprised of diverse cell types, we are using a new technology to measure protein levels on single cells in order to define the specific sub-populations that make up breast tumors that contribute to vessel invasion, the first step by which tumor cells disseminate to other organs.

This Komen funded project will additionally make use of a drug screening approach to identify drugs which enhance the efficacy of chemotherapy specifically in metastatic IBC. Candidate drugs identified through this screen will undergo rigorous preclinical testing, with the ultimate goal of developing new clinical trials for this particularly challenging type of breast cancer. New combination therapies for treating aggressive subtypes of breast cancer such as IBC will provide much-needed treatment options for patients with metastatic breast cancer, and will help Komen reach its goal of significantly reducing the number of breast cancer deaths in the U.S. by 2026.

Massachusetts

Late Recurrence of ER+ Breast Cancer: Risk Factors and Potential for Interventions
Research Leadership Grant - Komen Scholar
Principal Investigator: Eric Winer, M.D.
Institution: Dana-Farber Cancer Institute
New England Affiliate

Snapshot
Komen Scholar Eric Winer, M.D., will study risk factors like body mass index (BMI), weight gain, physical activity after diagnosis and dietary inflammatory score, that may impact late recurrence of estrogen receptor (ER+) breast cancer. The goal is to identify potential interventions to reduce late recurrence.

Abstract
Late recurrence of ER positive breast cancer is a major public health problem. Over half of all recurrences of ER positive disease occur more than 5 years from diagnosis and are commonly defined as late recurrences. Extended hormonal therapy decreases the risk to a small extent but has not had a dramatic impact on the monotonous and relentless annual risk of recurrence that extends for at least 20 years after diagnosis. Using the Nurses' Health Study cohorts, we will test whether lifestyle factors can impact on the risk of late recurrence. Factors of particular interest include weight gain and loss, dietary habits, exercise, and alcohol intake. At the same time, we will assemble a prospective cohort of women at risk of late recurrence and assess their willingness to participate in a study of late recurrence, their perceptions of risk, and any increase/decrease in breast cancer anxiety related to study participation. Given that late recurrence is responsible for significant morbidity and mortality, this project is directly relevant to the interests of over 75% of women with breast cancer who are diagnosed with hormonally sensitive disease.

Michigan

Multidisciplinary Training in the Biology of Breast Cancer Disparities (training program for young scientists)
Graduate Training in Disparities Research
Principal Investigator: Michele Cote, Ph.D.
Institution: Wayne State University
Greater Detroit Affiliate

Snapshot
Michele Cote, Ph.D., will train doctoral students to bridge basic, clinical and population sciences to better understand the disparities in breast cancer incidence (new cases) and mortality (death) between African American women and Caucasian women. Students will receive training in advocacy, philanthropy and education about breast cancer research.

Abstract
The Komen Graduate Training in Disparities Research program (GTDR) at Wayne State University (WSU) provides doctoral students the opportunity to bridge basic, clinical and population sciences in an environment in which the effect of breast cancer disparities is seen on a daily basis. The guiding philosophy for the GTDR program is to teach students to think critically, through coursework that emphasizes hypothesis-based taught by scientists from various fields, and through exposure to cutting-edge technology. Another important component of the training is the recognition that most diseases, including breast cancer, are due to many different causes, and impact populations differentially. The curriculum emphasizes the importance of learning to effectively communicate research results by providing opportunities for poster presentations, oral presentations and scientific writing, as well as continual interactions with our breast cancer Advocate, and community participation in conjunction with our Komen Greater Detroit Affiliate. The metropolitan Detroit area not only experiences disparities in breast cancer incidence and mortality between AAs and whites, but AA women here have higher breast cancer incidence and mortality rates than AA women in the United States. Close relationships with a large Komen Race for the Cure, now part of the Komen Greater Detroit Affiliate, allows our GTDR fellows the opportunity to interact with survivors and advocates on a regular basis. Knowing that their fundraising is directly supporting the education of future breast cancer researchers has been a highlight for many of our donors. Two trainees will be supported, and in addition to their scientific coursework, they will receive individual training on how to communicate with non-scientists, the role of scientists in advocacy and philanthropy, developing "an elevator pitch" and how to promote research in the community.

Michigan

Personalized Drug Screening Platform for Breast Cancer Brain Metastasis
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Aki Morikawa, M.D., Ph.D.
Institution: University of Michigan
Michigan Affiliate

Snapshot

Aki Morikawa, M.D., Ph.D., will study ways to improve treatment response for breast cancer patients with brain metastases. Her studies will provide real-time drug testing from patient brain metastasis samples to guide treatment decisions in the clinic and improve patient outcomes.

Project Summary

Breast cancer can sometimes spread, or metastasize, to create tumors in the brain. These tumors, called brain metastases, can often cause breast cancer patients to become very sick or lead to death. New therapies that target specific tumor molecules or biomarkers have helped to increase survival and quality of life for some patients with metastatic breast cancer, especially for hormone receptor positive and HER2 positive breast cancer patients. However, these targeted therapies do not work equally for all patients with breast cancer brain metastases. Some patients may not be able to afford multiple 'trial and error' attempts to select drugs that work before succumbing to cancer. Optimizing the way we select drug therapy would reduce breast cancer death by minimizing such 'trial and error' approach.

To solve this problem of matching the right patient with the right targeted therapy, there is an effort to see if there are certain genetic changes in breast cancer brain metastases that can be a target of these drugs. However, many times we do not know how these genetic changes influence the response to a drug. It would be ideal if we can test these drugs on cancer cells in real-time to see how well the cancer cells respond to certain drugs. We are currently able to grow cancer cells that are directly taken from the brain metastases of breast cancer patients who are undergoing surgery to remove brain metastases. In this research project, we plan to conduct drug testing on these cancer cells taken from breast cancer brain metastases to see if response or resistance to drug therapy is related to the genetic changes found in the brain metastasis.

For the results of this study to be useful to breast cancer patients, the results must be obtained within a reasonable amount of time to guide drug treatment decision making. Therefore, we will evaluate if this is a realistic approach in terms of how quickly we can conduct this drug testing from the time of cancer cell collection in the first part of this study. In the second part of this study, we will collect the cells that are not killed off by drug treatment and examine their genetic features to see if we can predict what drug or a combination of drugs may be helpful in treating these cancer cells that survive the initial drug therapy. This study will have the potential to provide valuable information on how to prioritize the most beneficial drug treatment plans and test new treatment strategies for patients with breast cancer brain metastases.

New Jersey

Targeting of a Key Enzyme in Breast Cancer Metastasis and Chemoresistance
Research Leadership Grant - Komen Scholar
Principal Investigator: Yibin Kang, Ph.D.
Institution: Princeton University
Central and South Jersey Affiliate

Snapshot

Komen Scholar Yibin Kang, Ph.D., will study the role of the protein called Aldh1a3 (Aldehyde Dehydrogenase 1 family, member A3) in breast cancer progression. Using preclinical models, he will help determine if Aldh1a3 inhibitors could be used to treat metastatic breast cancer.

Abstract

Despite hundreds of new drug approvals for cancer treatment over the last three decades, patients with advanced stages of triple negative breast cancer (TNBC) have seen little improvement in overall survival. Advanced cancer manifests as tumors resistant to modern medicines that have often spread throughout the body in a process known as cancer metastasis. Using cutting-edge genetic tools, our work at Princeton University has revealed fundamentally unique biology that drives breast cancer metastasis and resistance to therapy; hence fundamentally unique therapeutics are needed to treat metastasis. One target we identified is an enzyme normally active only in the developing body and not in adult tissues. In contrast, this enzyme is uniformly upregulated in adult tumors and functions to protect the cancer cells in stressful environments, such as during metastasis to the lung, bone, or liver, or during chemotherapy/radiotherapy. We have developed a set of small, molecular inhibitors against this target which have shown promise in treating advanced breast cancer in the laboratory setting. Here we hypothesize that application of these molecular inhibitors to multiple laboratory models and patient derived models of breast cancer will lead to the regression of metastatic disease. We further aim to characterize how these unique therapeutics kill the cancer cells such that we can discover new dosing strategies as well as monitor patient tumors for signs of a favorable response to the therapy. The successful completion of this project will result in the advancement of the first therapeutic that targets cancer metastasis-specific biology and may lead to the first therapy that can cure metastatic disease. This is highly significant as all current therapeutics target mechanisms that drive cancer growth, but do not address the root mechanisms of breast cancer metastasis. Here we aim to cripple the cancer's ability to survive in the metastatic environment, which, if successful, may lead to the resolution and cure of metastatic disease.

New York

Medication Reminder Application to Improve Medication Adherence in Women with Breast Cancer
Research Leadership Grant - Komen Scholar
Principal Investigator: Dawn Hershman, M.D.
Institution: Columbia University
Greater New York City Affiliate

Snapshot

Komen Scholar Dawn Hershman, M.D., will test a new way to improve treatment adherence in early stage and metastatic breast cancer patients. She will conduct two prospective clinical trials to assess the effectiveness and feasibility of a medication reminder application designed to improve adherence to both oral anticancer therapy and medications for chronic conditions. By increasing treatment adherence, this project could improve survival of people diagnosed with breast cancer.

