

Year	Grant Recipient	Research Institute	Abstracts
2007	Chatterjee, Samit PhD	Cold Spring Harbor Laboratory	Dr. Chatterjee, a Molecular Cell Biologist, studied the molecular determinants of cellular polarity. It is thought that dysregulation in cell polarity may be a preamble to formation of early epithelial breast malignancies. This proposal was executed at Cold Spring Harbor.
2007	Oliver, Aundra MD	Dana-Farber Cancer Institute	Dr. Oliver studied molecular pathways conferring Tamoxifen and Herceptin resistance to metastatic cells.
2007	Mayer, Erica MD, MPH	Dana-Farber Cancer Institute	Dr. Mayer studied the vascular injury and hypertensive liabilities of Avastin which limit its therapeutic potential. Understanding this problem could improve treatment regimes and ultimately outcomes as well.
2007	Lee, Donjoo PhD	Memorial Sloan Kettering	Dr. Lee, a Clinical Research Oncologist at the Memorial Sloan-Kettering Institute, developed a chemical synthesis of the potent novel carbohydrate-based glycopeptides anticancer vaccine candidate that will be evaluated for immunogenicity against a variety of human cancer.
2008	Choudhury, Sibgat PhD.	Dana-Farber Cancer Institute	Dr. Choudhury looked at putative mammary precursor cells that are resistant in breast tissue. Such cells were hoped to provide clues as to the progression of breast cancer.
2008	Fertuck, Kirsten PhD	Dana-Farber Cancer Institute	Dr. Fertuck is a cell biologist studying estrogen receptor signaling in a premier laboratory guided by Myles Brown. Estrogen has a well documented but only partially understood role in etiology of breast cancer even though the activity of several successful drugs are modeled on this important hormone. Dr. Fertuck's project was designed to provide a more precise picture of how estrogen interacts with the breast cancer genome thereby to improved chemotherapies and treatment regimes.
2008	Irie, Hanna Y MD, PhD.	Mount Sinai School of Medicine	Dr. Irie, a cell biologist, investigated the basis of the resistance of cancer cells to undergo programmed cell death. She sought to understand why certain genes render cancer cells immortal and difficult to eradicate.
2009	Bialucha, Carl Uli PhD	Cold Spring Harbor Laboratory	Dr. Bialucha has developed a sophisticated technology that can correctly identify the specific gene deletions that drive breast cancer. Results from these studies could lead to a new generation of therapies and diagnostic tools.
2009	Kutuk, Ozgur MD, PhD	Dana-Farber Cancer Institute	Resistance to chemotherapy is a major problem in the fight against breast cancer. Dr. Kutuk's research involved exploring the pathways of cell death activated by chemotherapeutics in breast cancer cells and the regulation of these pathways by Bcl-2 proteins.

2009	Bailey, Shannon T. MD	Dana-Farber Cancer Institute	Dr. Bailey's research focuses on how the estrogen receptor influences the cell death process.
2009	Zhang, Qing PhD	Dana-Farber Cancer Institute	Normal cells have a remarkable ability to sense oxygen and nutrients in their environment and to respond. Cancer cells possess the same machinery but respond in an unhealthy metastatic manner. Dr Zhang studied one such oxygen sensing system in breast cancer cells that is believed to provoke tumors to grow in an uncontrolled fashion.
2010	Zhou, Penghui MD	Dana-Farber Cancer Institute	It has always been a mystery as to why a person's own immune system doesn't fight off tumors as it does infections. In fact, the immune system's major weapon, the T-cell, does attack tumors, but it quickly gets deactivated in the tumor environment. Dr. Zhou dedicated his research to understanding why this occurs with the hopes of learning enough about this process to overcome it.
2010	Kochupurakkil, Bose PhD	Dana-Farber Cancer Institute	Specific aims of Dr. Kochupurakkil's proposed work were to determine the sub-type specificity of activated NF-kB in tumor samples; analyze the phenotype of mammary epithelial cells expressing constitutively active mutant of NF-kB and screen for drugs that will inhibit cell transformation; and determine the activation status of NF-kB in a large set of breast cancer cell lines and derive a gene expression signature for constitutively active NF-kB.
2010	Gajria, Devika, MD	Memorial Sloan Kettering	One of the great frustrations in treating breast cancer results from some patients being resistant to therapies that work successfully in others. Dr. Gajria believes that such resistance can be overcome by combining two novel clinical drugs whose activities could synergize and provide enough potency to overcome such resistance. Dr. Gajria will first find the most appropriate dosing regimen to administer this combination and then study it in breast cancer patients whose disease cannot be cured with other drugs.
2010	Kass, Elizabeth MD	Memorial Sloan Kettering	It would be of great value to understand how breast cancer develops. The research of Dr. Kass probed breast cancer tumorigenesis. Events that occur during the earliest stages of mammary development are believed to alter the lifetime risk of breast cancer. Her research seeks to elucidate how specific developmental changes in mammary epithelium affect the molecular mechanisms by which cells respond to DNA damage and potentially prevent tumor formation.

