



**Carlos Arteaga, M.D.**

**Discovery of Mechanisms of Resistance of Antiestrogen Therapy in ER+ Breast Cancer**

### **Snapshot**

Komen Scientific Advisory Board Member Carlos L. Arteaga, M.D., from University of Texas Southwestern Medical Center, will continue to investigate how ER+ breast cancers develop resistance to current antiestrogen therapies, like tamoxifen. Dr. Arteaga's work will allow doctors to offer patients a more precise treatment plan, which could include a combination of therapies, to stop drug-resistant breast cancer from developing or returning.

### **Investigator-Submitted Abstract**

In this application, we propose a comprehensive profiling using molecular biology approaches applied to operable ER-positive tumors whose proliferation remains high after antiestrogen therapy. This unbiased approach allows us to directly test the effect of therapy in patients and then focus on drug-resistant tumors where it is more likely novel mechanisms of drug resistance can be discovered. Knowledge of mechanisms of resistance to antiestrogens will inform clinical investigators and practicing oncologists about other agents to combine with the current treatment standards in an effort to improve the long-term outcome of patients with ER-positive breast cancer. In addition, we propose a comprehensive analysis of the role of the fibroblast growth factor receptor (FGFR) in endocrine resistance that should provide a basis for trials of FGFR antagonists, currently in early clinical development, in combination with antiestrogens in patients with ER+ breast cancer whose tumors also exhibit markers of FGFR dependence.



**Alan Ashworth, Ph.D.**

**Identification and Dissection of Breast Cancer Genetic Dependencies**

**Snapshot**

Komen Scholar Alan Ashworth, Ph.D., from University of California, San Francisco, will expand his genomics research to identify new breast cancer biomarkers and develop drugs that target these new biomarkers. This could provide better treatment options and improve outcomes for both women and men facing breast cancer.

**Investigator-Submitted Abstract**

One of the main issues for breast cancer patients and their physicians is the selection of the best treatment. For a significant number of patients, effective treatments already exist. However, for others the number and effectiveness of different treatment options is still limited. To address this, we propose to initiate a project aimed at identifying new ways to treat the disease. Specifically, we aim to identify those genes and proteins that when targeted with drugs result in the death of breast tumor cells. To do this, we will first identify sets of genes using a process known as functional genomics that exploits many of the tumor cell models that exist for breast cancer. As well as identifying the key proteins to target, we also aim to understand exactly which patients to use these potential new treatments in. This biomarker identification will maximize the potential for ensuring the right patient gets the best treatment and that overall, the outcome for the patient is better.



**Justin Balko, Ph.D., Pharm.D.**

**Breast Tumor MHC-II Expression Guides Breast Cancer Response to Immunotherapy**

**Snapshot**

Justin Balko, Ph.D., PharmD, from Vanderbilt University Medical Center, will determine ways to improve treatment response to anti-PD-1, an immunotherapy drug that boosts the immune response against cancer. Preliminary findings show that patients that have high levels of a protein called MHC-II respond well to anti-PD-1, whereas patients with low MHC-II levels do not. This work should help identify which patients are likely to benefit from anti-PD-1 and should help ensure patients that will benefit the most receive the treatment.

**Investigator-Submitted Abstract**

New therapies that target the immune system to cancer are changing the way we treat patients in many tumor types. However, only a small portion of patients with breast cancer have benefited from single-agent PD-1-targeting immunotherapy in early clinical trials. It is currently unclear why only a small percentage achieve responses. However, recent studies performed in our laboratory in breast cancer have identified a role for a marker called 'major histocompatibility complex-class II (MHC-II)' expression as being important for responses to immunotherapy. In melanoma, where many patients have now been treated with immunotherapy, we discovered that MHC-II-positive (+) tumors respond more frequently to PD-1-targeted immunotherapy and for a significantly longer duration than MHC-II-negative (-) tumors. Our preliminary data suggest that MHC-II expression on breast tumors directly influences how the immune system sees the tumor, and often makes the tumor utilize specific pathways to avoid being destroyed by immune cells.

Interestingly, our data suggest that one of the ways tumors avoid the immune system in this context is by upregulating a protein, called LAG3, on the surface of immune cells. LAG3 binds to MHC-II on the tumor cells and silences the activity of the immune cell. This causes the immune system to be suppressed and allows the tumor to continue to grow and metastasize unchecked.

However, there are currently new 'second-generation' immune therapies that target LAG3 being tested in clinical trials. In this proposal, we want to see if the combination of first generation (anti-PD-1) and second-generation (anti-LAG3) antibodies work best in MHC-II+ breast tumors. We also want to do laboratory studies to understand exactly why MHC-II+ tumors are more immunogenic and how they cause immune cells to express more LAG3. Finally, we want to leverage two new exciting clinical trials being initiated at our institution to determine whether MHC-II is a good biomarker for immunotherapy combinations in ER+ and triple-negative breast cancer. Overall, the work proposed in this grant will help us understand basic biology of MHC-II+ breast cancers, how to target the immune system directly at these tumors, and whether MHC-II is a good biomarker for patient selection for LAG3 and PD-1 antibody combinations. Our research group has an outstanding history of translating our laboratory findings to clinical trials, evidenced by the 2 trials referenced above, and we ultimately hope to translate the findings from this proposal to a clinical trial in breast cancer.



**Regina Barzilay, Ph.D.**

**Predicting Disease Progression from Imaging Data**

**Snapshot**

Regina Barzilay, Ph.D., from the Massachusetts Institute of Technology, will develop software that will predict breast cancer disease progression from imaging data. Dr. Barzilay will apply automated “deep learning” models to mammograms and associated clinical data to discover signs of early disease progression not visible to the human eye and identify those patients at higher risk for recurrence.

**Investigator-Submitted Abstract**

Our current ability to predict which breast cancer patients are likely to get recurrence is limited. In practical terms, it means that some patients are over-treated, while others are not getting personalized treatment they need. We proposed to augment existing disease progression approaches with deep learning models that utilize raw imaging data, in addition to traditional risk variables. There is substantial evidence in medical literature that indicates that mammograms contain multiple cues about cancer characteristics and its future progression. However, many of these visual characteristics are too subtle for human eye to capture, and as a result, these important cues are not utilized in the current progression model. Our hypothesis is that by utilizing this rich information in a powerful deep learning models, we can make more precise predictions about expected outcomes. Using past patient data, we will train and test these models in predicting recurrences and their type (local vs. non-local ones). All the code developed as part of this project will be publicly available.



**Paula Bos, Ph.D.**

**Harnessing Regulatory T Cell-Dependent Mechanisms for Brain Metastasis Therapy**

**Snapshot**

Paula Bos, Ph.D., from Virginia Commonwealth University, will investigate how a type of immune cell called regulatory T (Treg) cells support the growth of breast cancer cells that have spread (metastasized) to the brain. The goal of this work is to determine if targeting Treg cells can be used to treat patients with metastatic breast cancer in the brain.

**Investigator-Submitted Abstract**

Metastatic breast cancer leads to more than 40,000 deaths each year in the United States. While metastatic dissemination to other organs can be at least partially responsive to some therapies that result in improved survival, brain metastasis is inevitably fatal. Furthermore, tumors in the brain are often associated with neurological symptoms that seriously diminish quality of life. Solitary tumors are removed by surgery, but multiple tumors can only be treated to alleviate symptoms and cannot be cured. Clinical trials attempting to use the cancer patient's immune system to fight the tumor are ongoing and may benefit some patients with brain metastasis. However, much research is necessary to better understand the process of brain metastasis and to discover the knowledge required to design effective treatments to combat it.

We have shown that regulatory T (Treg) cells, a class of immune system cells that suppress immune responses, are necessary for primary and lung metastatic tumor growth. Moreover, we have learned that they do so by inhibiting the production of a factor called interferon-gamma (IFN $\gamma$ ). IFN $\gamma$  in turn, acts on other cells that migrate to the tumor site from the bone marrow, making them less able to promote primary tumor growth. In this proposal, we have developed a preclinical model of brain metastasis to study the mechanisms by which Treg cells contribute to brain metastatic growth. We will investigate the hypothesis that Treg cells promote brain metastasis through the regulation of bone marrow cells that are recruited into the brain tumors, and that killing Treg cells will contribute with other forms of therapy used to alleviate symptoms or in clinical trials.

Given that we lack the means of targeting Treg cells in humans, the results of our studies will provide the opportunity to devise innovative therapeutic options to interfere with their function in established brain metastatic settings. Importantly, our preclinical studies will evaluate a strategy to utilize cells from the bone marrow to treat brain metastasis, which might be easily translated into patients.



**Jose Javier Bravo-Cordero, Ph.D.**

**Targeting cancer cell-ECM interactions to prevent breast cancer metastasis**

### **Snapshot**

Jose Javier Bravo-Cordero, Ph.D., from the Icahn School of Medicine at Mount Sinai, will study how disseminated tumor cells (DTCs, or cells that leave the primary tumor and travel to other parts of the body) spread to and grow in a patient's bones. In particular, he will study how breast cancer cells can lay dormant or 'asleep' in the bone, leading to metastasis years after treatment. Through these studies, Dr. Bravo-Cordero hopes to learn how to stop breast cancer from spreading to or developing in the bone.

### **Investigator-Submitted Abstract**

The survival of breast cancer patients has not significantly improved in the last decade, indicating the need for more effective therapies. The primary cause of mortality of breast cancer patients is not the primary tumor; rather, they are caused by tumor cells that migrate out of the primary site and seed in other organs in the body, such as bone marrow or lungs, where they can form secondary tumors. This process is referred to as metastasis. Tumor cells can be detected in the bone marrow of cancer patients where they can lie dormant, non-proliferating, for years before growing into metastatic tumors. However, how dormant cells interact with the bone marrow extracellular matrix microenvironment to regulate dormancy is not understood. Estrogen receptor (ER+) breast cancer tumors have a tendency to metastasize to the bone marrow. ER+ breast cancer patients with disseminated tumor cells (DTCs) in the bone marrow have poor prognosis, experiencing relapse in the bone years after removal of the primary breast tumor. During this period, DTCs enter into a quiescent state in where they remain dormant (non-proliferating) before tumor relapse and metastasis are detected. In order to understand what are the mechanisms that mediate dormancy of tumor cells in the bone marrow, we have developed intravital imaging technologies to study dormant cells in preclinical models at the single cell level. We have found that dormant cells use specific pathways to interact with the extracellular matrix that surround them. ER+ tumor cells upregulate the collagen receptor, DDR1. Our goal is to explore the mechanisms that regulate dormancy of ER+ tumor cells in the bone marrow by focusing on the interactions between tumor cells and the extracellular matrix through DDR1. For this project, we will use in vivo imaging, proteomics and preclinical models to address these questions. A better understanding of the mechanisms that regulate tumor cell/extracellular matrix interaction during dormancy will allow the design of drugs to stop breast cancer metastasis.



**Kristin Brown, Ph.D.**

**Targeting Cell Metabolism to Circumvent Chemotherapy Resistance in TNBC**

**Snapshot**

Kristin Brown, Ph.D., from The University of Melbourne, will investigate the role of cholesterol lowering drugs to treat triple negative breast cancer (TNBC). Evidence suggests that cholesterol metabolism may play a role in chemotherapy resistance in TNBC. Dr. Brown will test the potential of FDA-approved drugs to lower cholesterol levels, called statins, to treat and make TNBC more vulnerable to chemotherapy.

**Investigator-Submitted Abstract**

Approximately 15-20% of women diagnosed with breast cancer are diagnosed with triple-negative breast cancer (TNBC), an aggressive form of the disease that frequently occurs in younger women. TNBC is difficult to treat because it lacks the targetable receptors - estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) - found in other forms of breast cancer. Consequently, conventional chemotherapy agents remain the mainstay of treatment for TNBC. Unfortunately, the majority of TNBC patients do not respond adequately to chemotherapy and the long-term prognosis for these patients is poor. There is an urgent need to identify mechanisms that promote chemotherapy resistance, and to develop combination therapy approaches to improve the efficacy of chemotherapy for treating TNBC.

Metabolism constitutes the set of chemical reactions that occur in every cell in the human body to support life. A fundamental difference in the metabolism of normal cells and cancer cells was first observed almost a century ago. In recent years, significant progress has been made in understanding the importance of metabolism in cancer and it is now widely recognized that cancer cells reprogram their metabolism to enable uncontrolled proliferation and survival. We have shown that reprogramming of cell metabolism is also an early response to chemotherapy exposure that contributes to chemotherapy resistance in TNBC. Adaptive reprogramming of cell metabolism fortuitously renders TNBC cells addicted to specific metabolic pathways. We propose that the unique metabolic requirements of chemotherapy-treated TNBC cells can be exploited for therapeutic gain.

Our study will investigate a novel chemotherapy resistance mechanism involving reprogramming of mevalonate metabolism. The mevalonate pathway is responsible for the synthesis of a variety of lipid compounds and is best known as the target of statins, a class of cholesterol lowering drugs. The mevalonate pathway has been implicated in multiple aspects of tumor development and tumor progression. Our objectives are: 1) to demonstrate that reprogramming of mevalonate metabolism is an adaptive response to chemotherapy exposure that limits the efficacy of chemotherapy for the treatment of TNBC, and 2) to provide preclinical evidence that inhibitors of the mevalonate pathway, including statins, can be employed to sensitize TNBCs to chemotherapy. We expect to show that inhibition of mevalonate metabolism is a viable and promising strategy to circumvent chemotherapy resistance and improve the treatment of TNBC.



**Joan Brugge, Ph.D.**

**Identification of Premalignant Changes in Breast Cells from BRCA1 Mutant Carriers**

**Snapshot**

Komen Scholar Joan Brugge, Ph.D., from Harvard Medical School, will study how loss of BRCA1 function leads to breast cancer, in order to develop therapies for patients with BRCA1-mutations.

**Investigator-Submitted Abstract**

Women who carry inherited mutations that inactivate the BRCA1 gene have a high risk (up to 80 %) of developing breast cancer. Currently, these women are encouraged to undergo mastectomy and oophorectomy operations before cancer has a chance to develop. Less invasive risk-reduction measures are desperately needed for these women, but development of new strategies is hampered because it is unclear exactly how BRCA1 mutation leads to cancer formation or why tumors form specifically in the breasts and ovaries. The goal of this proposal is to investigate how inherited mutation in BRCA1 leads to breast cancer so that better therapies can be developed to stop the disease. Importantly, we are using multiple cutting-edge technologies that provide us unprecedented ability to probe individual breast cells and see early changes in small subsets of cells in breast tissues from BRCA1-mutation carriers. Using these techniques, we have observed that a small subset of breast cells from women with BRCA1 mutations have not matured in the normal way. This type of alteration in maturation is important because it has been predicted to occur in the breast tumors of women with BRCA1 mutations, and inhibition of maturation is commonly associated with the development of other types of cancer. Thus, while the breast cells that we have discovered appear normal to pathologists, they may in fact be precursors of malignant tumors. We will use our state-of-the-art technologies, as well as new ways of growing breast cells from women with BRCA1 mutations and new pre-clinical models of BRCA loss, to address several key points: 1) to determine whether these non-maturing breast cells found in women with BRCA1 mutations behave differently from other breast cells, 2) to understand exactly how the mutation of BRCA1 causes this early change in normal breast tissue, 3) to test the hypothesis that these immature cells are the cells of- origin for breast cancer in this group of women. If this hypothesis is correct, then it is feasible that the development of therapeutic strategies targeting these cells for the stop the development of breast cancer in BRCA1-mutation carriers could be on the road to development over the next 10 years. Efforts to develop such strategies would be informed by the studies in this proposal that will identify unique features and potential vulnerabilities of the immature BRCA1-enriched cells. Importantly, the methods and approaches we are employing to investigate this particular inherited breast cancer syndrome could be used to learn more about other inherited cancer syndromes, and the insights we make for this group of women may help us understand how breast cancer develops more generally.