Abstract

Improvements in screening and treatment options in the past few decades have led to declining breast cancer mortality rates. As survival after breast cancer diagnosis increases, cardiovascular disease (CVD) has now become the leading cause of death in breast cancer patients, especially among older women. Despite the growing risk of death due to CVD, adherence to medications for chronic non-breast cancer conditions (diabetes, hypertension, high cholesterol) decreases after the first year of treatment. Of concern, Non-adherence to medications for cardiovascular conditions following a diagnosis of breast cancer is associated with an increased risk of a subsequent cardiac event such as a heart attack. In addition, patients with CVDs risk factors at the time of diagnosis have more hospitalizations and higher costs of care during their breast cancer treatment. Also of major concern, non-adherence to medications for chronic conditions is associated with non-adherence to hormonal therapy for breast cancer, which can increase the risk of breast cancer recurrence and death from breast cancer. Less is known about adherence to antineoplastic agents among patients with advanced disease. Recently, investigators have turned to Medication Reminder Applications (Med_App) to improve medication adherence. Medisafe is an app that can be used on a phone or tablet to help manage medications by sending daily reminders by text, email or push notification depending on preferences. The app shows not only which medication the patient should take, but also the reasoning for it. It tracks medication use, saves and analyzes usage history. For this proposal we will conduct two prospective trials to assess the efficacy and feasibility of Medisafe in improving adherence to both oral anticancer therapy and adherence to medications for chronic conditions in a diverse cohort of 150 patients with early stage breast cancer (AIM 1) and 75 patients with metastatic breast cancer (AIM 2). We will determine the effect of the assisted implementation of a Medication Assistance App on global medication adherence (ie adherence to all medications). We will evaluate self-reported adherence, medication refills, and downstream effects of medication compliance. We will also measure engagement and acceptance of the application in both English speaking and Spanish speaking women. If successful, results from this work will inform the optimal intervention delivery methods for a large multicenter randomized trial. Improving the delivery of known effective therapies has great potential to reduce the number of deaths in women with breast cancer.

New York

Triple Negative Breast Cancer in Women with African Ancestry
Research Leadership Grant - Scientific Advisory Board Member
Principal Investigator: Lisa Newman, M.D.
Institution: Weill Medical College at Cornell University
Greater New York City Affiliate

Snapshot

Komen Scientific Advisory Board Member Lisa Newman, M.D., will study how ancestry, particularly African ancestry, contributes to triple negative breast cancer (TNBC). She will compare gene expression in TNBC samples from patients from west Africa, east Africa, African Americans and Caucasian Americans to determine if shared ancestry, population migration and reproductive patterns contribute to the development of specific subtypes of TNBC. This work will better define TNBC subtypes in diverse populations, advance our understanding of breast cancer disparities and expand our knowledge of the root causes of TNBC so it can be stopped.

Abstract

Rationale: Breast cancers that are negative for the estrogen receptor, the progesterone receptor, and the HER2/neu marker are called triple negative breast cancer (TNBC); they tend to be biologically more aggressive and difficult-to-treat tumors. TNBC is more common among African American compared to Caucasian/White American patients, and this results in higher breast cancer death rates among African American women. TNBC is a marker of women that have inherited/familial breast cancer and it has different risk factors compared to non-TNBC for example, multiple pregnancies appear to increase the likelihood of developing TNBC but lowers the risk of non-TNBC. How reproductive patterns influence TNBC rates in different populations on an international basis is completely unknown. Research regarding the genetics of TNBC has revealed that there are several different TNBC patterns, and the pattern seen in an individual patient has implications regarding the optimal treatment and outcome. It is critically important to characterize the full spectrum of TNBC subtypes but unfortunately, no data currently exist regarding the TNBC genetic patterns of African American and sub-Saharan western African women, despite the increased prevalence of TNBC in both of these population subsets. Our group has established a unique international breast cancer research collaborative that features a repository of TNBC specimens from Ghanaian African (representing west Africa); Ethiopian (representing east Africa), African American, and White/Caucasian American patients. We have previously demonstrated that African American and Ghanaian patients have similarly high frequencies of TNBC; in contrast, White/Caucasian American and Ethiopians have similarly-low TNBC frequencies. Hypothesis: We hypothesize that the distribution and nature of TNBC subtypes varies between population subsets. We furthermore hypothesize that these population-based TNBC subtype associations will be related to shared ancestry, population migration, as well as reproductive patterns. We therefore expect that TNBC patterns will be relatively similar between African Americans and Ghanaians because of shared ancestry related to the trans-Atlantic slave trade between east Africa and the Americas. The east Africa slave trade involved forced population migration to Asia, accounting for less shared ancestry between contemporary African Americans and Ethiopians.

Research Aims and Study Design: Specific Aim #1 will evaluate TNBC subtypes by gene expression studies from two hundred samples, evenly distributed between African American, White/Caucasian American; Ghanaian; and Ethiopian patients. We will evaluate the known TNBC major subtypes via the publicly-available web-based tool TNBCtype. Specific Aim #2 will utilize anthropology research tools to generate hypotheses regarding the interactions of population migration patterns and reproductive risk factors on TNBC pathogenesis.

Significance and Impact: Our results will fill a critical gap in defining TNBC subtypes in diverse populations and will establish a unique resource of gene expression profiles in breast cancer patients with African ancestry. We

will furthermore establish a novel research field of anthropologic oncology, which can define root causes of mammary tumorigenesis based upon the study of population migration patterns and reproductive history.

New York

Exploiting PIK3CA Mutations to Improve PI3K-targeted Therapy for ER+ Metastatic Breast Cancer
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Neil Vasan, M.D., Ph.D.
Institution: Memorial Sloan-Kettering Cancer Center
Greater New York City Affiliate

Snapshot

Neil Vasan, M.D., Ph.D., will study how two common mutations to a breast cancer driver gene, PIK3CA, impact how patients with estrogen receptor positive (ER+) metastatic breast cancer respond to targeted therapies. The goal of this work is to identify which patients might benefit the most from targeted treatments.

Project Summary

Most breast cancers are driven by hormones, like estrogen or progesterone, and these hormones can help cancer cells grow and spread throughout the body, a process called metastasis. In about 40% of hormone-driven tumors, a gene called PIK3CA, a component of a protein group called the PI3K complex, can be turned on by a typo or mutation in the DNA. For these tumors, this mutation can become essential for the tumors to survive and spread. Drugs that target PI3K are being investigated in the clinic. However, some patients whose tumors contain specific mutations in PIK3CA respond better to these drugs than others. Identifying the patients who respond best to PI3K inhibitors is critical to improving patient response to treatment as well as quality of life, as these drugs are effective but have many side effects.

By evaluating large data sets, our research group has discovered frequent double PIK3CA mutations in 15% of hormone-driven PIK3CA mutated breast cancer. We have observed that breast cancer patients with double PIK3CA mutations respond better to anti-PI3K drugs. We have also found that these double mutations are on the same piece of DNA, which results in a protein with two mutations. We hypothesize that PIK3CA bearing two mutations is more active than PI3K bearing one, and tumor cells with two mutations in PI3K are more dependent on this molecule to survive and proliferate. In this project, we will test the hypothesis that double PIK3CA mutations synergize to drive breast cancer progression and are more sensitive to PI3K drugs than single PIK3CA mutations.

To do so, we will use both samples collected from patients treated with PI3K inhibitors and preclinical models available in our laboratory. We will use DNA sequencing to identify how often the two mutations are on the same piece of DNA in patient samples. Next, we will determine how these double mutations change the function of the protein. Then we will study how double mutations change a tumor's response to PI3K inhibitors in cells and in mice.

The clinical goal of this work will be to establish a basket clinical trial of PI3K inhibitors in ER+ MBC patients with compound PIK3CA mutations, with the goal of refining which patient population will benefit most from PI3K inhibitors, and thus reducing breast cancer deaths by 2026.

North Carolina

Optimizing HER2-Targeting Using RNA and DNA-based Predictive Algorithms (improving HER2-positive breast cancer treatment)
Research Leadership Grant - Scientific Advisory Board Member
Principal Investigator: Lisa Carey, M.D.
Institution: The University of North Carolina at Chapel Hill
North Carolina Triangle to the Coast Affiliate

Snapshot
Komen Scientific Advisory Board Member Lisa Carey, M.D., will study how HER2+ tumors respond to HER2-targeted therapies. This project will integrate and analyze data from more than 1,300 women participating in six neoadjuvant, first step treatment, clinical trials of HER2- targeted therapies to learn how therapy for HER+ breast cancer patients can be improved.