2011	Li, Yang PhD	Dana-Farber Cancer Institute	A major problem that plagues breast cancer therapy is the resistance that some patients have to drugs that can treat this disease. Dr. Li has discovered that patients with high levels of Lysosomal-associated protein transmembrane-4beta (LAPTM4B) are the very patients for whom chemotherapy is unsuccessful. This work alone is valuable in itself because it could be used to predict which patients will benefit from drug treatments and those who won't. Dr. Li advanced this by studying what mechanistic role LAPTM4B is playing in the process. He believes that LAPTM4B enables tumor cells to eliminate naturally existing cell death triggers, thereby allowing the tumor to continue to grow.
2011	Gucalp, Ayca MD	Memorial Sloan Kettering	Estrogen receptor and progesterone receptor negative breast cancer is known as "Triple Negative Breast Cancer" (TNBC). TNBC represents 15% of all breast cancers but accounts for a higher proportion of breast cancer related mortality each year. Interestingly, the androgen receptor has also been implicated in breast cancer as it is expressed in 60 – 80% of primary breast tumors. Dr. Gucalp believes that the androgen receptor plays a role in TNBC based on earlier work done at Memorial Sloan-Kettering that showed that an androgen receptor blocker can halt cell proliferation in TNBC cells. She is therefore proposing to do a small clinical trial using an experimental androgen antagonist, ARN-509, in patients with TNBC. She has the approval of Memorial Sloan-Kettering to do this small trial and the results may be available within 2 years. A positive finding would be wonderful for TNBC patients and will result in great publicity for the TBBCF.
2011	Walczak, Maciej MD	Memorial Sloan Kettering	A major challenge in fighting breast cancer is trying to block cancer cell metastasis – the process where cancer cells travel and proliferate into other organs. Japanese scientists have previously isolated a compound called "migrastatin" which is able to inhibit metastasis in vitro. Unfortunately, migrastatin has only modest efficacy and does not have the necessary properties to be a drug. Dr. Walczak synthesized and evaluated novel derivatives of migrastatin which should fix the problems of the parent compound and yield novel agents to prevent breast cancer metastasis.
2012	Brastianos, Pricilla MD	Dana-Farber Cancer Institute	Dr. Brastianos studied the unique gene mutations that lead to brain metastases which occur in breast cancer patients. Brain metastases occur in up to 30% of patients with metastatic breast cancer. Survival continues to be dismal and ranges from 3 months to 23 months after the diagnosis of a metastasis in the central nervous system. Using a rapid and robust technique called whole-exome sequencing; Dr. Brastianos looked to identify the genes that direct metastases to the brain thereby opening new avenues to both predict and to treat this currently terminal condition.
2012	Diab, Adi MD	Memorial Sloan Kettering	Dr. Diab evaluated the safety of two strategies called "cryoablation" and "immune therapy" in early stage breast cancer patients. "Cryoablation" is a procedure in which very cold temperatures are applied to kill the cancer cells. The killed cancer cells can be recognized by a person's immune system. The "immune therapy" in Dr. Diab's study is an FDA approved antibody drug called ipilimumab. It is believed that this combination could provide a new approach for treating breast cancer.