**Lisa Carey, M.D.**

## **Optimizing HER2-targeting Using RNA and DNA-based Predictive Algorithms**

### **Snapshot**

Komen Scientific Advisory Board Member Lisa Carey, M.D., from The University of North Carolina at Chapel Hill, will evaluate how HER2-positive tumors respond to HER2-targeted therapies. This project will integrate and analyze data from over 1,300 women participating in six neoadjuvant clinical trials of HER2-targeted therapy.

### **Investigator-Submitted 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 its 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.



**Alex Cheng, Ph.D.**

**Managing Treatment Burden and Capacity in Breast Cancer Patients**

**Snapshot**

Alex Cheng, Ph.D. and his mentor, Komen Scholar, Mia Levy, M.D., Ph.D., from Vanderbilt University, will analyze Electronic Health Record, SEER Medicare, prescription, claims, and patient survey data to assess the burden of breast cancer treatment on patients, and test whether tailoring treatment plans to reduce patient burden can lead to better outcomes for those breast cancer patients.

**Investigator-Submitted Abstract**

The complexity of medical care today makes it difficult for patients to navigate their care and for healthcare providers to monitor a patient's capacity to receive care even though treatment overburden can impact disease outcomes. A high burden can cause lower treatment plan compliance in patients with chronic diseases. Excessive treatment can also lead to wasted resources for the medical center, both from unnecessary procedures and from having to treat complications from noncompliance. Physicians who practice minimally disruptive care assess burden and tailor treatment plans giving a patient the maximum likelihood of recovery, while also taking into consideration the patient's limitations. To improve the effectiveness of this paradigm, providers and healthcare systems need reliable ways to identify and assist overburdened patients and patient populations sooner.

We are developing measures of treatment burden and capacity to manage care among patients with breast cancer. These measures will help the healthcare community to understand the enormous time and financial burdens that breast cancer patients face as a result of their treatment. The goal of our research is to use electronic medical record data to help patients, providers, and care coordinators better personalize care to fit patients' ability to manage treatment. Results from our study could enable actionable recommendations for treatment plans to patients undergoing breast cancer treatment based on their capacity to manage care. By helping patients better plan for the impact of treatment on their lives, this work is expected to improve outcomes and contribute to the Komen goal of decreasing breast cancer deaths by 50% by 2026.



**Kevin Cheung, M.D.**

**Can eradicated tumor cell clusters prevent metastasis? A preclinical study**

**Snapshot**

Kevin Cheung, M.D., from Fred Hutchinson Cancer Research Center, will determine if metastatic breast cancer (MBC) can be treated or stopped by blocking tumor cell clustering. Patients who have clusters of tumor cells, instead of single tumor cells, circulating in their blood are more likely to die of MBC. The goal of this study is to understand how tumor cells clusters form, and to determine if blocking tumor cell clustering could improve patient survival.

**Investigator-Submitted Abstract**

Tumor cell clusters are present in the circulation of up to 54% of metastatic breast cancer (MBC) patients and their frequency rises as patients' progress on therapy and develop drug resistance. We are still learning about the relationship between tumor cell clusters and MBC. What we know right now is that tumor cell clusters are 100 times more efficient at creating new metastases compared with single tumor cells. Tumor cell clusters are also much better at surviving chemotherapy. Each of these factors likely explains why MBC patients with circulating tumor cell clusters are much more likely to die from their disease than those patients without clusters.

My project focuses on ways to specifically eradicate tumor cell clusters. The best way to accomplish this is still unknown. One important piece to this puzzle is likely cell adhesion: the 'sticky tape of the cell.' Adhesion molecules are what hold tumor cell clusters together. We and other researchers have shown that if adhesion is broken, tumor cell clusters break apart and no longer metastasize. By targeting specific adhesion molecules, I hope to show that this strategy can eliminate cell clusters, offering a new hope for MBC patients with the highest burden of disease and fewest remaining treatment options.

My proposed studies will assess whether two adhesion molecules, integrin and fibronectin, are essential for clusters' survival. Integrin and fibronectin bind to each other like lock and key. Our preliminary data suggests that blocking the binding ability of integrin to fibronectin causes tumor cell clusters to undergo cell death. However, there are many types of integrin and we do not yet know which key fits the lock. Our proposed studies will identify and attempt to block the specific integrins that are most important to opening the door to cell cluster survival and metastasis. It turns out that most fibronectin is made by the liver, circulates in the blood, and then deposits in tissues. Our proposed studies will also figure out the role of circulating concentrations of fibronectin in the blood as it promotes metastasis. Since fibronectin helps cells stick together, we will test the idea that high levels of fibronectin are an important predictor of metastasis. We will use blood samples from an existing study to test these studies in pre- and postmenopausal women with breast cancer.

This is a novel concept and, as such, we believe that our approach will yield significant benefits for both researchers and MBC patients. Our studies could establish the preclinical data needed to start clinical trials of integrin blockade in MBC patients and establish that elevated fibronectin blood level is a risk factor for metastasis and potentially useful for selecting patients that could benefit from anti-cluster therapy. By shifting the paradigm from the individual tumor cell to the collective, our ultimate goal is to identify new approaches for combatting MBC, so that we can save lives.



**Katherine Cook, Ph.D.**

## **Targeting the Unfolded Protein Response Pathway to Prevent Therapeutic Resistance**

### **Snapshot**

Katherine Cook, Ph.D., from Wake Forest University, will investigate how diet can contribute to treatment resistance, both in hormonal therapies in ER+ breast cancer and with chemotherapy in triple negative breast cancer (TNBC). The goal of this research is to determine how dietary changes and drugs that target a protein called GRP78 can reduce treatment resistance in breast cancer.

### **Investigator-Submitted Abstract**

Background: Several studies have demonstrated a strong link between obesity and a greater risk of developing breast cancer. It is estimated that 3 out of 10 breast cancers may have been prevented if the women were not overweight, indicating the important role obesity in the etiology of breast cancer. Results from the breast international group (BIG) I-98 study indicate that obese women with ER+ breast cancer treated with tamoxifen had a poorer overall survival when compared to healthy weight women, implicating a causal link between obesity and endocrine therapy resistance. Obesity is also a predictor of poor response to chemotherapy, which is the first line of therapy for women with triple negative breast cancer (TNBC). In patients who received neoadjuvant anthracycline-based chemotherapy, a higher BMI was associated with worse pathological complete response, implicating obesity in the development of chemotherapy resistance.

The unfolded protein response (UPR) is a stress pathway found upregulated in obese patients' fat deposits. I previously showed upregulation of UPR component, glucose-regulated protein 78 (GRP78), in human breast tumors when compared with normal surrounding tissue. Moreover, I showed overexpression of GRP78 promoted endocrine therapy resistance and targeting GRP78 restored tamoxifen sensitivity in resistant tumors. I also showed that obesity upregulates GRP78 in tumors in a carcinogen-induced murine model of mammary neoplasia. My preliminary data shows obese mice are more likely to develop breast cancer and have a worse response rate to endocrine therapies than lean mice. Taken together, we hypothesize that consumption of a Western diet elevates GRP78 in the mammary glands and tumors to promote the therapeutic resistant phenotype.

We will investigate whether diet, e.g. Western diet (high in saturated fat and sugar) or Mediterranean diet (high in monounsaturated and polyunsaturated fat) impacts UPR signaling. Moreover, we will determine whether differing diets impact breast tumor formation in both ER+ and TNBC breast cancer models and whether diet modulates response to either antiestrogen therapies (ER+) or chemotherapy (TNBC). Furthermore, we will determine whether targeting GRP78 blocks obesity-mediated therapy resistance.

The impact of these studies can greatly affect the more than 60% of women who are overweight or obese and obesity-induced breast cancer. Moreover, obese women with breast cancer have higher mortality rates and do not respond as effectively to therapies, suggesting a link between obesity and drug resistance. It is currently unknown whether a Western diet affects GRP78 signaling to modulate therapeutic responsiveness in breast cancer. GRP78 inhibition could be a novel target to promote drug efficacy and reduce breast cancer mortality. My proposed study will aim to fill the current gaps in knowledge by answering these important questions.



**Subhamoy Dasgupta, Ph.D.**

**Targeting Metabolic Adaptations to Inhibit Breast Tumor Recurrence and Metastasis**

### **Snapshot**

Subhamoy Dasgupta, Ph.D., from Roswell Park Comprehensive Cancer Center, will determine if blocking a protein called PFKFB4 will increase the effectiveness of current breast cancer treatments. PFKFB4 is involved in generating energy in cells and has been shown to be elevated in breast tumors that return after treatment (recurrence) and spread (metastasize). The goal of this work is to determine if PFKFB4 is a good treatment target for overcoming treatment resistance and eliminating tumor recurrence.

### **Investigator-Submitted Abstract**

Innovations in breast cancer treatment and detection have increased the overall survival to almost 90% five-years after it was detected. Despite these advances breast cancer remains the second leading cause of cancer-related death in women. Breast cancer mortality is largely due to tumor recurrence which can occur sometimes even after a decade or two. Recurrent tumors are frequently found in different sites and very little is known about the tumor properties that allow them to survive the treatment regimen and recur. Thus, understanding the biological-mechanisms associated with drug resistance and tumor recurrence will provide us the opportunity to develop novel therapeutics, and reduce the pain and suffering from this disease. Our research identified that resistance develops due to activation of 'unknown' escape pathways which provide tumor cells necessary resources for survival. We identified a powerful metabolic enzyme named PFKFB4 which is one of the prime regulators of glucose-derived energy-generation process in breast tumor cells. This process, known as the glycolytic pathway is highly activated in majority of tumors but significantly elevated in aggressive breast tumors such as triple negative breast cancer. Analyzing breast cancer patient datasets, we found PFKFB4-activity signifies worse outcome in breast cancer patients. In preclinical models, we found PFKFB4 converts sugar carbon into building blocks of DNA, and inhibition of PFKFB4 significantly reduced tumor growth. DNA is required for the multiplication of tumor cells, allowing them to grow despite therapy. In this proposal we seek to evaluate whether PFKFB4 inhibition can increase the efficacy of current standards of care to eliminate resistant or residual tumors and stop tumor recurrence. There have been no new effective agents introduced into the clinic for treating recurrent tumors and it is clear that new strategies to block this complex system are needed to address both early and late recurrence of breast cancer. Cutting off the predominant energy generation process in recurrent breast tumors will substantially halt the tumor growth, and eventually reduce the mortality rate and cure the disease. Currently investigations are ongoing to discover specific inhibitors targeting PFKFB4 for treatment of other types of cancer, and this study will provide a strong rationale for a Phase I trial in therapy-resistant breast cancer patients.



**Mary (Nora) Disis, M.D.**

**Limiting the inflammation of obesity to prevent breast cancer**

### **Snapshot**

Komen Scholar Mary L. “Nora” Disis, M.D., from the University of Washington, will continue to develop a vaccine-based treatment to block obesity-related inflammation, with the goal of reducing the incidence of breast cancer in obese women.

### **Investigator-Submitted Abstract**

Obesity increases the risk of dying from breast cancer, especially in post-menopausal women. In 2007 about 50,500 women developed an obesity related cancer. By the year 2030, it is estimated that number will rise to 500,000 additional cases. How can we stop the development of obesity-related breast cancer? This proposal describes an innovative strategy for the development of a vaccine to block the inflammatory changes in obese fatty tissue that may result in breast cancer initiation.

Obese tissue is inflamed. This means that there are many immune system cells that are infiltrating fatty tissues. In some patients this inflammation is excessive and leads to the secretion of natural substances by the immune system cells called cytokines and chemokines. These natural substances can stimulate fatty tissue (breast) to proliferate. In obese individuals, the type of inflammatory environment is called “Type 1” and the primary cells responsible for the secretion of cytokines and chemokines are Type 1 immune cells (Th1 helper CD4 T cells, CD8 T cells and Type 1 macrophage). In normal weight individuals, the fat is also filled with immune cells. However, these immune cells turn off inflammation. This non-inflammatory environment is given the name “Type 2 inflammation”.

What causes Type I inflammation in fat tissue? As fat tissues expand the blood supply is lost. This lack of oxygen upregulates specific proteins turned on by the hypoxic signal. Moreover, the lack of oxygen sends a danger signal to the immune system and stimulates Type I T cells. We have found some of the proteins that become highly upregulated in hypoxia are immunogenic, that is, these proteins stimulate the immune system. Another early alteration in inflamed fat tissue is hormonal dysregulation. Several proteins that are involved in estrogen and progesterone metabolism are also upregulated, which may further stimulate the proliferation of breast tissue. We have also found proteins upregulated in hormonal pathways in obese individuals are also immunogenic. These proteins can act as candidates for a vaccine to stop inflammation.

We believe that a vaccine targeting multiple proteins associated with a variety of malfunctioning cellular processes in obese fatty tissue may be effective in directing Type 2 T cells to the site of inflammation. Data from our group has shown that regions exist in self-antigens that preferentially stimulate a Th2 or anti-inflammatory immune response. We intend to identify these segments and formulate a vaccine that will dampen Type I immunity.

Our aims are: (1) determine what proteins stimulate immunity in inflammatory obesity; (2) Use a web-based computer program to predict which portions of these proteins are most likely to be recognized by the immune system in the majority of the population. We will study which of these areas of the proteins stimulate the strongest Th2 response when exposed to human T cells; (3) test if the vaccine decreases inflammation in the fatty tissue of a pre-clinical model of diet-induced obesity. We will measure success by a decrease in CD8 T cells and an increase in T regulatory cells in the fat of vaccinated subjects.



**H. Shelton Earp, M.D.**  
**Carolina Breast Cancer Study**

**Snapshot**

The University of North Carolina will continue to support the Carolina Breast Cancer Study Phase 3 (CBCS3). CBCS3, one of the largest population-based studies of women with breast cancer, seeks to identify determinants of disparities in breast cancer clinical outcomes, including biologic, racial, socioeconomic, behavioral factors and identify modifiable factors in clinical care (delivery and access) that address the causes of disparities.

**Investigator-Submitted Abstract**

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

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

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



**Robert Faryabi, Ph.D.**

**Notch-Driven Epigenetic Program of Triple Negative Breast Cancer**

### **Snapshot**

Robert Faryabi, Ph.D., from University of Pennsylvania, will investigate how a protein called NOTCH contributes to triple negative breast cancer (TNBC) growth and resistance to chemotherapy. The goal of this study is to identify other proteins that work with NOTCH to drive TNBC growth. Using cutting-edge data science, Dr. Faryabi will discover new treatment strategies for TNBC patients that could improve survival by limiting drug resistance and recurrence in breast cancers.

### **Investigator-Submitted Abstract**

Breast cancer is the most prevalent and aggressive solid tumor among women. Breast cancer can be divided into multiple subtypes, one of which is triple-negative breast cancer (TNBC). This disease accounts for ~10% of all breast cancer cases, has lowest survival rate due to the lack of effective treatments. This underscores the importance of finding new treatments for therapy-resistant TNBC, which is even more complicated by the existence of various TNBC's subgroups. A promising approach for development of more effective treatment strategies is to select treatment options that best fit the precise characteristics of each subgroup. Unfortunately, the success of the precision treatments has been limited, in part, due to the lack of detailed and mechanistic understanding of drivers of each subgroup. An important contributor to the pathobiology of TNBC is Notch signaling. Hyperactive NOTCH leads to pathologic signals driving tumor growth, increased chemotherapy resistance, poor survival, and increasing chance of metastases. Although biomarkers for the Notch-active TNBC subgroup and drugs to target Notch have been developed recently, treating patients with Notch-targeted therapies has been ineffective to date, in part due to the limited understanding of how Notch signal controls these fundamental processes.