Abstract
We are interested in learning more about how HER2-positive tumors respond to HER2-targeted therapies. We propose to combine RNA and DNA-based information (molecular subtypes, immune signatures) with clinical information (patient outcomes) from multiple large clinical trials. Each trial included HER2-targeted therapies given before surgery (neoadjuvant) and looked at whether any tumor remained after treatment or not (pathologic complete response; pCR) and whether the cancer returned (event free survival; EFS). During each trial tumor samples were collected before HER2-targeted treatment and at surgery, after the completion of treatment. Each trial has been completed and examined on it's own. However, to examine EFS more patients are needed. By combining multiple clinical trials we will develop ways to identify patients where a more tailored therapy may be possible. For example, this may lead to identifying patients who need more or less aggressive HER2-targeted therapies. We will also be able to examine whether pCR is associated with EFS and if this association is also associated with certain subtypes of HER2-positive tumors. We hope to clarify when and if pCR can be used as a marker for how HER2-targeted therapies work (EFS) in clinical trials. Using pCR may shorten the time to FDA approval. We will also study tumors remaining after HER2 targeted treatment, called residual disease. Patients with residual disease have a worse outcome, so knowing more about how these tumors resisted HER2 targeted therapies, may lead to better options for these patients. The entire project will bring together six clinical trials. This Komen proposal will support the inclusion of PAMELA samples and clinical data into this large analysis. We will collaborate with colleagues at the University of Barcelona to receive and analyze tumor samples from pre-treatment and residual disease and receive clinical information from the PAMELA trial.

The PAMELA trial is a neoadjuvant trial designed to look at dual HER2- targeting in the neoadjuvant setting and to examine markers of response to these drugs. None of these patients received chemotherapy as part of their neoadjuvant treatment.

Understanding the different molecular subtypes of HER2-positive tumors and how they respond to HER2-targeted therapies is important. Identifying patient who are more or less likely to respond to HER2-targeted therapies could lead to less treatment for some, saving cost and side effects. Or leading to longer treatment for others, resulting in improvements in overall survival and longer times without a recurrence.

North Carolina

Defining Inflammation-Mediated Drug Resistance of ER+ Metastatic Breast
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Hector Franco, Ph.D.
Institution: The University of North Carolina at Chapel Hill
North Carolina Triangle to the Coast Affiliate

Snapshot

Hector Franco, Ph.D., will study how inflammation can both drive the spread of breast cancer cells throughout the body and drug resistance in estrogen receptor positive (ER+) breast cancer. His research will help to identify diagnostic markers and treatment targets for drug resistance and metastasis.

Project Summary

Despite the tremendous advances that have been made towards finding a cure for breast cancer and improving the lives of patients, breast cancer remains the second leading cause of cancer mortality in women. This is due mostly to the development of metastasis. Therefore, there is a pressing need to understand what causes metastasis and determine how to stop it.

Our research is focused on estrogen receptor positive (ER+) breast cancer, by far the most frequently occurring type of breast cancer in women. For the majority of ER+ breast cancer patients, endocrine therapy is the first choice for treatment. Despite the therapeutic successes of this class of drugs, most metastatic breast tumors arise from ER+ disease, due to the development of acquired drug resistance.
Recent evidence suggests that inflammation can play a key role in promoting more aggressive breast tumors and resistance to hormone therapies. We and others have uncovered an important mechanism showing that inflammatory molecules, found inside the milieu of some breast tumors, can drastically alter estrogen receptor function leading to the activation of genes that gave rise to more aggressive tumor cells. Based on this data, we will test the hypothesis that inflammatory signaling alters estrogen receptor function leading to resistance to therapy and increased metastasis. Initially, we will profile estrogen receptor function across the genome, in primary tumor samples and matched metastatic samples from the same patient. Then we will use pre-clinical models of human breast tumors to define how inflammatory and estrogen signaling work together to drive metastasis.

The studies outlined in this proposal will accomplish three important goals: (1) increase our knowledge of the drivers of metastatic ER+ tumors, (2) provide a new set of markers with diagnostic and prognostic potential, and (3) provide a new set of therapeutic targets for controlling breast cancer cell growth. This will impact breast cancer patients because it will directly address the paucity of information related to resistance to endocrine therapy and the aberrant functions of ER in metastasis. In addition, adjuvant therapy for ER+ tumors can last five, ten, sometimes many more years. This is a tremendous emotional and financial burden on patients. Thus, defining the ways to overcome endocrine resistance would have a profound impact on mortality and would lead to a reduction in deaths by 2026.

North Carolina

Identification of the Genetic Drivers of HER2-Enriched Subtype Breast Cancers
Research Leadership Grant - Komen Scholar
Principal Investigator: Charles Perou, Ph.D.
Institution: The University of North Carolina at Chapel Hill
North Carolina Triangle to the Coast Affiliate

Snapshot

Komen Scholar Charles Perou, Ph.D., will identify the genetic drivers of the HER2-enriched subtype of HER2+ breast cancer to better understand how this type of breast cancer responds to current therapies, providing new therapeutic targets that could then be tested in a clinical trial.

Abstract

HER2-positive breast cancer is a clinically and molecularly diverse group of breast cancers. Many treatment advances have been made against HER2-overexpressing breast cancers, however, we believe that additional therapeutic advances could be made through an improved understanding of the genetics of this disease subtype. Our past genomic studies on HER2-positive disease have shown that there are three major molecular intrinsic subtypes of tumors present within HER2-positive patients including the HER2-Enriched, Luminal A, and Luminal B subtypes. The HER2-Enriched molecular subtype is the major constituent group within HER2-positive breast cancers, and therefore, we propose here to study this subtype in more detail and to identify the so called "genetic drivers" of this disease subtype. We propose to accomplish this goal through a combined analysis of genetic (DNA), genomic (RNA/gene expression), and computational modeling (Dawn Rank Network Analysis) of two valuable resources; namely a resource that is multiple well-selected Patient Derived Xenograft tumors that will be experimentally manipulated and therapeutically tested, and a resource that is genomic and genetic data coming from two large randomized neoadjuvant trials of HER2-positive and Triple-Negative Breast Cancer patients. We will perform identical computational analyses of these two complementary data resources, identify commonalities across actual patient data and our model systems, and then use the model systems to explore the molecular mechanisms of response and resistance for HER2-Enriched subtype patients. If successful, these studies will identify the molecular drivers of this subtype of breast cancer, and provide personalized drug targets for a new phase of clinical trials.

Ohio

Assess Radiation Response with MRI Guided Preoperative Partial Breast Irradiation in Early Stage Breast Cancer (improving treatment delivery for early stage breast cancer)
Research Leadership Grant - Komen Scholar
Principal Investigator: Julia White, M.D.
Institution: The Ohio State University
Columbus Affiliate

Snapshot

Komen Scholar Julia White, M.D., will study ways to ensure more precise and accurate delivery of radiotherapy to breast tumors to improve therapeutic benefit for patients. She will also evaluate whether a preoperative dose of radiation to the tumor enhances immune response against triple-negative breast cancer (TNBC).

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 enabling technology and clinically test MRI-guided preoperative partial breast irradiation, a novel approach, for early stage breast cancer patients. The technology for deformable image registration between breast MRI and CT to improve treatment delivery accuracy will be developed. 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 (1) will be feasible, (2) will provide improved accuracy in target definition and treatment delivery, thus, improved treatment outcome, and (3) will 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.

Oregon

Mitigating Microenvironment Mediated Resistance in HR+ Breast Cancer (overcoming treatment resistance in hormone receptor-positive breast cancer)
Research Leadership Grant - Komen Scholar
Principal Investigator: Joe Gray, Ph.D.
Institution: Oregon Health & Science University
Oregon and SW Washington Affiliate

Snapshot
Komen Scholar Joe Gray, Ph.D., will improve metastatic hormone receptor positive (HR+) breast cancer treatment by identifying FDA-approved drugs that could improve the effectiveness of immune therapies. This could lead to better therapeutic strategies for these patients by enhancing the immune system's ability to kill the cancer.

Project Summary
Triple-negative breast cancer (TNBC) is a type of breast cancer that lacks expression of hormone receptors, which include the estrogen receptor and the progesterone receptor, and of HER2. Metastatic TNBC, where the cancer has spread to other parts of the body, is highly aggressive and has a shorter average survival compared to patients with other subtypes of metastatic breast cancer. In early-stage or localized TNBC, there are certain clinical features that can help identify patients in whom the cancer is more likely to return, also known as recurrence. However, not all TNBC patients with these features will experience a recurrence. To date, we do not fully understand the mechanisms that drive TNBC to metastasize. Distinguishing between signs of resistance to treatment and drivers of metastasis is key to developing tailored treatments to prevent recurrences and reduce overtreatment for patients for whom additional therapy may be unnecessary.

One method to identify signs of resistance to treatment or drivers of metastasis is to sequence and analyze the DNA of the tumor. New methods of evaluating cancers include sequencing technologies, which provide large amounts of data on tumor DNA. Additionally, current research also suggests that the immune system, the body's natural defense system against disease, also plays a critical role in shaping outcomes for TNBC patients. Combining information about the DNA, RNA and proteins in the tumor and surrounding immune cells will help improve our knowledge of the behavior of TNBC and develop strategies for treatment.