2012	Jhaveri, Komal, MD	NYU School of Medicine	Dr. Jhaveri is evaluating the effect of a potent class of drugs called HSP90 inhibitors in combination with the established standard-of-care therapy, Paclitaxel and Herceptin in patients with metastatic disease. HSP90 is a protein found in some cancers, and helps the cancer cell to divide and change at the alarming rates observed. In addition, Dr. Jhaveri is employing a "personalized" approach to patient selection by using an imaging agent developed at Memorial Sloan Kettering that tells the oncologist if HSP90 is present in the tumor. It is believed that this approach will lead to better care and outcomes for this patient group.
2013	Anczukow, Olga, PhD	Cold Spring Harbor Laboratory	Cancer is a very complex disease in which many cellular processes are deregulated. Understanding cellular processes and molecular interactions is necessary to understand how cancer starts and can be treated. Dr. Anczukow-Camarda works on "splicing", a critical step in gene expression that determines how genetic instructions in DNA are cut and pasted together as RNA intermediates to form the templates for producing proteins. By identifying splicing factors, this research will lead to new breast cancer therapies.
2013	Vora, Sadhna R. MD	Dana-Farber Cancer Institute	Roughly 30% of breast cancers demonstrate a mutation in the gene PIK3CA, which drives their growth by activation of the PI3K pathway. While these breast cancers may initially respond to drugs that target this pathway, they ultimately grow again by developing ways to overcome the action of the drug. Dr. Vora's work examines how tumors become resistant to these drugs and seeks ways to overcome resistance with combinations of drugs that target specific pathways that drive cancer.
2013	Gajria, Devika MD	Memorial Sloan Kettering	One of the great frustrations in treating breast cancer results from some patients being resistant to therapies that work successfully in others. Dr. Gajria believes that such resistance can be overcome by combining two novel clinical drugs whose activities could synergize and provide enough potency to overcome such resistance. Dr. Gajria is searching the most appropriate dosing regimen to administer this combination and then study it in breast cancer patients whose disease cannot be cured with other drugs.
2013	Rossetti, Stefano PhD	Roswell Park Alliance Foundation	Breast cancer cells typically produce more ribosomes, the cellular machines that synthesize proteins, to meet their increased metabolic demand. While increased ribosome production has been used for many years as a diagnostic and prognostic marker of breast cancer, it is currently unknown whether this feature is a cause or a consequence of breast cancer. This project aims to answer this long standing question. We plan to test whether increased ribosome production is a breast cancer "driver" capable of inducing early breast cancer stages.

2014	Carmona, Javier PhD	Memorial Sloan Kettering	The efficacy of targeted therapies in cancer patients is often limited by the emergence of resistance. Anti-HER2 agents, specifically trastuzumab, have significantly improved survival rates in HER2 positive breast cancer patients. However, a considerable number of patients exhibit primary resistance or become refractory after initial responses. Therefore, understanding the mechanisms by which cancer cells escape treatment is mandatory to design better therapeutic strategies. To do so, we will perform targeted exome sequencing on a clinical cohort of patients treated with HER2 agents that will uncover the genetic alterations triggering therapy refractoriness, and the mutations driving response to therapy. The validation of these findings will provide biomarkers useful for stratification of treatment regimens and identify potential new therapeutic targets.
2014	Page, David PhD	Memorial Sloan Kettering	The immune system is highly capable of recognizing and killing cancer, but is in constant struggle with cancer's evolving ability to 'escape' the immune response. A new drug called tremelimumab serves to restore the anti-cancer immune response by releasing a natural 'brake' found on a subset of immune cells. Dr. Page is conducting a clinical trial evaluating whether tremelimumab could be combined with therapeutic brain radiation to facilitate durable disease control in patients with newly diagnosed breast cancer brain metastases.
2014	Hofstatter, Erin MD	Smilow Cancer Hospital at Yale New Haven	Age appears to be the single most important risk factor for the development of breast cancer; however, why increasing age is associated with increasing incidence of breast cancer remains incompletely understood. In our study, we will examine epigenetic changes in breast tissue and blood samples from women with breast cancer at young (<45) and older ages (>65), and compare them to samples from age-matched healthy women. We hypothesize that women who accumulate more epigenetic changes at a younger age are at higher risk to develop breast cancer, and aim to identify an epigenetic pattern that could demonstrate premature "aging" of breast tissue.
2015	Dhimolea, Eugen PhD	Dana-Farber Cancer Institute	Most breast cancer patients are Estrogen Receptor (ER)-positive and are treated with antiestrogens after the surgical removal of the mammary tumor. Nonetheless approximately 1/3 of the patients develop metastases, frequently in the bone, that do not respond to treatment. The preference of breast cancer for dissemination to specific tissues (organotropism) indicates a favorable local microenvironment in these organs. While the antiestrogen resistance of ER+ metastatic tumors has been mainly attributed to acquisition of mutations, the role of the metastatic microenvironment in the emergence of these mutations has not been clarified. We will implant patient-derived breast cancer samples in an animal model of "humanized" bone tissue to determine how the bone marrow niche affects the selection of mutations that lead to antiestrogen resistance. This study is also expected to identify plausible therapeutic targets and potentially to generate a novel tool of personalized-medicine for the evaluation of treatment options in patients with advanced breast cancer.