An important effect of Notch signaling is to activate two important oncogenes MYC and CCND1. MYC is one of the most important genes promoting tumor growth and survival. CCND1 controls cell division and proliferation among other cellular processes. Despite their importance, it is difficult to directly target MYC and CCND1 with the existing drugs. Importantly, it is known that NOTCH regulates MYC and CCND1 in several forms of cancers including TNBC. We propose to leverage the regulatory relationships between Notch:Myc and Notch:CCND1 to better target these axes and limit growth and survival of TNBC tumors. However, in order to achieve this goal, we first need to understand the mechanisms by which NOTCH regulates MYC and CCND1 in TNBC. We plan to use cutting-edge functional genomics and machine learning methods to discover these mechanisms. Furthermore, it has been shown that other tumors develop resistance to available Notch inhibitors. To develop more potent therapeutic options, we plan to discover how drug-resistant cells circumvent the drug's effect and maintain expression of these critical NOTCH targets to grow and survive. To this end, we plan to identify other factors that cooperate with NOTCH in TNBC to drive abnormal cell growth and survival. We propose that these cooperating factors may be targeted in conjunction with Notch itself to alleviate the problem of resistance to Notch inhibitory drugs. We plan to use this knowledge to tailor our therapeutic strategies for individual patients with activated Notch signaling. By doing so, we hope to improve the survival of patients with this aggressive and difficult to treat form of breast cancer.





**William Foulkes, MBSS, Ph.D.**  
**Liquid Biopsies for Breast Cancer Diagnosis**

**Snapshot**

Komen Scholar William Foulkes, MBSS, Ph.D., from McGill University, will optimize and validate a simple blood test, known as a liquid biopsy, to diagnose and provide molecular information on breast tumors. The project could provide a clinical tool for low-resource communities that will reduce the delays between diagnosis and treatment, thus improving patient care and outcomes.

**Investigator-Submitted Abstract**

Research shows that timely diagnosis of breast cancer is directly linked to improved survival in patients. However, for some groups of patients, timely diagnosis is difficult to achieve. These include individuals who are part of underserved communities, such as people living in developing countries or in communities with lower socio-economic status in affluent countries. Biological and genetic factors can also play a role; for example, individuals of West-African descent have been observed to present at greater frequency with aggressive, late stage/grade disease when compared to Caucasian patients, even when living in communities where access to health care is not limiting. Accurate diagnosis of the type of tumor present in a patient can provide information vital to making the best decisions when choosing a therapy. For example, one type of breast cancer known as HRD (Homologous Repair Deficient) cancer is known to respond well to specific therapies such as PARP inhibitors and cisplatin, while different therapies are indicated for other tumor types. Therefore, correctly diagnosing a tumor type can make a crucial difference when choosing the appropriate therapy for a patient. Currently, breast cancer diagnosis usually involves imaging of the tumor to confirm its presence, referral to an oncologist, biopsy of the tumor followed by genetic testing. This process can take several weeks, sometimes more for patients who don't have easy access. Such delays can have an impact on survival for patients, particularly those who present with advanced disease, where rapid treatment is crucial.

The aim of our pilot study is to test a new diagnostic tool that would use a liquid biopsy – i.e. biopsy taken from a blood sample – to produce a molecular diagnostic to identify the tumor type in a patient. This is possible because, as tumors grow, they shed some of their cells into the bloodstreams; thus, it is possible to purify the DNA from blood plasma and detect the DNA that comes specifically from the tumor cells. We propose that sequencing this DNA can be used to establish a diagnosis without the need to biopsy the tumor directly. Since obtaining a blood sample is fast and easy, this new tool could significantly speed up the diagnostic procedure to guide treatment decisions.

Our study will be conducted at two sites. We will optimize the method in our Montreal laboratory with the help of patients from diverse local Montreal communities. This will tell us whether this new diagnostic tool provides the necessary information to be used as an alternative to direct biopsy of the tumor scientifically. We will also collect blood samples from patients in Ghana, West Africa, to see how well the protocol performs under field conditions where access to sophisticated laboratory facilities is limited. It is our hope that our results will support implementation of this new tool into clinical practice to improve patient care and survival rates for breast cancer patients.



**Rachel Ann Freedman, M.D., MPH**

**Why Do Older Women with Breast Cancer Do Worse?: A Longitudinal Cohort Study**

**Snapshot**

Rachel Freedman, M.D., MPH, from Dana-Farber Cancer Institute, will investigate ways to improve survival for breast cancer patients that are 70 years of age or older. Older patients often face worse outcomes when compared to their younger counterparts. The goal of this study is to identify tailored treatment methods that will improve survival for this population of patients.

**Investigator-Submitted Abstract**

Breast cancer is common in older women with the number of diagnoses increasing in frequency as the U.S. population ages. Although breast cancer in older women is often perceived to be indolent, breast cancer outcomes for older patients are often worse than those seen in younger patients, and inclusion of older patients to cancer clinical trials has been stagnant and inadequate. Further, compared with younger patients, improvements in breast cancer survival over time have occurred at a slower rate for those aged 75 years and older. The reasons for worse outcomes in older patients are not clear, but are likely related to under-treatment, treatment-related side effects, poor adherence to hormonal therapy treatments, and variable disease biology. In this proposal, we will launch a large cohort (sample) of newly diagnosed breast cancer patients who are age 70 years or older at three participating centers (2 urban, 1 rural) and will follow them closely over time. Using a combination of surveys, medical record reviews, and tissue/blood collections, our proposal, which is unique and first of its kind, will directly address disparities in outcomes for older patients. This study will include focused attention on under-treatment, adherence, reasons for treatment decisions, treatment barriers, patient-reported outcomes and tissue- and blood-based genomics (all of which have not been specifically studied in older populations), with the goal to significantly improve the degree of available evidence we have to inform the care of older patients. During the grant period, we will launch the cohort at three centers, enroll the first 200 patients, and begin analyses on patterns of care and adherence for these women, with the plan to expand the cohort to include 1000 patients at 10 centers over time, once additional large-scale funding is secured. We will use the information from our study to directly apply interventions for adherence, surveillance, and tailored treatment strategies. We anticipate that this longitudinal patient cohort will provide a wealth of information for years to come, with our short- and long-term goals sharply aimed at reducing breast cancer deaths in older breast cancer patients over the next decade.



**Karen Gelmon, M.D.**

**Using Fine Needle Aspirates as a Minimally Invasive Technique for Disease Monitoring Using Single Cell Genomics Methods in Triple Negative Breast Cancer (TNBC)**

**Snapshot**

Komen Scholar Karen Gelmon, M.D., from the Provincial Health Services Authority, will pilot a clinical trial using advanced technology to genetically sequence breast cancer tissue from triple negative breast cancer (TNBC) patients acquired during a less painful and risky biopsy procedure, called a Fine Needle Aspirate (FNA). This approach would allow better understanding of tumor differences, leading to improved treatments and diagnostics for TNBC patients.

**Investigator-Submitted Abstract**

Over the last decade we have become aware that cancers evolve over time. This means that they change, and these changes may cause the cancer to become resistant or not respond to the treatments that were planned at the time of the initial diagnosis. These changes can be important in both early breast cancer where the cancer is being treated to cure the cancer and in recurrent or advanced cancer when the cancer is being treated to control the disease including controlling symptoms and prolonging the life of the patient. In the past we have done biopsies of the cancer to try to determine if the cancer has changed. We have studied the biopsies in the laboratory for changes in the genes or in the DNA of the tumor. Repeated biopsies however are painful for the patient and may be dangerous with the risk of bleeding and infection. Recently we have also tried to understand those changes using new methods to look at DNA in the blood. But we are concerned that the blood alone may not tell the whole story. In our laboratory we have started to see if we can look at the cells of the tumor in a very comprehensive way by taking only a sample of the tumor called a fine needle sample that is much less invasive and much easier for the patient.

A fine needle aspirate (FNA) is a biopsy technique that uses a very small needle that is less painful, less risky and can be done on smaller masses. It also gets fewer cells. We have been able in preliminary tests to get enough cells from the tumor to use cutting edge technology to look at the genes and the DNA within single cells from FNAs. We believe that FNAs are easier for the patient and that new single cell methods in the lab will give more accurate readings of why the cancer may not respond to treatment.

We are proposing a small initial pilot study to enroll 20 persons with a new diagnosis of triple negative breast cancer and do a standard core biopsy, a FNA and a blood sample for circulating tumor DNA in the blood and compare the results. If we are able to do all of our studies on FNAs we will do a larger study in both early and late breast cancer as well as in other subtypes to further confirm this result. If this study is positive, we may spare patients the pain and risks of core biopsies as well as showing the benefit of single cell studies for looking at the DNA. Future studies may be able to follow cancers over time, so we learn more about how they change and how we can better treat them to avoid resistance to treatment. If we could see the changes in the tumors over time we may be able to adjust our treatments and have more successful therapies. We are doing this study in triple negative tumors as we have already done a lot of work in this subtype of breast cancer and as it is an aggressive type of breast cancer that needs better treatments and a better understanding as soon as we can.



**Sharon Giordano, M.D.**  
**Toxicities of Breast Cancer Treatment**

**Snapshot**

Komen Scholar Sharon Giordano, M.D., from University of Texas M.D. Anderson Cancer Center, will continue to compare the toxicities of treatments for breast cancer in a diverse population of young and old women. She will compare the toxicities of standard adjuvant chemotherapy, treatments for metastatic breast cancer, and toxicity due to interactions of cancer drugs with other medications. She will also study another important toxicity for breast cancer patients - financial toxicity of breast cancer treatment, and how financial burden may impact treatment adherence.

**Investigator-Submitted Abstract**

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



**Sharon Giordano, M.D.**

**ASSESS: A Novel Breast Cancer Decision Support Tool**

**Snapshot**

The University of Texas MD Anderson Cancer Center will develop a novel, online and easy-to-understand breast cancer decision support tool to help physicians and patients make shared decisions about adjuvant therapy. The tool will estimate the risk of breast cancer recurrence at 5 years and 10 years after diagnosis, overall survival, and the expected benefits of various adjuvant treatment modalities, providing important information that will inform treatment decisions.

**Investigator-Submitted Abstract**

Many patients and physicians struggle with weighing the risks and benefits of systemic treatments that might improve survival in early stage (stage I-III) breast cancer but could also cause substantial side effects. Our goal is to build a free, easy to understand, online tool that will report estimates of the risk of breast cancer recurrence and death with and without systemic treatments such as hormonal therapy and/or chemotherapy for individual patients. The decision support tool will use routinely available prognostic risk factors such as the size of the cancer, the number of lymph nodes affected by cancer, the histologic grade, estrogen receptor, HER2 receptor status of the cancer as well as the age and other medical illnesses of a patient to predict risk of recurrence at 5 years and 10 years after diagnosis. The tool will also show how this risk changes with systemic therapy. In addition, we also plan to provide information on the frequency of treatment toxicities from clinical trial data and observational cohorts. In the early 2000s, a widely popular web-site Adjuvant! Online was created for the same purpose but it was inactivated about two years ago. More recently, investigators in the United Kingdom created PREDICT (<http://predict.nhs.uk/>) that estimates overall survival at 10 years after diagnosis and shows the expected survival benefit from systemic therapies. However, unlike our proposed decision aid, PREDICT does not include estimates of breast cancer recurrence, and does not adjust for patient co-morbidity or provide information on toxicity. We will use data from large cancer registries including the California and British Columbia Cancer Registries and the NCI-SEER database to develop and validate our statistical model. We will use information from large randomized clinical trials to estimate benefit from different commonly used systemic therapies. We will solicit input from our intended users, breast cancer patients, patient advocates and oncologists to design the most user-friendly display and content for the decision support tool. The tool will be hosted on the Komen website and branded/owned by Susan G. Komen. The website will be updated as results from large randomized adjuvant clinical trials that lead to changing practice become available. To create a new publicly available tool that can make individualized recurrence risk and treatment benefits/harms predictions is important because it will allow better-informed shared decision making between patients and physicians. The tool could also be used to estimate residual risk after completion of all adjuvant therapy and select high residual risk patients for future adjuvant trials.



**Shom Goel, Ph.D.**

**Immunologic Mechanisms of Resistance to CDK4/6 Inhibition in Breast Cancer**

### **Snapshot**

Shom Goel, Ph.D., from Dana-Farber Cancer Institute, will investigate how to improve the effectiveness of a class of drugs called CDK4/6 inhibitors in the treatment of ER+ breast cancer. While these drugs prevent tumor growth, patients often develop resistance to them. The goal is to determine if treatment resistance can be overcome by combining these CDK4/6 inhibitors with immunotherapies (drugs that target and boost the immune response).

### **Investigator-Submitted Abstract**

Approximately 70 percent of breast cancers are estrogen receptor-positive (ER+), meaning that their cells make a protein called the estrogen receptor. ER+ breast cancers are the commonest cause of breast cancer death, and although several treatments are available, they become incurable if tumors spread to distant organs. The standard initial treatment for ER+ breast cancer is “hormonal therapy”, medication that blocks the effects of estrogen. Recently, a new class of drugs – CDK4/6 inhibitors – has also been approved to treat these cancers. These drugs stop cancer cells from dividing, and trials have shown that using hormonal therapy plus a CDK4/6 inhibitor controls tumor growth for longer than hormonal therapy alone.

Although CDK4/6 inhibitors are effective against ER+ cancer, tumors develop resistance over time, meaning that they start growing again even though treatment is ongoing. When this happens, patients must stop taking their CDK4/6 inhibitor and switch to new treatments, such as toxic chemotherapy. We do not understand the reasons behind CDK4/6 inhibitor resistance well and have no strategies to address it in the clinic. Here, I will address this gap in our knowledge, specifically asking whether weakening of the immune system’s attack against a cancer causes resistance. This idea stems from my previous studies showing that CDK4/6 inhibitors not only stop cancer cell division, but also work by stimulating the immune system to attack cancer cells. My most recent experiments suggest that the strength of this immune attack decreases over time, which might explain tumor regrowth.

The role of the immune system in mediating resistance to CDK4/6 inhibitors has not been studied before. I am well positioned to do this because we have created preclinical models of breast cancer that develop resistance to CDK4/6 inhibitors over time, mimicking the clinical situation. First, I will use these models to study whether the immune cells in CDK4/6 inhibitor-resistant tumors have become dysfunctional. Second, I will determine whether adding immunotherapies (drugs that activate the immune attack against cancer) to CDK4/6 inhibitors can re-stimulate the immune system and therefore shrink resistant tumors in these models. Finally, I will examine breast cancer biopsies obtained from 60 patients, both before and after their tumors developed CDK4/6 inhibitor resistance. I will study markers of immune cell function in these specimens to establish whether my results from these preclinical models are upheld in the clinic.

These studies could provide a new explanation for why breast cancers become resistant to CDK4/6 inhibitors. If immunotherapy can successfully reverse resistance in preclinical models, it will trigger clinical trials to determine whether the same is true for patients. Ultimately, this could transform outcomes for patients with metastatic ER+ breast cancers that have developed resistance to current first-line treatments.



**Joe Gray, Ph.D.**

**Mechanisms of Resistance to Treatment in Metastatic Breast Cancer**

**Snapshot**

Komen Scholar Joe Gray, Ph.D., from Oregon Health & Science University, will expand his research into the factors that influence the response to HER2-targeted therapies, including changes to DNA (called epigenetics), the tumor's microenvironment, and the timing of drug treatment. Dr. Gray will use this information to design more robust treatment strategies to overcome resistance to HER2-targeted therapy, especially for patients with metastatic HER2 positive disease.