We hypothesize that there are genomic and immune features that result in the development of metastatic TNBC. To test this, we will sequence and evaluate genomic and immune profiles in: 1) patients with metastatic TNBC at diagnosis who have paired breast and metastatic biopsies, and 2) patients with early-stage TNBC at diagnosis, comparing those who do versus do not recur. To identify mechanisms of resistance to treatment in patients with early stage TNBC who receive preoperative chemotherapy, we will compare these profiles before treatment (biopsy at diagnosis), at surgery and at time of recurrence, should that occur.

Altogether, this project will improve our understanding of changes in the biology of TNBC over time, identify factors that drive metastasis in TNBC, and evaluate new targeted therapies based on genomic and immune profiles in high-risk patients, and improve survival in TNBC.

Oregon

Targeting TGFβ to Improve Immunotherapy for Resistant Metastatic Breast Cancer
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Kristina Young, M.D., Ph.D.
Institution: Providence Portland Medical School
Oregon and SW Washington Affiliate

Snapshot

Kristina Young, M.D., Ph.D., will study how to increase the ability of the immune system to fight metastatic breast cancer. To do this, she will study how depleting one protein, TGFbeta, can help the immune system identify and attack breast cancer cells. These studies will help create new treatment strategies for eliminating metastatic breast cancer.

Project Summary

Metastatic breast cancer claims the lives of over 40,000 women each year; half of whom have hormone receptor positive (HR+) disease. While immunotherapy holds much promise for breast cancer patients, it has some limitations that we need to work to overcome. Specifically, HR+ breast cancer typically does not respond to the most common type of immune therapy termed "checkpoint blockade". This lack of response is tied to the activity of a molecule called TGFβ, which can overpower a strong anti-tumor T cell attack of the breast tumor. We found that blocking TGFβ specifically in the anti-tumor T cells can lead to better killing of cancer cells in response to radiation therapy. We hypothesize that TGFβ signaling in CD8 T cells limits anti-tumor immunity in metastatic breast cancer. Therefore, we propose to inhibit TGFβ specifically in the tumor-reactive CD8 T cells, part of the body's immune system. To overcome escape from T cell mediated immunotherapy we plan to radiate tumors which draws T cells into tumors and increases their ability to fight the tumor from an immune perspective.

Our experiments will directly test a personalized immunotherapy approach to treat metastatic breast cancer. This will particularly benefit women at high risk for the development of metastatic disease, whose negative tumor biology is driven by TGFβ signaling. The data generated will inform the design of a Phase 1 Trial of TGFβ-Resistant Adoptive T Cell Therapy + Radiation Therapy (TRACT-RT) for patients with metastatic breast cancer. This trial has the potential to impact the lives of women with metastatic HR+ breast cancer in the next 3-5 years. Our group is ideally positioned to bring this innovative and personalized treatment to women suffering from metastatic breast cancer.

Pennsylvania

Identification of Unique Drivers of ILC Progression (identify treatment targets for invasive lobular breast cancer)

Research Leadership Grant - Komen Scholar
Principal Investigator: Steffi Oesterreich, Ph.D.
Institution: University of Pittsburgh
Greater Pennsylvania Affiliate

Snapshot

Komen Scholar Steffi Oesterreich, Ph.D., will study why patients with invasive lobular carcinoma (ILC) have worse long-term survival compared to patients with invasive ductal carcinoma (IDC). She will study the role of the gene, CASR, and other top candidate genes in ILC preclinical models with the goal of understanding how these genes drive ILC progression, so that better treatments can be developed for patients with ILC.

Abstract

Invasive lobular cancer (ILC) accounts for ~10% of all breast cancer (~30,000 new cases per year). Although ILCs show better prognostic markers than invasive ductal cancer (IDC), patients with ILC show a similar or even worse (long-term) outcome compared to patients with IDC, and thus ILC represents a common disease with limited insight and great unmet clinical need. Our group has focused on developing a better understanding of ILC. Towards this goal, we have generated a number of models that represent aggressive ILC. Through collaborative efforts, we have also established an infrastructure in our clinic that allows collection of metastatic samples from patients with ILC. Over the last funding period of this SGK Leadership grant, we have begun to sequence metastases to the ovaries, and have identified a candidate gene called CASR as being very highly expressed in these metastatic lesions. CASR is mediating the cells' response to calcium and has previously been described to help cancer cells survive and move. We therefore hypothesize that altered expression of genes such as CASR make ILC tumors resistant to therapy, allow the tumor cells to survive, and thus ultimately cause metastatic disease. We also hypothesize that we can identify additional genes and pathways, using our unique model systems, as well as metastatic clinical samples. Specifically, in this proposal, we will study the role of CASR and other top candidate genes in ILC models. We will include studies in invasive ductal cancer (IDC) models for comparison. We will also collect metastatic samples from patients with ILC, focusing on the ovaries, abdomen, and eyes – all sites that are enriched in patients with metastatic ILC, but also bone, given that 95% of ILCs are ER+. We expect that learning about unique metastatic sites will educate us about the biology of ILC. We will utilize state-of-the-art technology to characterize CASR in these metastatic samples, but will also study these samples in an unbiased way in order to identity additional targets that might contribute to poor long-term outcome of some patients with ILC. We expect that completion of the proposed studies will enhance our understanding of how CASR and other genes drive progression in ILC pathogenesis. We will focus on genes for which pharmaceutical companies have already developed drugs, with the hope that some of our studies can be translated into the clinic in the near future. We also expect that some of our findings can be applied to IDC, as well as other cancers, since at least some of the signaling mechanisms might be shared.

Pennsylvania

Targeting Metabolic Vulnerabilities Associated with Metastasis
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Zachary Schug, Ph.D.
Institution: The Wistar Institute
Philadelphia Affiliate

Snapshot
Zachary Schug, Ph.D., will investigate how to block brain metastases by disrupting metabolism. His studies indicate that metastatic breast cancer cells use a different energy source than the original tumor, which can be a drug target for metastases. His goal is to "starve" brain metastases of this energy source.

Project Summary
As breast cancer develops and metastasizes, it undergoes dramatic changes in how it feeds itself. Further, the nutrients the cancer feeds on to grow can vary by the sites where it has spread. For instance, the available nutrients needed for cancer cells to grow in the breast tissue can be dramatically different from the nutrients that are available in metastatic sites like the brain or lungs. When tumors don't have access to their nutrients of choice, they can "starve" and fail to grow. However, cancers can sometimes adapt to "eat" different nutrients and learn to grow again. This is what often happens when breast cancers metastasize to other organs. Consequently, metastatic breast cancers become specifically dependent on the nutrients in their new environment. We believe that these adaptations represent a potential "Achilles heel" and if we can safely and precisely block breast cancers from using these new nutrient sources, we may be able to stop metastatic tumor growth and perhaps even help prevent metastasis from occurring in the first place.

We use pre-clinical models, innovative cell biology techniques, biochemistry, metabolomics (the study of small molecules produced by cells and tissues), and genomics to find new metabolic vulnerabilities in cancer. Our research has already discovered some of these nutrient changes and the enzymes that are involved. These targets are then fed into an active drug development program to create novel therapies for the improved treatment of breast cancer patients. We aim to create drugs that can be safely used to help prevent breast cancer metastasis to other organs and also to kill metastatic breast cancers. Some of the compounds we created have already shown strong effects on tumor growth. Our project will further test these compounds with the goal of eventually using them in clinical trials in the coming years. We believe that targeting cancer metabolism is a highly innovative approach that we hope to exploit in order to reduce metastatic burden in breast cancer patients.

Pennsylvania

Eleventh AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved
Scientific Partnerships and Programs
Principal Investigator: Michael Stewart
American Association for Cancer Research
Philadelphia Affiliate

Snapshot
The American Association for Cancer Research received funding to support the 11th AACR Conference on The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved. This conference brings together physicians, scientists, patient advocates, health care professionals and health care leaders to discuss the latest research aimed at understanding and eliminating the disparities in cancer that represent a major public health challenge in our country.

Pennsylvania

AACR: 2018 San Antonio Breast Cancer Symposium (SABCS) and 2019 Modernizing Population Sciences in the Digital Age Meeting
Scientific Partnerships and Programs
Principal Investigator: Michael Stewart
American Association for Cancer Research
Philadelphia Affiliate

Snapshot
The American Association for Cancer Research received funding to support breast cancer research education sessions at the 2018 San Antonio Breast Cancer Symposium (SABCS) and 2019 Modernizing Population Sciences in the Digital Age Meeting. At SABCS, scientists and clinicians discussed the latest advances in breast cancer research, treatment, prevention and health disparities. The Modernizing Population Sciences in the Digital Age Meeting will train researchers in how "big data" can be used to improve our understanding of cancer at a population-level.