2015	Ilic, Nina PhD	Dana-Farber Cancer Institute	Activating mutations in the PIK3CA gene are found in approximately 30% of breast cancers and promote growth of these tumors. Despite extensive efforts, direct pharmacologic inhibition of this mutant lesion has shown limited patient benefit in recent clinical trials. Therefore, to provide novel personalized treatment options for breast cancer patients, it is critical that we identify alternative gene vulnerabilities that can be targeted for therapy. To discover such mutant PIK3CA-specific vulnerabilities, we interrogated genome-wide genetic dependency data from multiple human cancer cell lines. Here we identified and subsequently validated three integral Krebs cycle genes, as specific gene-dependencies in this group of tumors. As a Terri Brodeur research fellow, Dr. Ilic will explore these newly identified metabolic vulnerabilities in PIK3CA mutant breast cancers to evaluate their potential for precise therapeutic strategies.
2015	Pavlova, Natasha PhD	Memorial Sloan Kettering	Dr. Pavlova's 2015 Terri Brodeur Breast Cancer Foundation fellowship award focuses on the investigation of metabolic adaptations which drive breast cancer metastasis. Cancer-specific metabolic alterations and their functional contribution to tumorigenesis have been under intense investigation in the recent years. However, we still lack a clear picture of how these alterations align with the multistep nature of tumorigenesis. In particular, relatively little is known about metabolic adaptations which distinguish metastatic cancer cells from their non-metastatic counterparts. As preliminary data indicate, metastatic isolates from triple negative breast cancer cells display distinct alterations in the biosynthesis and catabolism of amino acids. In the proposed study, Dr. Pavlova intends to investigate the functional contribution of these metabolic adaptations to metastatic colonization and growth, and determine whether such adaptations promote the resistance of metastatic cells to nutrient deprivation and oxidative stress. Furthermore, using pre-clinical models of breast cancer metastasis, Dr. Pavlova will explore whether such metabolic adaptations can be exploited as targets for anti-metastasis therapy.

2016	Albregues, Jean PhD	Cold Spring Harbor Laboratory	<p>Dr. Albregues' 2016 Terri Brodeur Breast Cancer Foundation fellowship award focuses on the regulation of breast cancer dormancy by the tumor microenvironment. Metastatic breast cancer relapse occurring years after a seemingly successful treatment is preceded by an interlude, termed dormancy, when the cancer remains non-proliferative and undetected at a secondary site. Unfortunately, these dormant tumor cells appear to be refractory to available therapies and the cues mediating their reawakening are largely unknown. Dr. Albregues' hypothesized that dormant cells are awakened by signals from inflammatory immune cells, which also provide cues for aggressive behavior of cancer cells in the primary tumor. To test this hypothesis, he will use newly developed in vitro and in vivo models of dormancy and reawakening. To visualize the interactions with the surroundings, the survival, and the proliferation of tumor cells in situ, he will use microscopy in lungs of living mice and determine how these parameters changes when the disseminated, dormant tumor cells are induced to reawaken. Using pharmacological and genetic approaches, he will identify and target specific signals between inflammatory and cancer cells during experimental manipulation of dormancy. Together, these approaches will allow him to determine how communications between tumor cells and inflammatory microenvironment contribute to the reawakening and therapy resistance of the dormant cells. This analysis will likely reveal new strategies for treatment of dormant disease.</p>
2016	Karaayvaz, Mihriban PhD	Mass General Hospital Cancer Center	<p>Making a major impact on the incidence and lethality of breast cancer will require a detailed understanding of the early events in breast cancer development, particularly in women who are at the highest risk of developing these cancers such as those who carry mutations in the BRCA1/2 genes. Unfortunately, few breast cancer studies are focused on these early events and on breast cancer prevention. We have established a method to analyze distinct cell populations from healthy mastectomy tissues of BRCA1/2 carriers and from tissues of patients undergoing reduction mammoplasty (non-carrier controls). Through detailed molecular analysis of these tissues, we will determine the key functional properties of the major breast cell populations in BRCA1/2 carriers compared to controls in order to determine the cause of abnormal function within these cell populations. Our preliminary data have revealed novel mechanisms of luminal progenitor (LP) cell regulation that may suggest a practical way to reverse cancer-associated LP deregulation and thereby decrease breast cancer risk. These studies are likely to have near-term impact, identifying new targets for breast cancer prevention for future clinical trials.</p>