**Investigator-Submitted Abstract**

Amplification of the HER2 gene occurs in about 20% of breast cancers. HER2+ breast tumors typically respond well to the HER2-targeted therapeutic agents that are now in routine clinical use. Unfortunately, the responses to these agents can be short, especially in metastatic disease. Clearly, work is urgently needed to understand and counter the mechanisms by which resistance arises. We now know that changes in the cancer (epi) genome and signals from the micro-environments in which the cells live can render the cells resistant to these treatments, and that alterations in drug treatment schedules can profoundly impact the efficacy of the drugs. We will explore mechanisms of resistance to HER2 targeted therapies using a collection HER2+ breast cancer cell lines that carry a variety of genomic and epigenomic modifications. These cell lines will be grown in the presence of thousands of different combinations of proteins and growth factors from the microenvironments in which breast tumors grow and metastasize, allowing us to assess how these micro-environmental factors alter tumor behavior. We will use information from these studies to design drug combinations that will counter the effects of (epi) genomic aberrations and microenvironmental signals that give rise to resistance to HER2 targeted therapies. Furthermore, we will investigate how sequential treatment using these drug combinations affects the efficacy of the combination in order to optimize the therapy. We anticipate that translation of these combinatorial treatment strategies to the clinic will increase overall survival duration substantially – especially for patients with metastatic HER2 positive disease.



**Jennifer Guerriero, Ph.D.**

**Harnessing Macrophages in Advanced Breast Cancer to Combat Drug Resistance**

**Snapshot**

Jennifer Guerriero, Ph.D., from Dana-Farber Cancer Institute, will investigate ways to improve treatment response to a type of drug called PARP inhibitors for patients with triple negative breast cancer (TNBC) that also have a BRCA gene mutation. These tumors often hijack the patient's immune system to become resistant or unresponsive to PARP inhibitors, which leads to tumor spread. The goal of this study is to determine if targeting macrophages, a type of immune cell, can improve response to PARP inhibitors and patient survival.

**Investigator-Submitted Abstract**

There are few effective treatment options for BRCA-mutated TNBC. PARP inhibitor therapy has recently emerged as a promising target for BRCA-mutated breast cancer and while responses are promising, the remissions have not been durable. Therefore, there is a critical need to develop novel strategies to overcome PARP inhibitor resistance. Activating the body's own immune system to fight cancer, called immunotherapy, has shown great promise for treatment of a number of human cancers and has resulted in durable clinical responses that can last up to a decade. Thus far, immunotherapy has had limited success in breast cancer. The main focus of immunotherapy has primarily been on manipulating cells of the immune system called T-cells. However, we have shown that other immune cells such as macrophages are central regulators of the complex breast tumor microenvironment. Tumor associated macrophages (TAMs) generally promote tumor progression by secreting factors that help the tumor cells grow. TNBC is largely associated with a high density of TAMs, which have been shown to promote tumor progression, metastasis, and resistance to chemotherapy. Clinically, a high density of macrophages has been significantly associated with a worse clinical outcome. Recently, it's been identified that BRCA-mutated, but not BRCA-wildtype, TNBC secrete factors that recruit highly suppressive macrophages to the tumor, which may limit the effectiveness of chemo- and immuno-therapy. Additionally, we find that inhibiting TAMs with clinically available compounds, such as anti-CSF-1R in combination with PARP inhibitors, overcomes PARP inhibitor resistance. Therefore, we will test the hypothesis that BRCA-deficient TNBC cells recruit highly suppressive TAMs to the tumor, and these TAMs limit the effectiveness of PARP inhibitor therapy and immunotherapy.

This project will focus on the novel goal of harnessing TAMs in BRCA-mutated TNBC to induce a durable anti-tumor response and overcome resistance to PARP inhibitors, including the possible eradication of primary and metastatic cancer. Successful completion of this project is likely to result in an accelerated path to the clinic and fulfills the urgent need to overcome resistance to PARP inhibitor therapy and will contribute to Komen's Bold Goal of reducing breast cancer deaths by 50 percent by the year 2026.





**Svasti Haricharan, Ph.D.**

**Mismatch Repair Defects and Endocrine Therapy Resistance in ER+ breast cancer**

### **Snapshot**

Svasti Haricharan, Ph.D., from Sanford Burnham Prebys Medical Discovery Institute, will develop a diagnostic assay that could predict which ER+ breast cancer patients may become resistant to hormone therapies. This would identify patients with an inability to repair damaged DNA, often seen in treatment-resistant cancers. Dr. Haricharan will also determine if existing FDA-approved drugs could be used to overcome treatment resistance.

### **Investigator-Submitted Abstract**

Despite extensive research, the fate of breast cancer patients is still largely determined by the presence of three proteins in their tumors: estrogen receptor, progesterone receptor, and a growth factor, HER2; a discovery made in the 1970s. Patients with tumors expressing ER are treated with endocrine therapy which inhibits ER function. About 1/3 of ER+ patients do not respond to this treatment and eventually die of the disease. Recently, my lab discovered that tumors with defects in their ability to repair mismatches in DNA are endocrine treatment resistant. Up to 30% of endocrine treatment resistant tumors show this defect, meaning that >10,000 women a year in the US alone need different therapeutic options than they normally get. My project will move this discovery into the clinic by 1) developing a simple diagnostic assay so that clinicians can identify tumors with defective mismatch repair (MMR) (Aim 1) 2) identifying existing FDA-approved drugs that can treat these tumors more effectively than endocrine treatment (Aims 2 and 3). We have great hope that the results of this study can save the lives of thousands of endocrine treatment resistant breast cancer patients every year.

The Susan G. Komen foundation has made it a major goal to discover new treatments for ER+ breast cancer and our study will contribute to this goal significantly as ~30% of endocrine therapy resistant, ER+ breast cancer patients can benefit from the new therapeutic alternatives discovered in this study. The Komen foundation also has a goal to fund research that will benefit patients within the next 10 years. This is why my project focuses on drugs already approved by the FDA, as this accelerates translation of research to patients. Even more importantly, because we can identify women whom we think will benefit from non-endocrine alternative therapeutics before we even begin treatment, we can focus future drug trials on those women alone. This increases the chances of the clinical trial being successful and will not jeopardize lives of women unnecessarily.

Every year, ~40,000 women diagnosed with ER+ breast cancer prove resistant to standard-of-care endocrine therapy. As yet, we have no predictive markers that enable clinicians to identify these women before they are given years of therapy that will not prove effective but has several, severe side-effects. Additionally, in those years, the cancer cells in the woman's body are growing, multiplying, and metastasizing. This proposal seeks to identify these women early in the timeline of their cancer, affording the clinician a crucial opportunity to personalize therapy to each woman. Overall, this proposal can contribute significantly to the Komen mission of reducing deaths due to breast cancer by 50% by 2026.



**Daniel Hayes, M.D.**

## **Novel Devices to Capture Circulating Tumor Cells**

### **Snapshot**

Komen Scholar Daniel Hayes, M.D., from the University of Michigan, will continue to develop “liquid biopsies” to evaluate the circulating tumor cells in a patient’s blood stream, and inform treatment decisions about targeted therapies. Dr. Hayes and team will also refine their current technology for collecting the liquid biopsies from patients.

### **Investigator-Submitted Abstract**

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

These data suggest that just counting CTC is not sufficient to direct patient care. Rather, CTC might serve as a “liquid biopsy,” permitting detailed characterization for markers that might predict benefit from “targeted” therapies, the goal of “Precision Medicine.” CTC might have several advantages over true biopsies. True biopsies are invasive, expensive, and difficult to perform repeatedly. Further, a biopsy only provides information about the specific site from which the tissue was drawn, while CTC in blood presumably come from all the sites, and therefore, provide a more comprehensive portrait of the patient’s entire tumor burden. Recently, several investigators, including Dr. Hayes’ laboratory, have shown that CTC can, indeed, be characterized for expression of important breast cancer markers, such as estrogen receptor, BCL2, HER2, Ki67, apoptosis, and markers of epithelial-mesenchymal transformation (EMT), which appears to be an important step in metastases. CTC can also be characterized for genetic abnormalities that might predict specific therapeutic responses.

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

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



**Reshma Jagsi, M.D., Ph.D.**

**PARP Inhibition and Radiotherapy for Patients with Inflammatory Breast Cancer**

**Snapshot**

Komen Scholar Reshma Jagsi, M.D., Ph.D., from The University of Michigan, will investigate the use of drugs called PARP inhibitors, in combination with radiation, to treat inflammatory breast cancer (IBC), a rare but aggressive form of breast cancer. This project will identify the biomarkers that could predict therapy response and lead to improving precision treatment for women with IBC.

**Investigator-Submitted Abstract**

Inflammatory breast cancer accounts for only about 2% of incident breast cancer, but it accounts for 10% of the deaths due to breast cancer. Many women with inflammatory breast cancer experience locoregional recurrence of the disease in the chest wall or regional lymph node basins, which cause significant symptoms and serve as a reservoir for the seeding and re-seeding of distant metastases. Novel strategies that intensify locoregional treatment have the potential to improve outcomes for these patients, whose outcomes remain inferior to those of other patients with breast cancer and whose needs are critical. Using a clinical trial that seeks to improve outcomes in these patients as the foundation for correlative scientific studies is important to inform our understanding of inflammatory breast cancer overall, as well as our understanding of how radiation therapy affects breast cancer cells and normal tissues, and how manipulating DNA repair might allow for safe intensification of treatment. Understanding how radiation treatment can safely be intensified is important to improve outcomes women with inflammatory breast cancer and many others with aggressive disease (such as patients whose tumors fail to respond to systemic therapy). We have the unique opportunity to conduct studies using specimens provided by patients participating in randomized clinical trial being led in the National Cancer Institute cooperative group system. What we learn about the mechanisms of inflammatory breast cancer, radiotherapy effects, the DNA damage response, and the mechanisms by which PARP inhibition and radiotherapy interact will be critical to inform future studies that attempt to improve the outcomes for women diagnosed with inflammatory breast cancer, as well as the efficacy and reduce the toxicity of radiotherapy in the management of cancer more generally. We hypothesize that concurrent administration of the PARP inhibitor olaparib and radiation therapy will lead to radiosensitization and that biomarkers of concurrent treatment response can be identified using combinatorial genomic and circulating biomarker analyses to aid in the personalized treatment of women with inflammatory breast cancer.



**Yibin Kang, Ph.D.**

**Scientific and Patient Advocate Sessions at the 17th Congress of the Metastasis Research Society & Young Investigator Satellite Meeting**

**Snapshot**

The Metastasis Research Society (MRS) will support a component of MRS's 17th Biennial Congress, a conference where researchers discuss experimental and clinical information known about metastasis and new opportunities for more effective intervention strategies. The funding will support early-career investigators to travel and present their research at the Young Investigator Satellite Meeting, held the day before the conference.



**Mary-Claire King, Ph.D.**

**Identification of New Genes for Inherited Breast Cancer by Next Generation Sequencing in High-Risk Families**

**Snapshot**

Komen Scholar Mary-Claire King, Ph.D., from University of Washington, will continue to screen for genetic mutations in families severely affected by breast cancer, potentially identifying novel mutations and mechanisms for inherited breast cancer.

**Investigator-Submitted Abstract**

The discoveries of BRCA1 and BRCA2 changed breast cancer treatment in remarkable ways. It is now possible for women to learn if they carry cancer-predisposing mutations in BRCA1 and BRCA2, and if so, to take steps to reduce their risk of breast and ovarian cancer. One of our greatest frustrations is to discover that a family severely affected with breast cancer carries no detected mutation in any gene. In our studies of extended families at high risk of breast cancer, we have confronted this frustration many times. Our analyses of >800 severely affected families suggest that many mutations and genes for breast cancer predisposition remain to be found. Indeed, most severely affected families remain unresolved. There are at least 18 genes with mutations responsible for inherited breast cancer. BRCA1 and BRCA2 are the best known, conferring extremely high risks of breast and ovarian cancer. Inherited mutations in TP53, CDH1, PTEN, STK11 are associated with very high risks of breast cancer in the contexts of rare syndromes. Inherited mutations in several genes in pathways critical to genomic integrity confer 2- to 4-fold increased risks of breast cancer; that is lifetime risks of 20% to 50%. These genes include Abraxas, ATM, BARD1, BRIP1, CHEK2, PALB2, RAD51C, RAD51D, ATR, BAP1, CHEK1, and GEN1. Recommendations for care of women with mutations in these more recently characterized genes include increased surveillance, including tools such as MRI that are not offered universally. In this Komen project, we will screen for novel mutations in the non-coding regions of breast cancer genes. Such mutations regulate the time and tissues of gene expression. The integration of high throughput genomics with information on regulatory elements with the genetic material and clinical information provided by our participating families provides an ideal opportunity to identify novel mutations and new mechanisms for inherited breast cancer. We will identify regulatory mutations specifically from families severely affected with breast cancer. If successful, our results will allow risk-reduction management strategies to be extended to many families for whom the genetic cause of breast cancer is currently unknown. This proposal has the potential to improve patient care in the next few years by yielding a more comprehensive genomic profile of breast cancer predisposition. The short-term goals are to better identify women at risk, and to allow closer surveillance. The long term goals are to contribute to the design of new risk-reduction strategies and a better understanding of the mechanisms involved in breast cancer development.



**Karin List, Ph.D.**

**Preclinical Testing of Matriptase as a Novel Target in Inflammatory Breast Cancer**

**Snapshot**

Karin List, Ph.D., from Wayne State University, will continue research to test a new drug that inhibits matriptase – an enzyme that helps tumors spread to distant sites – to determine if the drug can stop Inflammatory Breast Cancer (IBC) from growing or spreading. To validate and further test this treatment, Dr. List will use patient samples to develop new preclinical models of IBC to test this treatment, which will provide a valuable resource for the IBC research community to test new therapies. Currently there are very few model systems for this rare type of breast cancer.

**Investigator-Submitted Abstract**

Inflammatory breast cancer (IBC) is among the most aggressive and lethal forms of breast cancers characterized by rapid progression, local and distant metastases, younger age of onset, and high occurrence in African American women. Further complicating treatment is the fact that 20 – 40% of IBC cases are triple-negative breast cancers (TNBC), which excludes hormone therapy and HER2 targeting as treatment options. The poor prognosis for IBC patients emphasizes the need for new strategies to identify more efficient treatment opportunities.

Many breast tumors have elevated levels of proteases; protein-cutting enzymes that help the tumor invade tissue and spread to distant sites. Proteases can also cleave and activate growth factors that stimulate tumor growth (proliferation). Matriptase is located on the surface of the cells that form the milk ducts in the normal breast. Matriptase is often found at much higher levels in women with breast cancer than in healthy women. We recently demonstrated that matriptase acts as a so-called signaling protease i.e. it promotes breast cancer progression by cleaving, and thereby activating, an important growth factor called Hepatocyte Growth Factor (HGF) in human IBC cells lines. When active HGF binds to its receptor (c-Met) on the surface of breast cancer cells it elicits a variety of pro-cancerous signals that are involved in cancer cell growth, survival and invasion. Importantly, we found that both matriptase and c-Met are expressed in the vast majority of breast samples from patients with IBC. In this proposal we will continue to test a new drug (IN-1) targeting matriptase, which was developed by our collaborator Dr. Eric Marsault and his group. We have tested IN-1 in IBC cell culture models where it efficiently inhibits proliferation of the cancer cells. We propose to perform comprehensive testing of this very promising drug, alone and in combination with the FDA approved drug Cabozantinib which directly inhibits the activity of c-Met, in preclinical models of IBC tumors.

In addition, we propose to address a serious unmet need in current IBC research. Modeling IBC poses challenges compared to non-IBC for several reasons; 1) Only a handful of IBC derived cell lines are available to researchers and they do not generally display the characteristic erythema in the overlying skin with marked lymphatic permeation as seen in IBC; 2) In contrast to non-IBC, where more than a dozen transgenic models are available, no transgenic models of IBC currently exist. Here, we propose to establish and analyze IBC Patient Derived Xenograft (PDX) models from fresh patient tissue with the short term goal to advance testing of matriptase/c-Met targeting in IBC and generate preliminary data to assess the feasibility of establishing a multi-PI, multi-Cancer Center collaboration to build a unique “IBC Tissue Explant Biobank” with renewable, phenotypically and biologically stable PDX models that would be available to the IBC research community.