Pennsylvania

AACR: 2019 San Antonio Breast Cancer Symposium (SABCS)
Scientific Partnerships and Programs
Principal Investigator: Michael Stewart
American Association for Cancer Research
Philadelphia Affiliate

Snapshot
The American Association for Cancer Research will receive funding to support breast cancer research education sessions at the 2019 San Antonio Breast Cancer Symposium (SABCS). At SABCS, scientists and clinicians will discuss the latest advances in breast cancer research, treatment, prevention and health disparities and recognize the accomplishments of their peers. Scientific meetings like SABCS stimulate collaborations and partnerships among the leaders of the scientific and patient advocacy communities worldwide.

Tennessee

Triple Negative Breast Cancer: Subtypes, Molecular Targets, And Therapeutic Approaches
Research Leadership Grant - Komen Scholar
Principal Investigator: Jennifer Pietenpol, Ph.D.
Institution: Vanderbilt University Medical Center
Central Tennessee Affiliate

Snapshot
Komen Chief Scientific Advisor Jennifer Pietenpol, Ph.D., will identify therapeutic targets for different types of triple-negative breast cancer (TNBC) by combining genomic data mining and molecular biology. She will also identify genomic markers that can predict sensitivity or resistance to drugs called PI3K inhibitors. Overall, this project should improve the effectiveness of targeted therapies for TNBC.

Abstract
Genomic profiling has identified subtypes of breast cancer including difficult-to-treat cancers classified molecularly as triple-negative breast cancers (TNBC). Long-term follow-up of 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. With Komen funding, Dr. Pietenpol discovered that TNBC can be classified into six subtypes, each with distinct biologically relevant signaling pathways that can be targeted for therapeutic benefit and result in much more individualized, precision care for each TNBC patient. The ultimate outcome of this research is to successfully translate data from the laboratory to the clinic in the form of target-driven clinical trials and discover additional candidate targets as 'leads' for future investigation.

Tennessee

Metastatic Breast Cancer Immunotherapy via Systemic Delivery of STING Agonists
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: John Wilson, Ph.D.
Institution: Vanderbilt University
Central Tennessee Affiliate

Snapshot

John Wilson, Ph.D., will develop a safe and effective immunotherapy for treating metastatic breast cancer. He will test and improve an immunotherapy called STING-activating nanoparticles and combine this new technology with chemotherapy to eliminate breast cancer metastases.

Project Summary

Metastasis is the major barrier to long-term survival for the majority of women with a breast cancer diagnosis, and there is an urgent and unmet need for new therapies that can eliminate metastatic disease. The immune system plays a key role in fighting breast cancer; T cells have the ability find and destroy malignant cells, but tumors are able to disarm them. Checkpoint inhibitors are a type of immunotherapy (drug treatment) that work by reactivating these T cells, allowing them to complete their mission of destroying cancer cells. This therapy is transforming the treatment of a growing number of cancers with some patients exhibiting truly remarkable outcomes and, importantly, longer lasting positive outcomes. However, the vast majority of breast cancer patients do not respond to this type of immunotherapy because their tumors are "cold" in that they lack a sufficient number of T cells.

The goal of this proposal and the PI's research program is to bring immunotherapy to the forefront of breast cancer treatment so that patients with metastatic disease will achieve the unprecedented outcomes that are possible by harnessing the power and specificity of the immune system. Towards this goal, our team has pioneered nanoparticles that have been engineered to dramatically enhance the activity and therapeutic potential of a molecule that activates the STING pathway, which has been shown to play a critical role in the immune system's natural ability to recognize and destroy tumors cells. We will use this new technology to trigger a localized inflammatory response that "reprograms" breast tumors to generate anti-tumor T cells that migrate into metastatic sites and destroy breast cancer cells. We will evaluate both the safety and efficacy of the technology in mouse models of breast cancer as well as evaluate a rationally-designed combination therapy for enhancing response rates to immunotherapy in breast cancer. To ensure the success of the project, we have assembled a multidisciplinary team of Vanderbilt investigators with a common goal of translating the discoveries and technologies resulting from this project to the clinic.

Our work will impact metastatic breast cancer patients in the following ways. First, drugs that activate STING are in clinical trials, but they can only be administered directly into tumors, which is not feasible for the majority of metastatic breast cancer patients. Our technology allows STING activators to be delivered via the blood stream so that they can reach metastatic sites; this has the potential to open this class of drug to many more breast cancer patients. Second, our work will develop new combination therapies with these promising new drugs, with potential to inform new treatment strategies. Finally, we will learn more about how the STING pathway works, and how to design even better drugs to treat breast cancer. Collectively, through both development of new technologies and by answering important questions using breast cancer models, this work will directly contribute to achieving Komen's Bold Goal of reducing breast cancer deaths by 50% by 2026.

Texas

Proteogenomics of Endocrine Therapy Resistance (identify druggable targets in patients with enodocrine therapy resistance)
Research Leadership Grant - Komen Scholar
Principal Investigator: Matthew Ellis, Ph.D., M.B.
Institution: Baylor College of Medicine
Houston Affiliate

Snapshot
Komen Scholar Matthew Ellis, BSc., MB, BChir., Ph.D., will define druggable pathways and molecules in patients with endocrine therapy resistant advanced disease with the goal of generating new treatments for advanced breast cancer and metastasis.

Abstract
Patients succumb to metastatic breast cancer because we do not make an adequately sophisticated diagnosis. Certainly, we describe the disease well at the level of light microscopy, we accurately document the spread of the disease to distant organs with a variety of imaging techniques, but we base our drug decisions on a very small number of factors: estrogen receptor, progesterone receptor and Human Epithelial Growth Factor 2 Receptor (abbreviated to ER, PgR and HER2 respectively). Since we do not cure metastatic breast cancer, this clearly not enough information to advance more effective therapies. When molecular pathways and disease drivers remain undiagnosed, there can be no cure.

It was hoped that sequencing tumor DNA with new efficient techniques would provide an answer to the cure for breast cancer but only a small number of "actionable" mutations have emerged, including our discovery of HER2 mutations and a drug match for PIK3CA mutations. However, the clinical gains for patients from drugging these mutations has been modest. The transformative approach we propose is to analyze proteins in unbiased ways (proteomics) to take us to a new level of understanding of the disease processes that underlie lethal breast cancer. By analogy, if DNA is the computer hard drive of the cell, RNA the program that translates the DNA code to the movie, the proteins form the "computer screen" so the movie is visible. If we can't turn the protein-based computer screen "on", we can't possibly hope to understand the biological process activated by complex changes in the DNA that underlie the development of breast cancer.

We thus propose to transform our diagnostic approach with an unbiased and deep-scale analysis of all the proteins in the cell (proteomics). Almost all of the new drugs recently approved or in clinical trial target proteins and therefore a proteomics approach is a much more direct and theoretically more accurate assessment of the therapeutic vulnerabilities of cancer. Mass spectrometric proteomics is unbiased sequencing technique like DNA and RNA sequencing that provides information on over 10,000 proteins per tumor sample, a serious technical advance since we currently base treatment decisions on only three proteins. We also measure how active these proteins are by annotating a process called phosphorylation which modifies protein function. The proteomic information is organized by computational biologists who use bioinformatic tools and cloud computing to integrate the information from DNA, RNA and peptide sequencing into the pathways and driving biological processes active in an individual cancer.

As proof of principle, our proposal is to conduct a deep-scale proteogenomic analysis of 14 estrogen receptor positive breast cancers grown directly from patients in mice. After proteogenomic analysis has been completed we will test therapeutic hypotheses generated from the proteogenomics data to

demonstrate the potential of this approach when treating advanced breast cancer. By improving our approach to precision medicine this project will contribute to a reduction in breast cancer mortality by providing a new platform on which to base our next generation of new cancer treatments.

Texas

Targeting Hormone-Receptor Positive Metastatic Breast Cancer Through T cell Immunotherapy
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Valentina Hoyos Velez, M.D.
Institution: Baylor College of Medicine
Houston Affiliate

Snapshot
Valentina Hoyos Velez, M.D., will study how to teach T-cells, a component of the immune system, to target and kill breast cancer metastases with a specific estrogen receptor (ER) mutation. Her work aims to create a new immunotherapy option for metastatic breast cancer patients.

Project Summary
Hormone receptor-positive metastatic breast cancer (HR+MBC) is the most common type of MBC and accounts for most of the breast cancer deaths. Hormone therapy (HT) is the main treatment for this disease. Even though most patients benefit from HT, the cancer eventually stops responding to the treatment and progression of the disease occurs. Research has shown that one of the main reasons the cancer becomes resistant to HT is the development of new mutations of the estrogen receptor (ER). These ER mutations are found in 11-55% of HR+MBC patients who have been treated with HT and are associated with a poor prognosis and decreased survival.