2016	Stover, Daniel MD	Dana-Farber Cancer Institute	<p>The host immune system is critical in the control and elimination of tumors in many cancer types. In breast cancer, tumor infiltrating immune cells have been associated with both response to chemotherapy and overall outcome for patients. Understanding what immune cell populations infiltrate tumors may help guide which patients are likely to benefit from chemotherapy and provide targets to improve the efficacy of chemo- and other therapies. Within breast cancer, estrogen receptor (ER)-positive breast cancers comprise the majority of all breast cancers but the role of immune cells remains less well-understood relative to other breast cancer subtypes. We developed evidence that immune cells play a critical role in response to chemotherapy in a subset of patients with ER-positive breast cancers. As a Terri Brodeur Fellow, Dr. Stover will integrate large, publicly available datasets to investigate immune cell signatures in thousands of breast tumors. In parallel, he will work to understand immune cell subsets in breast cancer biopsies of patients on clinical trials of chemotherapy and immune-directed therapies. Ultimately, his goal is to develop biologically rational, immune-based biomarkers to guide therapy, including chemotherapy and immune-directed therapies.</p>
2016	Toska, Eneda PhD	Memorial Sloan Kettering	<p>Mutations in the PIK3CA gene are the most frequent genomic alterations in estrogen receptor (ER)-positive breast cancers. One treatment strategy is the use of drugs that inhibit the gene's signaling pathway—however, many patients eventually become resistant to this type of therapy. Further, PI3K signaling pathway inhibition has been shown to increase ER activity, which then increases cells' dependency on ER and estrogen—fueling growth. However, very little is known about the molecular basis of the crosstalk between the PI3K pathway and ER function. To better understand this relationship, we have identified genes that both contribute to PI3K inhibition resistance and are necessary for the ER-PI3K crosstalk. As a Terri Brodeur research fellow, Dr. Toska will explore these newly identified mechanisms of resistance and examine their role on patient biopsies pre-and-on treatment to PI3K inhibitors. With this in mind, she aims to expose new therapeutic targets that could potentially increase treatment success.</p>
2017	Li, Ji PhD	Dana-Farber Cancer Institute	<p>Basal-like breast tumors comprise a heterogeneous group that accounts for about 15% of all breast cancers. They are highly aggressive and generally fail to respond to targeted therapies. Thus, there is a great need to identify novel vulnerabilities and develop novel therapies for this aggressive breast tumor type. The epithelial-to-mesenchymal transition (EMT) is often reactivated during tumor formation. Compared to other breast cancer subtypes, basal-like breast cancers display the highest degree of mesenchymal and stem-like features, which are responsible for tumor initiation, metastasis and therapeutic resistance. We have recently identified genes that regulate EMT in breast cancer using a genome scale screen and identified several RNA splicing factors that are upregulated in basal-like breast cancers and promote the breast tumor formation. We propose to systematically characterize the role of alternative splicing in breast cancer and EMT using genomic, molecular and cellular biology, and computational approaches, and investigate its role in breast tumor metastasis and therapeutic resistance. These studies may lead to new approaches to treat basal-like/triple negative breast cancers.</p>

2017

Meyer, Aaron, PhD

Metastatic spread drives the majority of breast cancer mortality and, to do so, requires tumor cells to both disseminate and avoid clearance by the immune system. Inhibiting TAM receptors has shown promising results in models of breast cancer by blocking tumor cell dissemination, preventing resistance to existing therapies, and relieving immune suppression. Based on these results, the first therapies targeting these receptors are now in early clinical studies. However, a better understanding of when and where these receptors drive breast cancer progression is needed to identify which patients will benefit from these therapies. As a Terri Brodeur Fellow, Dr. Meyer will use a computational model to direct design of new inhibitors for the TAM receptors. Using these well-characterized compounds, he will examine the in vivo effects of inhibiting different TAM receptor complements. By measuring the cellular and molecular consequences of each treatment, and which changes correspond to a therapeutic benefit, he hopes to both develop a clearer picture of when and where these receptors drive breast cancer progression. This information will, in turn, help to address which patients will benefit from these therapies.