**Xia Liu, Ph.D.**

**Targeting Prometastatic Neutrophils to Inhibit Breast Cancer Metastasis**

**Snapshot**

Xia Liu, Ph.D., from Northwestern University Feinberg School of Medicine, will determine if targeting neutrophils, the most abundant immune cell in the body, can suppress breast cancer metastasis. Preliminary studies indicate that neutrophils can help the tumor spread through an enzyme called Alox5. The goal of this study is to determine if drugs that target Alox5 can stop the spread of breast cancer.

**Investigator-Submitted Abstract**

Breast cancer is the most frequent cancer among women in the United States with over 230,000 new cases and 40,000 deaths every year. Among all the types of breast cancers, triple-negative breast cancers, which are not stimulated to grow from exposure to hormones estrogen and progesterone and protein Her2, are more aggressive than other breast cancers and have fewer treatment options. Metastases, a stage of breast cancer where the tumor cells have released from the breast and travel to other organs in the body, are the cause of 90% of breast cancer deaths. Therefore, it is critical and urgent to find the effective treatment to inhibit metastasis. In our previous study, we found that tumor cells frequently interact with neutrophils which is the most abundant immune cells in our blood, during their travel in the blood to the distant organs. However, the consequence of their interaction is unknown. Based on recent studies demonstrating that neutrophils can promote metastasis, we will determine whether neutrophils promote metastasis by interacting with tumor cells in the blood, and identify the molecules mediating their interaction in both triple negative breast cancer patients and a specific preclinical model that can grow human breast cancers. After their identification, we will determine whether these molecules can be used to predict metastasis in the patients. Since anti-asthma drug Zileuton has been found can stop neutrophils from promoting metastasis by inhibiting Alox5 enzyme, we will determine whether another two natural products Hyperforin and Boswellia which have the same function as Zileuton to inhibit Alox5 enzyme, can also inhibit metastasis-promoting function of neutrophils, and the mechanisms why inhibition of this enzyme can block metastasis. At last, previous studies indicate that neutrophils have the ability to inhibit functions of T cells by expressing PD-L1 protein on their surface. Since T cells play the key role in our immune system to kill cancer cells before they form the cancer in our body, this is another explanation for metastasis-promoting function of neutrophils. The immunotherapy known as anti-PD-1 treatment has developed and generated great excitement for its ability to help T cell recognize and attack tumor cells. We will explore whether combining the PD-1 treatment (to help T cell recognize tumor cells) with Alox5 inhibitors (to stop neutrophils from inhibiting T cells function) can enhance their efficacy to block metastasis. We expect to develop more effective and less toxic treatments for metastatic breast cancer.



**Xin Lu, Ph.D.**

**Single Cell Study of Unique Leukocyte Subset Containing Metastatic Tumor Vesicles**

**Snapshot**

Xin Lu, Ph.D., from University of Notre Dame, will investigate how neutrophils, the most abundant immune cell in the body, support metastatic breast cancer (MBC). Preliminary studies indicate that neutrophils can ingest material released from tumor cells, turning them into 'bad' neutrophils that help cancer spread. The goal of this study is to determine if 'bad' neutrophils can be targeted, thus stopping MBC.

**Investigator-Submitted Abstract**

It is now well established that cancer progression and metastasis depends on the helps from non-cancerous cells in the tumor microenvironment. Among the non-cancerous cells, immune cells are often hijacked by breast cancer cells in a way that, rather than attacking cancer cells, they actually promote cancer growth and metastasis. Neutrophils are the most abundant type of immune cells in the body, and previous reports suggest both promoting and inhibiting roles of neutrophils in metastasis. The key mechanism that switches neutrophils from anti-tumor to pro-tumor cells remains poorly understood. Therefore, there is an urgent need to answer this question because, until we solve this problem, therapeutic intervention of metastatic breast cancer by targeting neutrophils will likely remain an unreachable goal.

Our approach to identify the controlling mechanism that turns "good" neutrophils into "bad" neutrophils is based on our surprising new findings. We found that, in a preclinical model of metastatic breast cancer, neutrophils in the blood and in the lung contain vesicle structures that originate from primary cancer cells. We further showed that breast cancer cells secrete a large amount of tiny extracellular vesicles, raising the possibility that neutrophils may have internalized these extracellular vesicles. Lastly, we showed that these internalized tumor vesicle (ITV)-positive neutrophils increased the number of lung metastases. Taken together, we form our hypothesis that breast cancer cells employ a previously unrecognized mechanism to promote metastasis, through inducing the formation of ITV-positive neutrophils which will modify the "soil" in the distant organs and foster the growth of metastasis.

We have designed a comprehensive series of experiments to identify the details of this process. First, we will further cauterize the ITV-positive neutrophils and elucidate the process for their formation using cell biology and genetic approaches. Second, we will perform experiments to determine whether the ITV-positive neutrophils are both necessary and sufficient to drive lung metastasis. Last, by utilizing cutting-edge single cell technologies, we will understand what molecules are transferred from cancer cells to neutrophils through ITVs, and how these molecules instigate neutrophil to create the "pre-metastatic niche".

Overall, our study has the potential to change how we view the metastatic process, and through this potentially paradigm-shifting outcome, we expect to dramatically advance our understanding of breast cancer metastasis. Our goal and indeed the significance of our study is that, by unraveling the identity and molecular mechanism of ITV-positive neutrophils in preclinical models and clinical samples, we will develop new approaches to detect these "bad" neutrophils to predict metastasis, as well as target them to treat metastasis.





**H. Kim Lyerly, M.D.**

**2018 Duke-Susan G. Komen Fundamentals and Accelerating Anticancer Agent Development and Validation (AAADV) Workshop**

**Snapshot**

Duke University supports the Accelerating Anti-Cancer Drug Development and Validation (AAADV) Workshop and the Duke/Susan G. Komen Fundamentals course for patient advocates. The goal of the Fundamentals course is to introduce patient advocates to the Federal Drug Administration's (FDA) drug development and approval process. The Fundamentals course will focus on how advocates can work more effectively with all stakeholders in the research process – industry, academia, government and technology – to ensure that the patient voice is incorporated across all conversations and decision making.



**David Mankoff, M.D., Ph.D.**

**Molecular Imaging of Breast Cancer Metabolism to Predict In Vivo Cancer Behavior**

### **Snapshot**

Komen Scholar David Mankoff, M.D., Ph.D., from University of Pennsylvania, will develop new imaging methods, based on MRI and PET imaging, to measure response to therapy. These studies focus on metastatic breast cancer and have the potential to develop new ways to measure treatment response and detecting drug resistant tumors.

### **Investigator-Submitted Abstract**

Research over the past decade has shown that cancer metabolism, specifically cancer's reliance on different biochemicals to provide energy and building blocks for growth, play an important role in breast cancer behavior. Breast cancer has numerous alterations in metabolism, for example, increased rates of glucose consumption in most cancers. Prior research has taken advantage of these alternations to develop imaging methods such as 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) to identify sites of breast cancer and to measure its response to treatment. Our prior research, which measured the quantitative rate of glucose metabolism and the flow of blood to the tumor, indicated specific patterns of glucose metabolism pre and post-therapy in breast cancer patients strongly predicted the success or failure of chemotherapy. At the same, studies performed mostly in cells and pre-clinical models showed that the metabolism of other biochemicals, especially the amino acid glutamine, play an important role in cancer growth and survival. We now plan to build on our earlier patient results and recent advances in the science of cancer metabolism and cancer metabolism imaging by creating a multi-disciplinary molecular/metabolic breast cancer imaging group at Penn. We will carry out first-in-woman PET imaging studies of glutamine metabolism and combined glutamine/glucose metabolism. We will also preliminarily investigate complementary methods using magnetic resonance to measure glutamate levels. We will validate these methods by comparing imaging results to established measures of breast cancer tumor biology and then later test the imaging methods as predictors of response to treatment, focusing on breast cancer patients with large local tumors and patients with distant metastases, where our prior results showed PET imaging measures to be most predictive. Successful completion of our research will provide: (1) new insights into the importance of breast cancer metabolism in breast cancer patients, (2) new measures to predict and evaluate the success of breast cancer treatments, and, (3) possible new avenues for overcoming resistance in breast cancers that fail to respond to initial treatment.



**Ingrid Mayer, M.D.**

**Large Scale Profiling of Triple-Negative Breast Cancer and Implications for Clinical Outcome**

**Snapshot**

Komen Scholar Ingrid Mayer, M.D., from Vanderbilt University Medical Center, will study genomic changes from surgically removed breast cancer tissue and blood samples with circulating tumor DNA, both before and after treatment. Identifying these changes will lead to factors that predict chemotherapy resistance, recurrence, and relapse-free survival.

**Investigator-Submitted Abstract**

Triple-negative breast cancers (TNBC) represent about 15% of all breast cancers but are much more commonly found in young and African-American women and are also much more aggressive (i.e. high risk of spread [metastasis] and consequent rapid death) than other breast cancer types. New treatments, beyond chemotherapy, are very much needed for TNBC. However, because TNBC are heterogeneous, finding a lead for new targeted-treatments (potentially more effective and less toxic than chemotherapy) has been challenging. Patients with TNBC that don't have a good response to their initial standard of care chemotherapy given prior to surgery (i.e. still have viable tumor in the breast or lymph nodes at the time of the surgery) are at the highest risk of metastatic recurrence (spread) of their tumor. These patients have the opportunity to participate in a large NCI-sponsored clinical trial called EA1131, in which they are randomized to receive two different kinds of chemotherapy (aplatinum agent or capecitabine) post-operatively, to see if one of them is better than the other, in reducing the risk of recurrence of their TNBC.

We propose to: 1) Collect the tumor block removed at the time of the surgery from patients participating in the EA1131 clinical trial, perform extensive gene/ molecular profiling in the tumor, to see if any of the gene alterations found in these tumors can predict which patients are at the highest risk of metastatic recurrence 2) Collect blood from patients participating in the EA1131 clinical trial before and after their trial chemotherapy administration, perform gene/molecular profiling in microscopic pieces of the tumor's genetic material that circulates in the blood (called circulating DNA or ctDNA), to see if the molecular changes in this gene material in the blood that happen over time can predict which patients are at the highest risk of recurrence Since this profiling is being done with new technologies and in large scale, we believe this broad gene/ molecular profiling of the tumor and of the serial blood collections will identify genomic alterations that are causing higher risk of metastatic recurrence, so we can do something about it. Additionally, the gene/molecular profiling findings will give us important clues about potential new targeted treatments that this group of patients that are found to still have very high risk of recurrence would be candidates for. Ultimately, this targeted early intervention could have a tremendous beneficial impact in the risk of recurrence and death from TNBC, which is our overall goal.



**Valerie McCormack, Ph.D.**

**African Breast Cancer - Disparities in Outcomes Postdoctoral Fellow**

### **Snapshot**

Valerie McCormack Ph.D., from the International Agency for Research on Cancer, will work on the African Breast Cancer – Disparities in Outcomes (ABC-DO) study. ABC-DO is the first African international study of breast cancer outcomes which examines biological, health-system, and sociocultural factors that influence a woman’s journey with breast cancer to identify the factors that contribute to poor survival in sub-Saharan Africa.

### **Investigator-Submitted Abstract**

The African Breast Cancer – Disparities in Outcomes (ABC-DO) study is the first multi-country cohort of women with breast cancer in sub-Saharan Africa. ABC-DO aims to identify sociocultural, health system and biological barriers to improve key time-stamped events along the entire journey with breast cancer, namely stage at diagnosis, treatments received and overall survival from breast cancer. Funded by the Komen Foundation in 2014, by 2018 the study has successfully recruited over 2100 women with breast cancer in public sector hospitals in Namibia, Nigeria, Uganda, Zambia and South Africa. Through mHealth study implementation and follow-up, cohort attrition is low, data completeness is high and data are rich, including on receptor status and treatment information. Given the value of ABC-DO, the co-PIs at the International Agency for Research on Cancer (IARC) and the London School of Hygiene and Tropical Medicine have applied for research grants to support cohort continuation to 5 years (current median is 2.2 years, range: 1-3.5, outcomes are due at end of 2018). The present application is a request for funding of a postdoctoral fellow (PD) to work on ABC-DO from mid-2018 for one year to continue study management and co-ordination, evaluate breast cancer treatment in the sub-Saharan African setting, and identify a specific target population for an efficient down-staging intervention.



**Donald McDonnell, Ph.D.**

**Targeting the GRHL2/AGR2/LYPD3 Axis in Breast Cancer**

### **Snapshot**

Komen Scholar Donald McDonnell, Ph.D., from Duke University, will define the roles of the proteins AGR2 and LYPD3 in breast cancer progression. Dr. McDonnell's goal is to find new therapeutic targets for patients with ER-positive breast cancers that are resistant to endocrine therapy.

### **Investigator-Submitted Abstract**

Notwithstanding the positive clinical activity of endocrine therapies, it is clear that the rapid onset of resistance to this class of drugs is an impediment to durable clinical responses in patients with estrogen receptor positive (ER+) breast cancer. Informed by recent advances in our understanding of ER pharmacology in breast cancer, it now appears that the increased activity of pathways and processes involved in tumor progression, which occurs under selective pressure of existing endocrine therapies, allows some ER-regulated processes to escape the regulatory activity of this transcription factor. Anticipating the need for new therapeutics for patients with endocrine therapy resistant breast cancers, we have begun to explore additional pathways, the targeting of which will yield drugs that may have utility as single agents, or which can be used in combination with contemporary breast cancer therapeutics. Of significance, in this regard, are our findings that have 1) identified the Ly6/PLAUR domain-containing protein 3 (LYPD3) as a protein whose expression is consistently upregulated in endocrine resistant models of breast cancer, 2) demonstrated that the expression of Anterior Gradient 2 (AGR2), a ligand of LYPD3 and a direct downstream target of ER signaling in hormone-sensitive cells, escapes regulation by ER in the setting of resistance, 3) determined that inhibition of AGR2 or LYPD3 expression quantitatively inhibits proliferation and migration in cellular models of endocrine therapy resistant breast cancer, and 4) validated that overexpression of AGR2 compromises tamoxifen efficacy in animal models of this disease. These preliminary data highlight the potential importance of the AGR2/LYPD3 axis in the progression of breast cancer. Research goals and objectives: We have access to humanized antibodies that inactivate AGR2 and LYPD3 and we will evaluate the potential utility of these neutralizing antibodies alone or in combination with other breast cancer therapeutics in validated models of breast tumor growth and metastasis. It is anticipated that positive results from such a study will facilitate near-term clinical evaluation of this treatment modality in breast cancer. Notwithstanding the potential positive actions of the available antibodies, we also propose to dissect the AGR2/LYPD3 signaling axis in breast cancer with the objective of informing approaches to maximally inhibit this pathway to achieve a clinically useful outcome in as broad a spectrum of breast cancers as possible. At the conclusion of this project we expect to have defined the mechanisms by which AGR2 and LYPD3 impact processes of pathological importance in breast cancer, identified vulnerabilities in these pathways that are amenable to therapeutic intervention, and evaluated the potential of neutralizing antibodies directed against the AGR2/LYPD3 proteins as potential breast cancer therapeutics.



**Laura Tester Meyer**

**Susan G. Komen Breast Cancer Challenge at Obesity Week 2017**

**Snapshot**

The Obesity Society supports two Susan G. Komen® Breast Cancer Challenge Awards. Junior investigators were invited to submit short proposals for research that would shed light on how obesity is associated with poorer outcomes for metastatic breast cancer patients or the role obesity plays in breast cancer disparities.



**Kathy Miller, M.D.**

**iMETX (Individualized Metabolic RX): A Pilot Study of an Environmental Intervention to Increase Energy Expenditure among Breast Cancer Survivors**

**Snapshot**

Komen Scholar Kathy Miller, M.D., from Indiana University, will evaluate the benefits of exercise for breast cancer survivors through two pilot clinical trials: iMETX and low intensity vibration (LIV). The iMETX trial will add physical tasks into the patient's daily routine and determine how this affects patients' fitness and biomarkers of disease. The LIV study will evaluate whether LIV therapy can improve muscle function and bone/muscle quality in post-menopausal women starting aromatase inhibitor therapy. These studies aim to help breast cancer patients overcome the negative effects of therapy on their muscle function.