Clinical trials have shown promising results using immunotherapies for the treatment of multiple cancers, including breast cancer. They work by stimulating the patient's own immune system. Our immune system is a collection of special cells that help protect us from things that are foreign to our bodies like virus, bacteria or cancer cells and they travel throughout our body in our blood. One of the most important immune cells are T cells. This project will take advantage of ER mutations, which result in unique versions of the ER present only in the tumor cells, transforming them into ideal targets for T cell attack.

We plan to take patient's own T cells through a simple blood draw and train them in the laboratory to recognize and attack the mutated ER found in the patient's cancer cells. Our group has vast experience generating such T cell therapies for various types of cancers. Results of the clinical trials so far show that these cells can have potent anti-tumor effects when the T cells are given back to the patient through an intravenous injection. These T cells will specifically kill only cells that have the ER mutations and not normal cells. Therefore, there are much fewer side effects associated with this treatment compared to chemotherapies. Based on previous research using immunotherapies, we know that when successful, the results are long lasting for patients and even curative. We have been able to translate our research into clinical trials, making T cell therapies available to patients in a short period of time with approximately 5 years from bench to bedside. With the recent FDA approval of T cell therapies for several cancers, we are confident that the proposed approach has the potential to reduce the number of breast cancer deaths in the near future.

Texas

Engaging the Immune System to Improve Metastatic Breast Cancer Treatment
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Wen Jiang, M.D., Ph.D.
Institution: The University of Texas Southwestern Medical Center
Dallas County Affiliate

Snapshot
Wen Jiang, M.D., Ph.D., will determine the most effective way to use a nanoparticle "engager" molecule to stimulate the immune system to identify and attack cancer cells. This nanoparticle tool will improve the effectiveness of immunotherapy for metastatic breast cancer patients.

Project Summary
Approximately 250,000 new breast cancer diagnoses are made each year, and in 10% of these patients, the cancer has spread, or metastasized, to other organs (stage IV breast cancer). Unlike early-stage breast cancers, metastatic breast cancer carries a dismal prognosis, with a 5-year survival rate of only 20%. Metastatic breast cancer is also more likely to be resistant to treatment, as over 70% of patients with metastatic diseases eventually become resistant to treatments. Therefore, identifying new and effective treatments for highly aggressive metastatic breast cancers is an urgent and yet unmet need.

Recently, there have been successes in using immunotherapy, or using the body's natural defense system, to treat drug-resistant metastatic melanoma, lung cancer, and renal cell carcinoma. These advances have provided new hope for breast cancer patients. By harnessing the power of the body's immune system, we can potentially eradicate some of the most aggressive cancers, including metastatic breast cancer. Applying this principle, our group recently found a strategy to educate the body's natural immune system to recognize breast cancers by targeting specific markers on tumor and immune cells. This process acts as a way to stimulate the immune system to target and kill tumor cells. Our current proposal aims to translate this novel treatment strategy into a new class of cancer immunotherapy by developing a system that can help guide a certain class of immune cells called phagocytes in the body to recognize and destroy breast cancer cells within the body, thus potentially providing a cure for this deadly disease.

Since 20% of breast cancers produce too much HER2, our current study will test this hypothesis by first designing a therapeutic compound in which phagocytes recognize the HER2 receptor. We will evaluate the responses from the immune cells and examine the antitumor effect this treatment against metastatic HER2+ breast cancers. Our goal here is to further expand the use of cancer immunotherapy in metastatic breast cancer using a first-in-class immunotherapeutic that harnesses the power of the body's own immune system to eliminate metastatic breast cancers. The completion of the current phase of study will enable rapid translation of our platform into clinical trials, which will allow us to accomplish the ultimate goal of reducing breast cancer mortality by 50% by 2026.

Texas

Targeting Epigenetics to Treat Endocrine-resistant Metastatic Breast Cancer
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Kexin Xu, Ph.D.
Institution: University of Texas Health Science Center at San Antonio
San Antonio Affiliate

Snapshot
Kexin Xu, Ph.D., will study how to reverse changes to DNA that can lead to hormonal therapy resistance. She will study how one DNA modification molecule, EZH2, can be targeted to help patients with drug-resistant metastatic breast cancer respond to hormonal therapy, thereby improving patient survival.

Project Summary
70-80% of all breast cancers express the estrogen receptor a (ERa), a receptor that is activated by the hormone estrogen. Active ERa is known to fuel uncontrolled growth of breast cancer cells. Endocrine therapies, such as tamoxifen and aromatase inhibitors (AI), shut off ERa signaling, and therefore have become the standard treatment for ERa-positive (ERa+) breast cancer. Unfortunately, 30-40% of patients with localized early-stage breast tumors and nearly all patients with metastatic breast cancer eventually become resistant to endocrine therapies. Thus, it is urgent to understand the reasons for acquired resistance and to develop new therapeutic approaches to restore sensitivity to endocrine therapy for patients with metastatic breast cancer. These new treatment options could effectively eradicate metastatic, treatment-resistant breast cancer and improve the overall survival rates for breast cancer patients.

Epigenetics, modifications to DNA without changing DNA sequence, is a common way that cancer cells hijack normal cell functions to develop malignant behaviors. Alterations in epigenetics cause cancer without changing DNA codes. Thus, unlike genetic mutations, epigenetic changes in cancer cells can be pharmacologically reversed to their normal state. This makes the idea of epigenetic therapy in cancer very promising. A major form of epigenetic modifications is DNA methylation. Global or widespread alterations of DNA methylation have been repeatedly observed in metastatic endocrine therapy-resistant breast cancer. Our preliminary studies have pinpointed several methylated DNA sites that can create tamoxifen-resistant phenotype. In addition, we found an epigenetic regulator called EZH2, which changes methylation intensity at specific regions and contributes to the development of endocrine therapy resistance. Most importantly, we demonstrated that EZH2 is a very promising therapeutic target in ERα+ metastatic breast cancer that becomes resistant to hormone therapy. Small-molecule inhibitors of EZH2, which show encouraging results in clinical trials, significantly blocked the growth of endocrine resistant tumors in mice. Therefore, in this project we will screen for the DNA methylation sites that cause endocrine resistance and investigate how EZH2 regulates this epigenetic program. Our ultimate goals are to determine the therapeutic potentials of EZH2-targeting drugs in the treatment of metastatic endocrine resistant breast cancer and to identify an epigenetic biomarker for identifying patients who are most likely to benefit from this epigenetic therapy. Considering the promising progress of EZH2 inhibitors in clinical studies, findings from our work can be easily and instantly tailored to the development of a targeted therapy that will particularly benefit breast cancer patients with metastatic, endocrine-resistant tumors.

Texas

Conquer Metastatic Breast Cancer by Novel Network-Decoded Drug Combinations
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Song Yi, Ph.D.
Institution: The University of Texas at Austin
Greater Central and East Texas Affiliate

Snapshot
Song Yi, Ph.D., will sequence DNA to identify new treatment combinations for metastatic triple-negative breast cancer (TNBC). Drugs called PARP inhibitors are one of the few targeted treatment options for TNBC patients, but many patients become resistant to these drugs. This project aims to identify a new way to combine treatments to prevent PARP inhibitor resistance.

Project Summary
There are several different types of breast cancer which can have varying levels of aggressiveness. The breast cancer subtype known as triple-negative breast cancer (TNBC) is a very severe cancer that is likely to spread throughout the body. This is, in part, because TNBC tumors are difficult to treat with targeted therapies. PARP inhibitors have emerged as a possible therapeutic option for these patients. However, not all TNBC patients respond equally to PARP inhibitors, and often the cancer will become drug resistant after a short time. Systematic methods to identify factors that predispose a patient to respond effectively to a drug could help reduce breast cancer deaths.

The complexity of drug response and resistance stems, at least in part, from the fact that different patients often carry genetic mutations ('escape routes'), which can lead to different drug responses. In breast cancer, proteins within a cell interact, or "signal," with each other in complex interaction networks. We hypothesize that mutations in cancer play important roles in altering signaling networks, and that these signaling networks that are critical for normal responses to drug treatment. In this project, we will use an integrative approach to evaluate the functional outcome of specific mutations in TNBC cells. We will also use a combination of experimental and computational approaches to unravel important functional network miscommunications responsible for drug resistance. Excitingly, our established data science framework identified novel candidates for potential combination therapy with PARP inhibitors. Together, this project will provide information on how to prioritize cancer-causing mutations and uncover patient-specific signaling mechanisms. This is a critical step towards personalized precision medicine in TNBC therapy. Furthermore, this work will identify novel drug combinations for TNBC, which stand to not only find their potential cures, but also save more patient lives.

Utah

Targeting the Cripto Pathway and Cellular Plasticity to Treat Metastatic Breast Cancer
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Benjamin Spike, Ph.D.
Institution: University of Utah
Utah Field Office

Snapshot
Benjamin Spike, Ph.D., will study the ability to block a small protein, Cripto, which is often increased in breast cancer and linked to metastasis. Studies from the Spike lab indicate that Cripto blocks normal cell function and helps cells evade treatment. His research aims to create Cripto-directed therapies to prevent breast cancer progression and metastasis.

Project Summary
Within an individual cancer, the cancerous cells may be quite different from one another based on various changes to their DNA or methods that control repair or routine maintenance. Some cells may acquire more changes over time, or the changes acquired may be different based on the type of stress the cells were exposed to in the body i.e. lack of nutrients from unorganized tumor growth, immune system attack on cancer cells, or even stresses associated with partially effective clinical therapies. The ability of cells to flexibly adapt to these types of stress can be referred to as a type of cellular plasticity. This plasticity represents one of the most challenging aspects of cancer treatment. Some treatments are very effective against most cancer cells in a patient's tumor, but some individual cells with cellular plasticity may withstand the treatment or and begin to regrow to form new tumors or spread to new sites in the body. Our prior studies suggest that blocking a protein called Cripto could prevent tumor cells from adapting, surviving and growing when they are under various stresses that they encounter in patients. This Komen funded project will allow for determination of which breast cancer cells need Cripto under stress to grow, and will also identify what other factors they need. With this information, we can target them directly and prevent tumor cell survival and adaptation to stress even when such cells are rare.

Using tissue donated by breast cancer patients, we can grow multi-cellular structures in the lab that resemble the tumors in a patient using specialized 3D environments. We can then use these structures to understand how Cripto is active under stressful conditions and how it can be targeted as a treatment. Additionally, since breast cancer cells vary from person to person, we will determine if Cripto is important only for certain breast cancer subtypes or if it is important in all different types from the diversity of the breast cancer patients that donated tissue for the studies.

Because many stages of breast cancer including initiation, drug resistance, recurrence and metastasis likely require cell plasticity, our studies into its underlying mechanisms have the potential to significantly contribute to Komen's bold goal of reducing breast cancer lethality by 50% or more by 2026. If we can identify existing treatments that elicit a Cripto response in breast cancers that is required for cell spreading dissemination, growth or survival at distant sites throughout the body, we should be able to combine Cripto blocking strategies with these treatments to more effectively destroy cancer cells.

Utah

Augmenting (improving) Effects of Immunotherapy for Metastatic Breast Cancer
Research Leadership Grant - Komen Scholar
Principal Investigator: Alana Welm, Ph.D.
Institution: University of Utah
Utah Field Office

Snapshot

Komen Scholar Alana Welm, Ph.D., will determine how a protein called RON contributes to metastatic breast cancer (MBC) and to identify new approaches to improve immunotherapy response by blocking RON in MBC. The preclinical experiments proposed in this project should pave the way for a future clinical trial for MBC patients.

Abstract

Even before diagnosis of a primary tumor, breast cancer cells can disseminate to distant organs, where they may remain in a dormant and clinically undetectable state for many years. Eventual growth of these disseminated cells into a metastatic recurrence, typically in bone, liver, lung or brain, occurs in 20-30% of patients. Metastatic disease accounts for an overwhelming proportion of breast cancer mortality because, unfortunately, metastatic breast cancer is not curable. The mechanisms of metastatic recurrence are poorly understood, but almost certainly require tumor cells to adapt to and modify their new environment, and to evade the body's immune system. Using mouse models, we have identified a protein, Ron kinase, which supports the growth of breast cancer cells at metastatic sites. Although Ron acts on the tumor cells themselves, we found that this protein also plays a very critical role in influencing the surrounding immune cells. Our published work has shown that Ron suppresses immune reactions to tumors, which allows metastases to grow. Inhibition of Ron using a new drug was able to reduce metastasis in mice. Combination of the Ron inhibitor with approved immunotherapy drugs showed even more remarkable effects in these animals, with complete tumor clearance in some mice. A major goal of this proposal is to test a new, clinically-available Ron inhibitor in combination with FDA-approved immunotherapies to shrink metastatic tumors. Additionally, we will determine how Ron regulates immune responses to tumors in order to elucidate the best strategies for therapy. Although the proposed work will be done in mice, we are conducting a parallel clinical trial in metastatic breast cancer patients to test safety of the Ron inhibitor, merestinib, in combination with common breast cancer therapies. Taken together, the human clinical trial safety data and the mouse immune modulation experiments should pave the way for a future clinical trial in metastatic breast cancer patients in combination with immunotherapy.

Virginia

Targeting Pathways Activated in Metastatic Breast Cancer
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Joshua Harrell, Ph.D.
Institution: Virginia Commonwealth University
Central Virginia Affiliate

Snapshot

Joshua Harrell, Ph.D., will use triple negative breast cancer (TNBC) patient-derived models from the NCI-MATCH clinical trial to find new combinations of drugs to prevent treatment resistance and metastasis. He will study different combinations of FDA-approved drugs for their ability to kill breast cancer cells and stop breast cancer recurrence and metastasis.

Project Summary

There are many different types of breast cancer. One type is known as triple-negative breast cancer (TNBC). It is very aggressive, and often before the breast tumor is removed the cancer cells spread to and grow as metastases within vital organs. There are currently very few drugs that effectively inhibit the growth of TNBC metastases, and our studies seek to identify new combination therapies that may be effective treatments for TNBC. By specifically testing a unique set of metastasis models, we are seeking to provide new treatment options for current patients with advanced disease.

A few years ago the National Cancer Institute started the MATCH clinical trial. This study uses genetic testing of tumors to identify changes to DNA (mutations) that may be effectively treated with specific drugs; according to the DNA test, the patients are then treated with a specific drug that targets those mutated cells. Unfortunately, it is rare that one drug will work long-term to prevent the cancer from growing. This research project seeks to identify secondary drugs or combinations of treatments that can be provided to the patient in addition to the NCI-MATCH assigned drug for effective treatment of metastatic breast cancer.

In order to identify new effective combinations of medications we are using model systems known as patient-derived xenografts (PDXs). These are tumors that were isolated from patients and used as models for research. In these studies, we will first assess 50 genes that are commonly mutated in a variety of cancers and segregate each PDX into NCI-MATCH defined treatment groups. The PDXs will be prepared and treated with the NCI-MATCH assigned drug individually, and then combined with one of more than 1,000 FDA-approved drugs. The three best identified drug combinations that are the most effective at killing the PDX cells will then be tested on PDX tumors in other preclinical models. The drug combinations that are most effective will then be tested on established metastases, including metastases that have become not responsive to chemotherapeutic treatments in patients through clinical trials.

Recent studies within my laboratory have focused on the identification of new drug combinations for breast cancer, and in parallel, learning how metastases differ compared to primary breast tumors. In these studies, we seek to combine these insights and provide new rational treatment options that can be tested in clinical trials of metastatic breast cancer patients starting in 2022. With this focus, we are striving to help reach Komen's Bold Goal of reducing breast cancer deaths in the U.S by at least 50% by 2026.

Washington, DC

Graduate Training in Breast Cancer Disparities at Lombardi Cancer Center
Graduate Training in Disparities Research
Principal Investigator: Lucile Adams-Campbell, Ph.D.
Institution: Georgetown University
National Capital Field Office

Snapshot
Lucile Adams-Campbell, Ph.D., will train the next generation of early career breast cancer investigators. Trainees will study ways to help reduce disparities in underserved and minority breast cancer survivors.

Project Summary
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 and 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 classroom training, 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.

International - Australia

Tackling Breast Cancer Heterogeneity for the Complete Eradiation of Metastases
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Delphine Merino, Ph.D.
Institution: La Trobe University, Olivia Newton Cancer Center

Snapshot
Delphine Merino, Ph.D., will use cutting-edge technology to identify genes that help breast cancer cells spread to distant organs (metastasize) and become resistant to standard treatments. She will determine if the metastatic breast cancer cells have common genetic features that can be used to design new treatments. The goal of her research is to find the "Achilles heel" of metastatic breast cancer so this devastating disease can be better treated and eliminated.

Abstract
Breast cancer is still a leading cause of cancer deaths among women due to two reasons: 1) tumors have spread to distant organs as metastases, or 2) these tumors are resistant to standard therapies. To prevent metastasis recurrence and improve treatment outcomes, there is a need for comprehensive studies that identify, track and analyze the tumor cells responsible for disease recurrence (e.g. tumor spreading and resistance to current treatments).

My research proposal aims to understand the genetic properties of the cells which are responsible for metastases and drug resistance. This will be achieved by using innovative cellular barcoding technologies to label ('barcode') thousands of individual cancer cells from patient biopsies, prior to transplantation into mice. The fate of these labelled tumor cells will be investigated in different organs over time, in the presence and absence of different therapies. This model will be analyzed using cutting-edge microscopy and gene sequencing to afford important insights into the characteristics of metastases. The data generated in this proposal will be analyzed using new computational models that enable predictions of drug sensitivity and may help design new combinational therapies to improve breast cancer outcomes.
This will lead to a reduction in breast cancer deaths in 3 ways:

1- Identifying networks of genes that can rationally be targeted for the prevention and treatment of metastases. Our preliminary results indicate that a new class of drugs, the 'BH3-mimitics', may have a therapeutic benefit for patients with metastatic triple negative breast cancer. This drug may be effective in the treatment of brain and bone metastases, which are associated with poor outcome and decreased quality of life. If our results are promising, this drug will be tested in clinical trials.
2- Characterizing the biological properties of cells that are responsible for resistance to chemotherapy; therefore, an accurate assessment of the diversity of metastatic tumor cells will allow the design of new combinational therapies for the treatment of patient with recurrent disease.
3- Because of the differences between metastatic tumor cells, it is unclear how well a given tissue sample represents the patient's disease for diagnostic, monitoring, and treatment purposes. This project will help optimize the use of tumor and blood biopsies for patients with breast cancer, an essential step towards personalized medicine.