**Investigator-Submitted Abstract**

In a previous study Dr. Miller and her team used state of the art technology to measure the impact of various treatments including surgery and radiation, anti-estrogen therapy, and chemotherapy on patient's daily activities (the amount of energy they use) and physical fitness (ability to generate muscular power) during the first year after diagnosis. We found that many patients are more debilitated at diagnosis than previously recognized. Both chemotherapy and anti-estrogen therapy have a profound effect. Within 6 months patients replaced muscle with fat leading to a significant reduction in muscle power and endurance. Spontaneous recovery was rare – in fact, many were even more debilitated at 12 months. Our data suggested that common exercise recommendations for high load resistance training and at least 150 minutes of aerobic exercise a week would be far beyond many of our patients' physical ability after therapy, leading to the soreness, injury, frustration, and early discontinuation (or failure to initiate an exercise program in the first place). Patients also told us of their struggles to fit regular exercise into their busy lives.

Working with colleagues at the Nelson Center for Environmental Science, we've developed a truly individual intervention to increase patients' physical activity. We start with a fitness assessment and monitor patients' activity for 3 weeks. After learning what they are physically capable of doing as well as how much they are moving and where they spend their time, we'll send patients individual movement prescriptions every 3 days for 12 weeks. The goal is to help patients find ways to move more within their daily lives, rather than asking them to go somewhere else to do something new. Patients will be active participants in this pilot trial, viewing their own data on the iMETX website and contributing feedback in real time. After the 12-week intervention, we'll repeat the fitness testing to measure the degree of improvement. Then we'll continue to monitor active for another 12 weeks to see if the changes in movement persist.



**Gordon Mills, M.D., Ph.D.**  
**Combinatorial Adaptive Resistance Therapy In Breast Cancer**

**Snapshot**

Komen Scholar Gordon Mills, M.D., Ph.D., from Oregon Health & Science University, will expand his work to identify and target pathways of drug resistance in triple negative breast cancer. His project is focusing on reversing resistance to drugs called PARP inhibitors. Dr. Mills hopes to identify and validate different combinations of therapies to enhance the effects of treatment and increase the number of patients that can benefit from this therapy.

**Investigator-Submitted Abstract**

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





**Taru Muranen, Ph.D.**

**Mechanisms of Stroma-Mediated Drug Resistance in ER+ Breast Cancers**

**Snapshot**

Taru Muranen, Ph.D., from Beth Israel Deaconess Medical Center, will study how the tumor environment (area surrounding the breast tumor) can cause ER+ breast cancer to become resistant to hormone therapy. Dr. Muranen will use this information to discover new ways to overcome treatment resistance in ER+ breast cancer.

**Investigator-Submitted Abstract**

The microenvironment that tumors exist in consists of the tumor cells, immune cells, and stromal cells. The stromal cells, most often fibroblasts, secrete proteins, such as collagens that create structural support that is critical for all tissues. Previous data from us and others have shown that the tumor microenvironment and the matrix proteins promote drug resistance, but the reasons for this are still relatively unknown. The research proposed here seeks key insights into what elements of the tumor microenvironment make cancer cells resistant to therapy and will aid in discovering new ways to treat ER+ breast cancers that have become resistant to standard care.

ER+ breast cancers that have become resistant to standard care, often display hyper-activation of the PI3K pathway that regulates metabolism, cell growth and proliferation. Drugs targeting the PI3K pathway are currently being evaluated in clinical trials; unfortunately, these drugs have not been very successful in eradicating the tumor cells. Our preliminary data show that the stromal cells of the tumor microenvironment, actively secrete proteins that protect ER+ breast cancer cells from PI3K-targeted therapies and promote drug resistance. These secreted proteins in turn activate survival proteins in the cancer cells, allowing the cancer cells to resist cell death. This proposal expands on these findings and will: 1) identify molecules secreted by the stromal cells in the tumor microenvironment that protect ER+ breast cancer cells from PI3K targeted therapies, and 2) reveal the molecular pathways in the tumor cells themselves that are activated in response to secreted molecules. This approach will give us detailed insight into drug resistance programs and molecules that promote drug resistance in the tumor microenvironment. More importantly, this information will allow us to target these molecules in order to stop the microenvironmental protection of cancer cells and will lead to the design of new and more effective therapies for ER+ breast cancers that have relapsed on standard therapy.



**Darran O'Connor, Ph.D.**

**BET Inhibition as a Therapeutic Strategy for ER+ Invasive Lobular Breast Cancer**

**Snapshot**

Darran O'Connor, Ph.D., from the Royal College of Surgeons in Ireland, will study how a form of ER+ breast cancer called invasive lobular carcinoma (ILC) can be made more responsive to hormone therapies. Dr. O'Connor will study how a protein called Brd3 contributes to resistance to hormone therapies in ILC, and whether drugs that target Brd3 can overcome treatment resistance.

**Investigator-Submitted Abstract**

Invasive lobular breast cancer (ILC) is a form of hormone receptor-positive (ER+) breast cancer that accounts for about 10-15% of all new breast cancer cases diagnosed. Since it is ER+, it is treated the same way as all other ER+ breast cancer, with surgery, radiotherapy, anti-hormone therapy (and in many cases, chemotherapy). However, patients with ILC do not have the same clinical course as other ER+ patients. Their cancer is more likely to (i) spread to the ovaries and digestive system, (ii) occur in both breasts, (iii) come back in the other breast (iv) be unresponsive to additional chemotherapy (as well as having the same problems with hormone therapy-resistance as other forms of ER+ breast cancer). In addition to a different clinical course, the tests used to determine treatment options for ER+ patients (such as OncotypeDx), give very different results for ILC patients, making it difficult to determine the most appropriate treatment plan. As such, the lack of tailored options for ILC patients represents an unmet clinical need and it is time we start to consider ILC as a distinct type of ER+ breast cancer and devise new treatment options specifically for these patients.

As part of a large European Commission-funded project aimed at discovering rational therapeutic options for hard-to-treat breast cancer subtypes, I discovered that ILC patients with high levels of a molecule called Brd3 had a much worse outcome than patients with low levels. I further confirmed this in another group of patients who were part of the METABRIC study, a joint Canada-UK project to accurately describe breast cancer at the molecular level. Brd3 is a member of a family called BET proteins that control many key processes in cells, including growth and survival. There are a selection of drugs that target this family now in clinical development, called BET inhibitors. I found that if I used these drugs to block the activity of Brd3, ER+ ILC cells that were resistant to anti-hormone treatment stopped growing, suggesting that this may be a rational target for the treatment of ILC patients who no longer respond to anti-hormone therapy.

However, not all ILC cells responded in the same way to the drugs. Some cells died (responsive cells), some cells survived but grew more slowly (resistant cells). We have discovered that the resistant cells survived by using a protective mechanism involving continued activity of a survival signal, which is normally switched off by BET inhibitors. Combining the BET inhibitor with a drug that targeted this survival signal successfully killed all the resistant cells. In this project, we aim to test the use of Brd targeting drugs in a pre-clinical model of ILC, as well as the combination with the drug that targets the survival signal, using sensitive and resistant ILC cell lines implanted into mice. In doing so, we will complete the final step prior to a clinical trial in ILC patients that are resistant to current therapy.



**Julie Palmer, Sc.D.**

**Family History, Genetics, and Environment: Breast Cancer Risk in U.S. Black Women**

### **Snapshot**

Komen Scholar Julie Palmer, Sc.D., from Boston University, will develop a risk prediction tool that will consider the different risk factors for ER+ and ER- breast cancer, along with age-related incidence patterns in African-American women. This tool will help identify African-American women who would benefit from earlier and more frequent screening or alternative modes of screening.

### **Investigator-Submitted Abstract**

Breast cancer mortality is 40% higher in African American (AA) women than in other U.S. women. Reasons for the disparity include a later stage at diagnosis and a higher incidence of cancers that lack hormone receptors (ER-). There is a need for better risk prediction in AA women so that those who are truly at high risk will be appropriately referred for screening, including mammography at ages below the current age guidelines and for alternative modes of screening that may be more effective at detecting ER- cancer. Existing breast cancer risk prediction tools, such as the well-known "Gail model" have been shown to underestimate risk for many AA women, which has contributed to low numbers of AA women eligible for breast cancer risk-reduction trials. Recent research has demonstrated that some risk factors differ in their associations with ER+ and ER- breast cancer. At the same time, incidence rates differ for ER+ and ER- breast cancer by race and change across age. Lack of consideration of these differences may explain why traditional risk prediction models work less well for AA women, among whom a third of breast cancers may be ER-, than for white women, among whom the great majority of tumors are ER+. We propose to develop a risk prediction tool that will take into account the differential risk factors for ER+ and ER- breast cancer, along with the differing age-incidence patterns for these two major subtypes. Model development will be based on analyses of data from three large studies of breast cancer in AA women. It will then be tested in the Black Women's Health Study, with follow-up of 59,000 women over 18 years. We will examine how well the new model predicts breast cancer in the overall study population and separately according to whether women have a mother, sister, or daughter with breast cancer. We will also take into account whether study participants carry BRCA1/2 mutations or mutations in similar genes that are strongly related to breast cancer risk. An improved breast cancer risk prediction tool for AA women will be extremely useful, especially for younger women for whom the balance of benefit and harms of mammography are widely debated. In the era of personalized medicine, cancer screening should be based on more than age and family history. This cannot happen until tools to support decision-making in all patient populations are available. The novel risk prediction model developed in our research can be used by primary care providers to identify AA women who would benefit from earlier or more frequent mammographic screening or from alternative modes of screening such as breast MRI. In addition, the new tool will be useful for enrolling AA women into risk-reduction trials and for provider/patient discussions of whether or not to take drugs to reduce breast cancer risk such as raloxifene. More effective risk prediction in AA women will lead to earlier detection and treatment and, therefore, to a reduction in death from breast cancer.



**Ann Partridge, M.D., MPH**  
**Breast Cancer In Young Women**

### **Snapshot**

Komen Scholar Ann Partridge, M.D., MPH, from Dana-Farber Cancer Institute, will identify ways to improve outcomes for young women with breast cancer. She will evaluate disease characteristics (i.e. genetics), treatment side effects, social and behavioral concerns (i.e. fertility), and survival outcomes of treatment and surgery decisions. By studying the unique issues that impact young women with breast cancer, she hopes to identify predictors of outcome and interventions that could reduce breast cancer morbidity and mortality in this vulnerable population.

### **Investigator-Submitted Abstract**

When young women are diagnosed with breast cancer, they are more likely to suffer both physically and emotionally than older women. Many prior studies have tried to evaluate the reasons for this in various groups of women, however there are rarely enough young women in any given study to learn about their unique issues. Recognizing that there are substantial limitations to the prior research, and especially given that most studies have not had enough young women with details regarding their disease, treatment, and medical and psychosocial outcomes, we started a large prospective study focused on young women with breast cancer. We have been asking women since 2006 to participate in this research in an effort to learn more about breast cancer in young women so that we can help to improve how they do in both the short and long run, both medically and emotionally. To date, we have enrolled over 1,302 women in our 12th 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, and physical characteristics in the year after treatment. As the cohort matures, we will be able to evaluate later outcomes as well as evaluate for unique tumor biology and genetics of this large cohort of young women. To our knowledge, this is the only study of its kind and successful completion of this project will uniquely advance our understanding of breast cancer in young women and leads areas to target for intervention which will lead to reductions in breast cancer morbidity and mortality in this vulnerable population.



**Jennifer Pietenpol, Ph.D.**

**Triple Negative Breast Cancer: Subtypes, Molecular Targets, And Therapeutic Approaches**

**Snapshot**

Komen Chief Scientific Advisor, Jennifer Pietenpol, Ph.D., from Vanderbilt University Medical Center, will continue to lead a clinical trial for patients with metastatic TNBC to evaluate the efficacy of cisplatin, a DNA damaging agent, and a drug called GDC-0032. The trial will develop a set of genetic biomarkers to predict sensitivity or resistance to these therapies.

**Investigator-Provided 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.



**Daniela Quail, Ph.D.**

**Impact of obesity-associated inflammation on breast cancer metastasis**

**Snapshot**

Daniela Quail, Ph.D., from McGill University, will investigate how obesity can help breast cancer spread (metastasize) to the lung. The goal of this study is to better understand how obesity supports metastasis to the lung, so that it can be stopped.

**Investigator-Submitted Abstract**

Metastasis (cancer spread) is the leading cause of breast cancer-related mortality. The ability of a tumor cell to successfully metastasize from one organ to another is influenced by inflammation within the circulation (blood). Obesity causes chronic inflammation and affects over one third of adults in the United States and Canada. Moreover, an additional third of the population is overweight, and 20% of lean people are metabolically obese (i.e. they have adverse symptoms of obesity, even though they appear thin). Due to these shocking statistics, obesity now rivals smoking as the leading preventable risk factor for cancer incidence and mortality.

In breast cancer patients, obesity more than doubles the relative risk of death from metastasis. Of particular interest is lung metastasis, given the high frequency of breast cancer progression to this site in patients, and the association between obesity and multiple lung-inflammatory conditions (e.g. asthma). Despite that a large proportion of the population is overweight/obese, the vast majority of preclinical studies use lean models to study breast cancer metastasis. This is problematic, because breast cancer might act differently in a lean person compared to an obese person. In support of this notion, using preclinical models of obesity, we recently discovered that lung tissue is drastically changed with weight gain, creating an environment that can nourish cancer cells that have spread to this organ. Importantly, we have found that 10% weight loss is sufficient to reverse this effect, leading to reduced breast cancer metastasis. These are significant findings because the lung is one of the most frequent sites of metastasis, which causes death in patients.

The objective of the proposed study is to build on these findings and provide additional insight into how overweight/obesity affects breast cancer metastasis using preclinical models and patient samples - this will inform whether a subset of patients may benefit from obesity-specific adjuvant therapies, or weight loss/dietary interventions. We hypothesize that breast cancer progresses differently in obese compared to lean individuals, and therefore, obese patients require different treatment considerations. We predict that our findings are relevant not only to obese breast cancer patients, but also to overweight and lean/metabolically obese patients. Importantly, our finding that weight loss may be sufficient to reverse the effects of obesity suggest that lifestyle interventions ought to be explored for the treatment of metastatic breast cancer.



**Amelie Ramirez, Dr.PH.**

## **Improving Adherence to Endocrine Hormonal Therapy among Breast Cancer Patients**

### **Snapshot**

Komen Scholar Amelie Ramirez, Dr.PH., the University of Texas Health Science Center at San Antonio, will develop and pilot-test a bilingual, culturally tailored, personalized, interactive mobile application, in combination with patient navigation, to promote and improve adherence to endocrine hormonal therapy among breast cancer patients. If successful, this intervention could save lives by improving endocrine therapy adherence, leading to better outcomes.

### **Investigator-Submitted Abstract**

Adjuvant endocrine hormonal therapy (EHT) is highly effective and appropriate for nearly all breast cancer patients with hormone receptor-positive tumors, which represent 75% of all breast cancer diagnoses. Long-term use of EHT reduces cancer recurrence rates and cuts the risk of death nearly in half during the second decade after diagnosis, research shows. Despite the proven benefits, about 33% of women who are prescribed EHT do not take their medication as prescribed (less than 80% take their daily dosage) and are thus at higher risk of recurrence and death.

The purpose of this education randomized controlled study is to develop and pilot-test a bilingual, culturally tailored, personalized, interactive mobile application (app) in combination with patient navigation to promote and improve adherence to endocrine hormonal therapy (EHT) among breast cancer patients. The intervention aims to empower patients' self-monitoring and management, as well as facilitate patient education, early identification and reporting of side effects, delivery of self-care advice, and timely feedback through direct interaction between the patient and the oncology team when necessary.

The theory-based intervention emphasizes the importance of increasing patient education, enhancing self-efficacy, facilitating communication with the medical team and helping patients to develop self-care skills to outcomes possible, including improvement in quality of life, overall survival, and life expectancy. We hypothesizes that: 1) patients in the mobile app and navigation intervention group will have higher rates of EHT adherence at size month that usual EHT care; and 2) intervention participants will have higher self-efficacy to identify side effects, use self-care skills, communicate with their oncology care team and adhere to EHT as prescribed than those in the usual care control group.

The proposed two-year study involved a 2-group randomized control trial with 3-time assessments (baseline, 3 and 6 months) and will enroll 120 breast cancer patients who are prescribed EHT and are attending the breast clinic and the Cancer Therapy and Research Center (CTRC), a National Cancer Institute-designated cancer center at the University of Texas Health Science Center at San Antonio. The intervention group will receive two components: 1) a bilingual culturally tailored, personalized, interactive mobile app; and 2) support from a patient navigator. The control group will receive the usual care and information provided by the CTCRC's breast clinic and pharmacy to patients undergoing oral EHT. The intervention components are based in Social Cognitive Theory and elements of Motivational Interviewing.

This innovative interactive, multi-communication intervention using a mobile app and patient navigation could reduce medical costs and improve breast cancer outcomes by reducing recurrence and improving quality of life, overall survival and life expectancy among breast cancer patients.



**Kevin Roarty, Ph.D.**

**Wnt pathway regulation of metastatic progression in TNBC**

### **Snapshot**

Kevin Roarty, Ph.D., from Baylor College of Medicine, will investigate a new potential target for the treatment of triple negative breast cancer (TNBC). Dr. Roarty will also identify how some TNBC subtypes are better at spreading (metastasizing) than others. The goal of this research is to identify new treatment options for patients diagnosed with this type of aggressive breast cancer.

### **Investigator-Submitted Abstract**

Metastasis accounts for nearly all breast cancer-related deaths. Breast cancer heterogeneity refers to the cellular complexity of a tumor at several levels. Much like a community of unique individuals with an assortment of jobs and responsibilities, cancer cells are diverse in many respects and engage in dynamic reciprocal interactions throughout tumor progression. Triple negative breast cancers (TNBCs), which lack expression of key ER, PR, and HER2 targets, exhibit substantial cellular heterogeneity, and this level of cellular complexity is thought to account for metastatic progression and treatment resistance. From a therapeutic standpoint, a key challenge remains to appropriately identify these cellular interactions within tumors and understand how they evolve and actively cooperate to drive metastatic progression. Our preliminary studies in multiple TNBC breast cancer models identified two distinct tumor cell subpopulations that exhibit characteristics of two TNBC subtypes of breast cancer, basal-like and claudin-low. We further demonstrated the importance of a cell signaling pathway known as Wnt in regulating these basal-like and claudin-low tumor cell subpopulations during breast cancer progression, as well as the transition in progression from micro- to macro-metastatic disease as tumor cells colonize the lungs. Genetically interrupting the balance of Wnt pathways changed the composition and traits of these tumor cells, through a process known as cellular plasticity, prompting a more invasive phenotype. A significant increase in the proportion of claudin-low to basal-like subpopulations within multiple tumor models also correlated with greater metastatic capability. This proposal will test the hypothesis that claudin-low and basal-like tumor cell subpopulations, regulated by Wnt signaling, cooperate in a manner that is advantageous for their dissemination and survival during metastasis. The current studies will leverage novel experimental tools and approaches to actively identify these distinct cell populations, monitor their dynamics and cooperation in real-time using sophisticated microscopy, and discover the mechanisms regulating these cell-cell interactions during dissemination and metastatic colonization. The ultimate goal of the proposed studies will be to discover novel molecular and cellular interactions facilitating the cooperation and plasticity between these cell entities and leverage these findings to render metastatic progression of TNBCs therapeutically vulnerable. Disrupting these cellular interactions by selective targeting of Wnt signaling at key stages of disease, either alone or in combination with other therapies, may block progression and reduce metastatic burden to help improve TNBC patient outcome.





**Payal Shah, M.D.**

**Biomarkers of PARPi Response and Immunogenicity in BRCA-associated MBC**

**Snapshot**

Payal Shah, M.D., from University of Pennsylvania, will test the response to PARP inhibitor treatment in combination with anti-estrogen therapy in patients with hormone positive, BRCA1/2 mutant metastatic breast cancer (MBC). The goal of this research is to identify biological markers that can predict which patients with metastatic breast cancer will benefit from immunotherapy (treatments that target the immune system) and lead to better, more specific treatment for metastatic patients with fewer side effects.

**Investigator-Submitted Abstract**

**Background:** Inherited BRCA1/2 gene mutations cause DNA repair defects, predisposing carriers to breast cancer (BC). Two treatment strategies in patients with BRCA mutation-associated (BRCAm+) metastatic BC (MBC) are: (1) Poly-ADP ribose polymerase inhibitors (PARPi), which further damage DNA, and (2) immunotherapy, which may have activity in BRCAm+ tumors that accumulate more mutations. The oral PARPi olaparib (O) was shown to be more effective with fewer side effects than chemotherapy in patients with BRCAm+ MBC, though the effect was less pronounced in patients with hormone receptor-positive (HR+) MBC. Features indicating that a tumor will respond to PARPi (aka PARPi biomarkers) include loss of the normal second copy of the BRCA1/2 gene resulting in 2 of 2 copies of the gene being altered (gene-specific loss of heterozygosity, LOH); the degree of DNA repair deficiency, called homologous recombination deficiency (HRD), and a characteristic BRCA-like pattern of mutations in the tumor ("mutational signature"). Immunotherapy studies in BRCA carriers are ongoing, and potential biomarkers are still being discovered. Recent data from our group suggest an inverse correlation between responsiveness to PARPi and responsiveness to immunotherapy in BRCAm+ BC. **Hypothesis:** We hypothesize that in patients with tumors that keep a normal BRCA1/2 gene copy ("LOH-absent"), PARPi will be less effective. We furthermore hypothesize that these patients' LOH-absent tumors will show features suggesting that immunotherapy would be effective. **Methods:** We will conduct phase I and II trials of O with an anti-estrogen-based combination of palbociclib (P) and fulvestrant (F) in patients with BRCAm+ MBC. We selected this combination of treatments to improve upon the effect of O alone in HR+ BRCAm+ MBC by also targeting hormone signaling. We will perform laboratory assays in pre-treatment tumor biopsies from these patients to achieve our objectives. **Objectives:** (1) evaluate the side effect profiles and effectiveness of O, P and F in phase I/II trials in patients with BRCAm+, HR+ MBC; (2) correlate potential PARPi biomarkers (gene-specific LOH, HRD scores, mutational signatures) in pre-treatment tumor samples with treatment response; (3) To characterize features of immunotherapy responsiveness in BRCAm+, HR+, MBC by measuring a) the quantity and functioning of CD8+ T-cells ("killer" immune cells) in the tumor; b) the amount of accumulated mutations in the tumor, c) patient- and tumor-specific proteins recognizable by the immune system ("neoantigens"), and other genomic tests. **Impact:** To our knowledge, this will be the first study looking at these potential predictors of PARPi response alongside a clinical trial treating patients with BRCAm+ MBC with a PARPi. This work will also describe how responsive to immunotherapy BRCAm+ MBC tumors are overall and in relation to their sensitivity to PARPi, which may yield broader insights into the immunotherapy responsiveness of non-BRCAm+ breast cancers as well.



**Sohrab Shah, Ph.D.**

**Exploiting New Patterns of Genome Damage in TNBC**

**Snapshot**

Komen Scholar Sohrab Shah, Ph.D., from Memorial Sloan Kettering Cancer Center, will to apply cutting-edge genomics and analytics to improve our understanding of triple negative breast cancer (TNBC). Dr. Shah will combine the latest genetic sequencing technology with advanced data analysis tools to identify new sub-groups of the disease that will help determine which TNBC patients can benefit from specific therapies.

**Investigator-Submitted Abstract**

We will study how mutations in the DNA of cancer cells of the most lethal form of breast cancer, triple negative breast cancer, can be used to discover new groups of patients. We will use state-of-the-art DNA sequencing technologies to measure the DNA of individual cancer cells and therefore create an ultra-detailed picture of how these cancers are changing over time. We hope these detailed views will reveal previously unseen patterns of DNA mutations in triple negative breast cancers, thereby providing new directions to pursue treatment approaches. We predict our study will shed light on how and why triple negative breast cancer patients often suffer treatment failure. We will identify new clues on how to arrive at more successful outcomes for this at-risk group of patients.



**Michael Stewart**

**AACR: 2017 San Antonio Breast Cancer Symposium (SABCS)**

**Snapshot**

The American Association for Cancer Research supports programs at the San Antonio Breast Cancer Symposium (SABCS) where scientists and clinicians discuss the latest advances in breast cancer research, treatment, and health disparities as well as being recognized for their accomplishments by their peers. Scientific meetings like SABCS offer investigators networking opportunities and stimulate collaborative interdisciplinary interactions and partnerships among the leaders of the scientific and patient advocacy communities worldwide.



**Anna Storniolo, M.D.**

**Susan G. Komen Tissue Bank at the IU Simon Cancer Center - Infrastructure Support**

### **Snapshot**

Indiana University (IU) will support the Susan G. Komen Tissue Bank (KTB) at the IU Simon Cancer Center, the world's only biorepository of normal breast tissue. This grant supports the collection and storage of whole blood, DNA, serum, plasma, and healthy breast tissue from women not known to have breast cancer, as well as the distribution of the samples to researchers worldwide. The availability of such normal tissue has the potential to revolutionize the understanding of changes that happen in a normal breast and how these molecular mechanisms are altered in the malignant process

### **Investigator-Submitted Abstract**

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

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



**Joe Taube, Ph.D.**

**Intrinsic Epigenomic Regulation of Metastatic Outgrowth in ER-Positive Cancers**

**Snapshot**

Joe Taube, Ph.D., from Baylor University, will identify the changes that occur within breast cancer cells that allow them to travel throughout the body and form new tumors in other organs. Dr. Taube seeks to learn how breast cancer cells change as they travel through the body. Once the tumor cells arrive at a new organ site, these cells once again change to be able to grow in the new site forming metastases. A better understanding of this process should reveal new targets to stop metastasis and improve patient outcomes.

**Investigator-Submitted Abstract**

Metastasis is the major cause of death for patients with breast cancer. Primary tumors shed cells into circulation, yet many cells will not survive. Further still, many tumor cells will lodge in other organs and fail to grow. Nevertheless, it is the rare "successful" metastatic cells which must be targeted to improve patient outcome.

While the precise features of metastasis-initiating cells have been difficult to determine, a new model that emphasizes the cellular plasticity between epithelial (strong cell-cell adhesion, low motility) and mesenchymal (low cell-cell adhesion, high motility) states as indicative of metastatic competence has increasing support. Conversions between epithelial and mesenchymal states occur through a cellular program known as the epithelial-mesenchymal transition (EMT) and its reversal, the mesenchymal-epithelial transition (MET). In this model, activation of EMT in the primary tumor leads to migratory and invasive properties needed to disseminate from the primary tumor, survive in circulation and seed micrometastases. Then, in the metastatic microenvironment, these disseminated tumor cells undergo MET, possibly within the first two-three cell divisions, to acquire the proliferative phenotype necessary for metastatic outgrowth. Thus, the intrinsic cellular plasticity that governs the interconversion between epithelial and mesenchymal phenotypes is likely to be a major factor driving the formation of proliferative metastases. Furthermore, for a cell to oscillate through EMT states, a change in gene expression programs must occur. For instance, we recently showed that cycling between EMT and MET in mammary epithelial cells induces extensive but reversible epigenetic reprogramming at key proliferation-regulating genes.

Thus, we propose to test the hypothesis metastasis-seeding cells must pass through an epigenetically controlled barrier to lose their EMT-conferred, metastasis-initiating properties, undergo partial MET, re-differentiate and activate the cell cycle. By engaging in close collaboration and mentorship with fellow investigators and patient advocates at the beginning of my independent research faculty career, I anticipate making advances in both the basic understanding of how metastasis outgrowth occurs as well as discovering novel strategies to target metastatic proliferation. Together, we will improve treatment options for patients with existing metastatic breast cancer and for patients at risk for developing metastatic breast cancer.



**Melinda Telli, M.D.**  
**Optimizing Therapy of TNBC**

**Snapshot**

Komen Scholar Melinda Telli, M.D., from Stanford University, will support a clinical trial that will evaluate changes in the immune system in response to therapy in triple negative breast cancer. This will further develop a novel therapy, called Tavo-EP, which may enhance the patient's immune system and improve responses to current immunotherapy.

**Investigator-Submitted Abstract**

Emerging data suggest that some patients with triple-negative breast cancer (TNBC) could benefit from the addition of immune-based therapy. Importantly, the presence or absence of the body's immune cells around a tumor has been shown to influence how likely that tumor is to respond to both chemotherapy and immunotherapy. Efforts to fully characterize the types and location of immune cells in TNBCs are critically important to gain a better understanding of how the body's immune response to the tumor influences response to both standard chemotherapy and immunotherapy in TNBC. One way that cancers can mask themselves from the immune system is by producing large amounts of a protein called PD-L1. When PD-L1 binds to a protein called PD-1 on immune cells, it essentially turns that immune cell off. Antibody drugs targeting PD-1 (pembrolizumab, nivolumab) or PD-L1 (atezolizumab, avelumab, durvalumab) have in recent years garnered FDA approvals for the treatment of multiple malignancies. As yet, none of these drugs have been FDA approved in breast cancer. To date in metastatic TNBC, responses to these drugs have been very modest and appear to require an immunologically "hot" tumor to be effective. "Hot" tumors are infiltrated with many immune cells while "cold" tumors are not. Given that many TNBC tumors are immunologically "cold", efforts to enhance the body's immune response against the tumor are of major clinical interest.

This study will assess a new gene therapy approach that is directly injected into tumors and forces expression of an inflammatory molecule IL-12 that can convert "cold" tumors into highly inflamed immunologically "hot" lesions while demonstrating a high safety profile. Recent exciting data assessing a combination of this intratumoral plasmid IL-12 plus the PD-1 blocker pembrolizumab reported a high response rate in advanced melanoma patients with immunologically "cold" tumors predicted to not respond to pembrolizumab alone. These data support the mechanism of action of IL-12 as an immune sensitizer and provide the rationale to investigate this combined approach in advanced TNBC. The hypothesis of this study is that biomarkers of anti-tumor immunity correlate with response to platinum-based therapy in TNBC patients treated in the pre-operative setting. Further hypotheses are that anti-tumor immunity is diminished in the previously treated metastatic TNBC setting and that the anti-tumor immune response can be bolstered by the intratumoral injection of plasmid IL-12. In addition, we hypothesize that the combination of plasmid IL-12 and the PD-1 blocking antibody pembrolizumab can improve upon historical rates of response to PD-1 blockers in patients with previously treated metastatic or recurrent TNBC. If successful, this research will provide important evidence that will lead to a novel intratumoral therapy strategy to augment response to PD-1/PD-L1 blockade in advanced TNBC. Further, this strategy has great potential for ultimate expansion to the curable TNBC setting.



**Amit Tiwari, Ph.D.**

**Targeting Anthracycline Resistance as a Novel Strategy to Treat TNBC**

**Snapshot**

Amit Tiwari, Ph.D., from University of Toledo, will investigate how Drp1, a protein found at high levels in chemotherapy-resistant triple negative breast cancer (TNBC), helps cancer cells survive. Dr. Tiwari has discovered a new class of drugs that target Drp1 and will determine if these drugs can be used to overcome treatment resistance in TNBC and improve patient survival.