My team will use samples from patients who are generously donating samples, when treated in our center or during the BROCADE rapid autopsy program. My skills in translational research and my established collaborative links with the pharmaceutical industry have me poised to further improve the health of patients with advanced disease and therefore reduce deaths from breast cancer.

International - Canada

Novel Treatment and Prognostic Methods to Eliminate Metastatic Breast Cancer
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Karla Williams, Ph.D.
Institution: University of British Columbia

Snapshot

Karla Williams, Ph.D., will investigate how breast cancer cells spread (metastasize) throughout the body. Her studies will lead to better ways to detect metastasis early and provide drug targets for the treatment of metastatic breast cancer.

Project summary

The main cause of breast cancer patient related death is metastasis. Metastasis is the spread of cancer cells from a primary tumor site to other areas in the body causing organ damage from the growing metastases. While our understanding of metastasis has improved significantly over the past few decades, we are still unable to accurately identify patients who are at risk for developing metastatic disease and when these metastatic tumors appear treatment options are very limited.

We have identified small feet-like structures, called invadopodia, in breast cancer cells and think that these structures help the cancer cells move throughout the body. We also think that these 'feet' may initiate or support the growth of breast cancer cells at distant sites, possibly even waking up sleeping cells (dormant breast cancer cells) 5-10 years after treatment. As these 'feet-like' structures likely function at specific steps in the metastatic process it will be important to understand their biology. By understanding their biology and the proteins used in their formation we can develop and test drugs that target them and stop them from forming. Our goal is to determine where and how they function and then by stopping their formation we will be able to figure out when targeting them would benefit a patient. We have identified a few proteins that we think are important for the function of these 'feet' and some of these already have FDA-approved inhibitor. If proven successful, this could translate rapidly into clinical therapies for breast cancer patients since the inhibitors are already FDA-approved.

We have also discovered an abnormal sugar in breast cancer patient tumors and on small tumor cell fragments in patient blood. High levels of this sugar seem to increase the risk of breast cancer metastasis. We are working towards the development of a blood and tissue-based test to identify patients likely to develop metastatic disease. We aim to validate our test to show that high levels of this sugar can tell if someone is at high risk for developing metastatic disease. By doing this, high risk patients could be offered treatments to reduce their risk of developing metastatic disease.

Our research will not stop the genesis of breast cancer, but it will make powerful strides towards ending metastasis, the most significant cause of breast cancer-related death.

International - France

Uncovering International Disparities in Metastatic Breast Cancer Outcomes
Career Catalyst Research Grant: Conquering Metastasis
Principal Investigator: Melina Arnold, Ph.D.
Institution: International Agency for Research on Cancer

Snapshot

Melina Arnold, Ph.D., will conduct the first international study to determine how many people have (prevalence) new and recurrent metastatic breast cancer (MBC) among high-income countries, such as the U.S. and Norway. She will compare the prevalence and survival outcomes of MBC in these places, and identify factors that contribute to differences in MBC outcomes. This work will find opportunities to improve both monitoring and treatment of MBC to eliminate avoidable deaths from this disease.

Project Summary

A diagnosis of metastatic breast cancer, i.e. when cancer cells compromise organs and bones, can be devastating. For many women this may come after a long journey of being diagnosed and treated for early breast cancer and the belief that they were cured. Others might be found to have metastatic breast cancer at their first diagnosis of breast cancer. This latter group is referred to as women with 'de novo' metastatic breast cancer. Yet, it is more common for metastatic breast cancer to occur months or sometimes several years after completion of treatment for early, non-metastatic, breast cancer. This is also called recurrent metastatic breast cancer. While the number of women diagnosed with 'de novo' metastatic breast cancer is known and routinely registered in cancer registries that cover a certain area and population, the number of women that experience recurrent metastatic breast cancer is unknown as no routine statistics exist.

The aim of this project is to collect data on how many women get diagnosed and live with metastatic breast cancer in the U.S. and four other high-income countries. This will include women both with 'de novo' and recurrent metastatic breast cancer. Furthermore, their survival experience will be assessed and compared across countries. Knowing the burden and survival experience of women with metastatic breast cancer is important for several reasons. It can help doctors improve the clinical guidance for women with metastatic breast cancer and extend lives through more personalized treatment and better use of clinical information after diagnosis. It can also give a better idea of how women with early-stage breast cancer should be followed in order to decrease their chance of developing metastatic breast cancer. And finally, looking at this from an international perspective can help identifying room for improvement and how countries can learn from each other. Filling this critical data gap is thus vital for future research on metastatic breast cancer and the lives of many women as it has the potential to reduce the number of breast cancer deaths in the future.

International - France

African Breast Cancer Disparities in Outcomes @ 3 Years
Global Research Grant
Principal Investigator: Valerie McCormack, Ph.D.
Institution: International Agency for Research on Cancer

Snapshot
The International Agency for Research on Cancer (IARC) will continue the African Breast Cancer-Disparities in Outcomes (ABC-DO) study in South Africa, Namibia, Uganda, Nigeria and Zambia. This is the first international study of African breast cancer patients to examine the factors that contribute to poor survival to improve breast cancer outcomes.

Abstract
Low breast cancer survival rates in many sub-Saharan Africa (SSA) countries reflect, at a macro-level, disadvantaged populations with poor access to healthcare systems not well adapted to the specialized services necessary for cancer diagnosis and treatment. Although this picture is seemingly discouraging, ABC-DO has identified modifiable factors meaning that interventions can be made to substantially improve survival and prevent breast cancer deaths in these resource-limited settings. For example: (i) The ABC-DO cohort found that greater breast cancer awareness is a stronger independent predictor of early presentation than socioeconomic position, revealing that BC awareness campaigns alone can contribute to down-staging. (ii) Some patients do not return for their histology results and never commence treatment: Zambian local investigator Dr. Parham is piloting a feasibility study of a one stop diagnostic process with fine-needle aspiration cytology to tackle this problem in Zambia 23. (iii) Introduction of an efficient routine receptor determination is needed as few patients can afford to get this done privately and treatment proceeds in the absence of this knowledge. (iv) Examination of treatments received show inefficient resource allocation: stage II patients not receiving therapies that are instead provided to poor prognosis stage IV patients24. (v) Knowledge of the extent and reasons for treatment non-adherence - due to cost, preference of traditional healers, severe side-effects in the HIV+ patient, patient's choice (e.g. thinking they are already cured), will inform patient profile-specific interventions to be implemented such as education, reminders and active support from navigators throughout the BC treatment journey to reduce drop-out; improve treatment completion through cancer association supported transport and accommodation during hospital stays; and alerting the clinical care team to more efficient treatment allocation. Regular contact using mHealth, which has been shown to work well in the core ABC-DO study, can equally be successfully implemented to evaluate future interventions.

The ABC-DO-Plus survivorship research will provide the first comprehensive assessment of the long-term health care, psychosocial and support needs of breast cancer survivors in SSA, and its findings will inform policy guidelines on how to identify at risk patients, and will help to implement strategies on how best to ensure their timely access to relevant services (e.g. palliative care, breast reconstruction, mental health care). Such care improved for HIV patients in SSA, indicating that care improvement for cancer survivors are also a realistic target.

International - Italy

Advanced breast Cancer Fifth ESO-ESMO International Consensus Conference
Scientific Partnerships and Programs
Principal Investigator: Alberto Costa
The European School of Oncology will
Susan G. Komen Italia

Snapshot
The European School of Oncology will receive funding to support the Advanced Breast Cancer 5th European School of Oncology and European Society of Medical Oncology (ESO-ESMO) International Consensus Conference (ABC5). The ABC meetings bring together health professionals and patient advocates from around the world. The goal of this conference is to develop international consensus guidelines for the management of advanced breast cancer and identify research priorities to improve care and outcomes for people living with advanced breast cancer.

International – South Africa

Cancer in Africa: innovation, strategies, implementation
Global Research Grant
Principal Investigator: Belmira Rodrigues
Institution: African Organization for Research and training in Cancer

Snapshot
The African Organization for Research Training in Cancer (AORTIC) will receive funding to host the 12th International Conference on Cancer in Africa. The conference attracts more than 1,000 experts from around the world to discuss innovations, strategies and implementation plans for cancer control in Africa. This meeting is a unique opportunity to promote global collaborations and share knowledge to improve cancer outcomes in Africa.