**Investigator-Submitted Abstract**

Triple negative breast cancer (TNBC) is the most aggressive and lethal form of breast cancer, resulting in one-fourth of all breast cancer deaths. Chemotherapeutic regimens, particularly those containing anthracyclines (drugs like doxorubicin (Adriamycin) or epirubicin (Ellence)), are the mainstay of TNBC therapy. Anthracyclines are highly effective because they are excellent at killing rapidly dividing TNBC cancer cells, not only by damaging their DNA, but also inducing a cellular suicide or death program, known as apoptosis. During the course of treatment, however, many patients stop responding to anthracycline-based therapy. In addition, these patients also stop responding to all of the currently used therapies in the clinic (such as taxanes, cyclophosphamide, and targeted therapies) that are aimed to produce apoptosis in TNBC cells. This situation is often referred to as multi-drug resistance (MDR). In patients with MDR, the tumor comes back in a more aggressive form and quickly spreads to other parts of body, a process known as metastasis, resulting in patient survival of less than one year. Increasing the anthracycline dose is not an acceptable option as this will increase the risk of adverse effects or even cardiotoxicity (e.g. damage to the heart) related deaths. Understanding what produces anthracycline resistance in TNBC and exploring new opportunities to treat TNBC resistance can save and extend the lives of many TNBC patients. The overall impact of this project is based on the idea that it may be possible to kill apoptosis-resistant TNBC cells with new compounds that induce a unique non-apoptotic form of cell death that is not triggered or activated by DNA damage. In our efforts to overcome anthracycline resistance, we have discovered a new class of compounds that induce a non-apoptotic cell death in anthracycline - resistant TNBC cells. We found that these novel agents can overcome anthracycline resistance by specifically inhibiting a mitochondrial (organelle in the cells that produces energy) protein known as dynamin related protein-1 (Drp1). Drp1 was found to be expressed in high amounts in TNBC cells and even in greater amounts in those that are treated with anthracycline therapy. The proposed study will help to a) establish the role of Drp1 in TNBC resistance and determine the extent to which Drp1 contributes to overall survival of TNBC patients; b) revolutionize treatment with the most promising, safe and effective, non-apoptotic class of molecules to overcome anthracycline resistance in TNBC patients and prolong their survival; c) launch an early stage, promising breast cancer researcher to an independent research career who has an ultimate goal of ending TNBC resistance, incidence and mortality within the next decade.



**Rebecca Watters, Ph.D.**

**Identification and Targeting of Clinically Actionable Genes in Bone Metastases**

**Snapshot**

Rebecca Watters, Ph.D., from University of Pittsburgh, will identify and test new drugs to target breast cancer cells that have spread (or metastasized) to the bone. In preliminary studies, Dr. Watters identified genes that may contribute to the growth and spread of bone metastases. The goal of this study is to determine if drugs targeting these genes would be an effective treatment for patients with bone metastases.

**Investigator-Submitted Abstract**

Currently, ~3.1 million Americans are living with breast cancer and ~30% of these patients will go on to develop stage IV metastatic disease. Bone metastases occur in 65-80% of this metastatic group, specifically those with estrogen receptor (ER) positive tumors, thus representing a significant proportion of breast cancer patients. Bone metastases result in increased morbidity and pain due to bone fractures and nerve compression. Current standard of care involves surgery for fractures and treatment to block osteoclasts, which are cells that break down bone. Hormonal therapy targeting ER will stop tumor growth, but can also lead to increased bone loss, resulting in fractures and patients developing endocrine therapy resistance after 5 years of treatment. These measures cannot prevent new bone metastases from forming and may cause undesirable side effects such as mood swings, fatigue syndrome, and chronic pain. There is an obvious unmet need for new therapeutic targets to treat breast cancer related bone metastasis. Our goal is to identify and validate new therapeutics to target breast cancer bone metastasis. My previous research involved sequencing pairs of patient primary ER-positive breast tumors and bone metastases to identify altered genes in breast cancer cells that occurred after metastatic growth in the bone. Analysis revealed increased levels of EPHA3, PTPRD, PTCH1, and PDGFRA genes, whose actions can be targeted pharmacologically, deeming them "clinically actionable." These elevated genes were seen in long-term endocrine-deprived cases that had developed resistance to therapy, but were absent in newly diagnosed bone metastasis cases where patients had never received treatment (de novo). These genes have been associated with growth and progression of cancer. We hypothesize that targeting these clinical actionable genes will provide a novel approach to targeting bone metastases in patients that have developed endocrine resistance. To test this hypothesis, we will validate if this gene set has elevated expressed in an independent group of bone metastases from breast cancer patients. These genes will be targeted in ER positive and long-term estrogen deprived/resistant cell lines via CRISPR genome editing and approved pharmacological drugs in unique pre-clinical models involving an engineered bone device and mice implanted with tumors derived from patient bone metastases for potential expedited translation to the clinic. This study is crucial, since stage IV breast cancer therapy shifts from curative to palliative, as it is a rare exception based on current science, that a patient with distant disease can be cured of breast cancer. The impact of our study is significant as we aim to identify novel therapeutics to treat patients living with bone metastases, thus resulting in a decrease of deaths, since these patients account for the majority of ~40,000 individuals in the US that die each year due to breast cancer.





**Danny Welch, Ph.D.**

**Regulation Of Metastasis By Mitochondrial DNA**

**Snapshot**

Komen Scholar Danny Welch, Ph.D., from the University of Kansas Medical Center, will continue to study the role of genes that suppress the ability of breast cancer cells to survive in other parts of the body, a key step in metastasis. By understanding why and how metastasis happens, new targets can be identified for therapy and guide treatment decisions.

**Investigator-Provided Abstract**

More than 90% of cancer related morbidity (the complications associated with cancer, such as pain, weight loss, bleeding, impairment of normal organ function) and mortality (death) are directly attributable to the spread of cancer to nearby or distant secondary sites within the body. Cancer spread and colonization is termed metastasis. The proposed research is designed to answer three fundamental questions and is organized into three projects. Project #1 asks the question: Why do metastases develop in some people, but not others, with otherwise equivalent risk factors? Some people develop cancer while others – with the same behaviors and risk factors – do not. Like-wise some patients develop metastases while others do not despite being apparently equivalent. For example, African-American patients with breast cancer or prostate cancer frequently develop more aggressive disease than their Caucasian counterparts. While Project #1 is the primary focus but since there are long intervals between experiments for Project #1, two additional very focused projects will continue as time permits. All three projects still address the questions above. Project #2. The KISS1 metastasis suppressor gene, discovered by us, encodes a polypeptide precursor that can be processed into smaller peptides (kisspeptins) which have roles in cancer metastasis, pregnancy, and puberty. KISS1 dramatically reduces metastasis when re-expressed in pre-clinical models. While the precise molecular mechanisms governing KISS1 function are not yet known, we have observed that KISS1 renders cells that have already departed the primary tumor incapable of dividing in other tissues. This property portends well for KISS1 as a therapeutic, since most tumors have been shedding cells for many months to years by the time they are diagnosed. Recently, we have found that KISS1 controls mitochondrial reproduction. We propose to begin dissecting the mechanisms by which KISS1 regulates those processes. Project #3 explores the mechanisms underlying the function of Breast cancer metastasis suppressor 1 (BRMS1). BRMS1 is produced in a wide variety of normal human and pre-clinical tissues and the protein is typically found predominately in the nucleus where it associates with machinery that regulates gene expression. Recent data suggest an alternative mechanism of action – regulation by cellular machinery that controls cell division. We will: (1) determine BRMS1 interactors using yeast two-hybrid screening and co-immunoprecipitation; and (2) use alanine scanning site-directed mutagenesis to mutate a domain we previously identified as essential for metastasis suppression.



**Antonio Wolff, M.D.**

**Involving Family to Improve Communication in Breast Cancer Care (Sharing in Care)**

**Snapshot**

Komen Scholar Antonio Wolff, M.D., from Johns Hopkins University School of Medicine, will continue to run a pilot clinical trial aimed at improving communications between patients, caregivers and doctors in an outpatient setting. The study will determine if improved communication leads to better management of the patient's care and better quality of life.

**Investigator-Submitted Abstract**

Breast cancer is the most common cancer among survivors in the US and is second only to lung cancer in contributing to cancer death among women. Most breast cancer patients receive help from family in making complex decisions about treatment, handling logistically demanding care coordination, and managing symptoms and side effects. Although family members (as defined by each patient) play a vital role in cancer care, they are not formally recognized or assessed in care delivery, and their need for information and support is typically unmet. Lack of attention to family in care delivery is an important gap that too often leaves families without adequate information about patient health and treatments. This may prevent families and patients from engaging in open conversations, cause them unnecessary anxiety, and negatively affect the quality of cancer care and delivery. Communication is particularly important in cancer care, as the optimal course of action is determined through longitudinal discussion of prognosis, treatments, and patient goals, preferences, and concerns. Strategies to improve communication for serious illnesses such as cancer have been developed, but typically target a specific decision, conversation, or setting, most often the inpatient hospital. There is growing agreement that communication among patients, families, and providers should be initiated early and continue throughout the disease trajectory. However, little is known about how to provide both patients and families with access to timely information about patient health and mechanisms to communicate directly with health care providers, as proposed in this study.

The goal of this study is to test a multicomponent intervention to strengthen communication and longitudinal partnerships among women with breast cancer and their family members. Recent work by the study team demonstrated the feasibility, acceptability, and benefit of intervention components which will be combined into a single model of care. Our preliminary studies indicate that clarifying patient and family expectations regarding the role of family and providing family with timely and comprehensive information about patient health (as desired by the patient) leads to more effective family involvement, more frequent patient-family-provider interactions, more patient-centered communication, and greater preparedness to manage care.

This two-part prospective study will evaluate the feasibility of delivering a multicomponent communication intervention in the outpatient setting comprising: (1) a patient-family agenda-setting checklist completed immediately before a regularly scheduled oncology visit, (2) facilitated registration for the patient portal (for patient and family member, as desired by the patient), and (3) access to doctor's electronic visit notes. In Aim 1 we will enroll 60 patients who are in active treatment for breast cancer and focus on patients who typically attend oncology visits with a family member or trusted friend as they are already present and involved in communication. We will compare study outcomes of patients and family members who are in the intervention group and receive the multicomponent communication intervention (n=30) with patients and family members who are in the control group and receive usual oncology care (n=30). We are asking whether intervention group patients and families have higher quality communication with oncology providers, a better understanding of patient's cancer, are more confident in managing patient's care and are more satisfied with cancer care than control group patients and families after 3 months follow-up. We will also examine symptoms of anxiety.



**Antonio Wolff, M.D.**

**The Translational Breast Cancer Research Consortium**

### **Snapshot**

The Translational Breast Cancer Research Consortium (TBCRC) is a collaboration of 19 of the top U.S. academic medical centers administered out of Johns Hopkins University. TBCRC develops and conducts innovative, high-impact, biologically-driven translational research projects and clinical trials investigating new treatment approaches for breast cancer. Led by Komen Scholar, Antonio Wolff, M.D., the TBCRC has developed 50 clinical trials, about half of which have focused on metastatic breast cancer, drug resistance and/or recurrence since 2006.

### **Investigator-Submitted 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 nineteen 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. To date, fifty trials have been designed, 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.



**Tsu-Yin Wu, Ph.D.**

**Evidence-Based Sustainable Strategies for Early Diagnosis of Breast Cancer in China**

**Snapshot**

Tsu-Yin Wu, Ph.D. RN, FAAN, from the University of Michigan, Lansing, will deploy the Evidence-Based Sustainable Strategies for Early Diagnosis of Breast Cancer in China research study. This study will determine whether an educational intervention can increase the number of women that are screened through public programs and reduce the breast cancer stage at diagnosis, leading to improved outcomes. The study builds on Komen's previous work in China, and aims to educate patients, train primary health care providers, and improve outcomes in breast cancer patients through timely diagnosis.

**Investigator-Submitted Abstract**

There is currently limited research devoted to breast cancer education and early detection in low-income countries (LMICs). The lack of evidence on the interventions to improve education and early detection have hindered the development of cancer control policies and actions in LMICs, including China. The goal of the current study is to reduce the incidence of late diagnosis in primary breast cancer cases and improve quality of life (QOL) for women in China affected by this disease. In particular, to improve the rates for early diagnosis of breast cancer of women with symptomatic lesions leading to prompt and effective treatment. The study showed that QOL of patients with early stage breast cancer is better than those at late stage. As results, early diagnosis and treatment can improve QOL of breast cancer patients.

Findings from the current study will establish contextually relevant empirical support on the efficacy of well-planned evidence-based intervention in improving breast cancer outcomes. The study will provide critical information for planning effective cancer control programs, providing guidance and support in implementation of future screening programs that integrate health systems in an equitable and sustainable way.



**Xiaoqing Wu, Ph.D.**

## **Chemo-Sensitization of Triple Negative Breast Cancer by Targeting HuR**

### **Snapshot**

Xiaoqing Wu, Ph.D., from The University of Kansas Center for Research, will study a protein, HuR, which may contribute to chemotherapy resistance in triple negative breast cancer (TNBC). HuR is found at high levels in TNBC and is believed to help it grow and spread. Dr. Wu will investigate how targeting HuR could overcome TNBC resistance to chemotherapy, and thus become a new treatment target for this aggressive cancer type.

### **Investigator-Submitted Abstract**

Significant advances have been made in preventing, diagnosing and treating breast cancer. Yet, over 40,000 people die annually from breast cancer. Breast cancer, especially triple negative breast cancer (TNBC), has a high recurrence rate. Approximately, 34% patients with TNBC experience early distant recurrence (averaging 2.6 years after diagnosis); compared to all other breast cancer subtypes which have a distant recurrence rate of 20% (averaging 5 years after diagnosis). Most current chemotherapies for TNBC work by stimulating cell death. None stop tumor promoting proteins (oncoproteins) driving tumor cell proliferation.

A key factor in cancer's recurrence is resistance to chemotherapy. This is largely due to the overexpression of the various tumor-driving oncoproteins. Efforts to design and develop new therapies to improve the survival and quality of life of TNBC patients must include strategies targeting those oncoproteins fueling TNBC cell growth and resistance. Hu antigen R (HuR) is an oncoprotein abundant in breast and many other cancers. Our preliminary data show that a TNBC cell line with reduced HuR levels shows delayed cancer development and growth in preclinical models. Data from our lab also shows the same cell line without HuR is unable to form tumors in these models. HuR is a Ribonucleic acid (RNA) binding protein that helps Messenger RNA (mRNA) deliver genetic information to known "oncogenes" to stimulate cancer's growth and spread. Additionally, chemotherapy (like docetaxel) increases cytosolic HuR in cancer cells and subsequently the targeted oncogenes. As a result, TNBC cells tend to become resistant to chemotherapy. These findings support researching HuR as a promising target for treating TNBC, especially for overcoming TNBC's chemo-resistance.

We hypothesize that small molecule inhibitors blocking this HuR-mRNA interaction will weaken the HuR tumor-promoting function by breaking down and reducing translation ability of target genes critical for TNBC's progression and chemo-resistance. Our top HuR-inhibitor (KH-3) inhibits a TNBC cell line's growth in vitro (cells in lab dishes) and in vivo (cells in mice). It also increases the effectiveness of docetaxel treatment in this cell line; even after this cell line becomes resistant to docetaxel. The goals of this proposal are to further explore HuR as a potential target for therapy to overcome chemo-resistance in TNBC; and to validate KH-3 as a potential, new drug agent to sensitize TNBCs (with high HuR) to chemotherapy. In this study, we will examine the anti-cancer activities of KH-3 in combination with docetaxel or doxorubicin in other TNBC cell lines and pre-clinical models. We will also use state-of-the-art technologies to better identify and understand how and why this combined treatment works. If successful, TNBC patients with HuR overexpression could ultimately have a targeted therapy to overcome TNBC chemo-resistance and possibly stop recurrence.