2017

Parsons, Heather, MD

Dana-Farber Cancer Institute

This year, breast cancer will claim the lives of more than 500,000 people worldwide. Most of these will be women in whom the disease has spread to the rest of the body, known as metastatic breast cancer. Women living with metastatic breast cancer typically receive ongoing, single-agent treatments that are effective for a while, but at some point, the disease develops resistance, evading a previously effective therapy and growing again. HER2-overexpressing (HER2-positive) breast cancer is a subtype that accounts for 20-25% of breast cancers, and is associated with faster growing tumors, higher rates of recurrence, and higher rates of brain metastases. Though we have effective treatments for HER2-positive metastatic breast cancer, inevitably the disease develops resistance and progresses. Understanding how and why metastatic breast cancer develops resistance is difficult, but is critical to the development of better treatments for women with this disease. Evidence increasingly suggests that tumors evolve genomically over time and in the face of ongoing systemic therapies. A major obstacle to understanding treatment resistance is access to metastatic tumor tissue, as patients with metastatic breast cancer do not typically undergo multiple, sequential biopsies. Both tumor and normal cells shed DNA into the circulation, and even a small amount of circulating tumor DNA (ctDNA) is detectable via next-generation sequencing technologies that are able to “read” the DNA code. As a Terri Brodeur fellow, Dr. Parsons aims to identify, via the ctDNA changes in the tumor, DNA that cause treatment resistance in patients with HER2-positive metastatic breast cancer. She hypothesizes that she will see more of these changes in the ctDNA of patients with metastatic breast cancer who have had extensive treatment than those who have not or those with early-stage breast cancer. These changes may explain why these cancers develop resistance to treatment. By knowing what these changes are, Dr. Parsons aims to enable the development of better treatments for women with HER2-positive metastatic breast cancer. She intends to use the findings to design better studies, and ultimately, treatments for women with metastatic breast cancer. This project has the potential to transform our understanding of metastatic breast cancer, and to significantly advance the use of ctDNA to better understand metastatic cancer.

2018	Dasgupta, Arko, PhD	Fred Hutchinson Cancer Research Center	<p>Breast cancer is a major killer in the United States and metastases are the primary cause of breast cancer-related deaths. Approximately 30% of breast cancer patients will develop metastases during their lifetime. Few prognostic factors predict metastases as well as the presence of dormant disseminated tumor cells (DTCs) – cells that have escaped from the primary breast tumor early in the disease and exist in a dormant state in distant organs until they develop in some patients as overt metastases. Clinical evidence suggests that eradication of DTCs would prevent metastasis, however, currently no therapies specifically target these metastases-initiating cells. Indeed, DTCs are resistant to chemotherapy and other targeted therapies, and very little is known about what enables DTC survival despite multiple rounds of chemotherapy. Breast DTCs reside in a perivascular niche (PVN) – areas within a tissue that are occupied by blood vessels – of distant tissues such as lung, bone marrow, brain, liver and lymph node. Importantly, chemotherapy itself has been shown to elicit responses that alter the tumor microenvironment that also contribute to chemo-resistance in other cancers such as prostate cancer. This may be associated with the induction of DNA damage and the consequent change in factors released by blood vessels – a phenomena that remains unexplored in the context of breast DTCs. Preliminary data generated by Dr. Dasgupta suggests that the PVN protect DTCs from chemotherapy. Accordingly, eradicating DTCs for metastasis prevention will require a much deeper understanding the dynamic relationship between DTCs and their microenvironment (PVN).</p>
2018	Sun, Sheng, PhD	Mass General Hospital Cancer Center	<p>The majority of breast cancers express hormone receptors, and therapies that antagonize hormonal signaling via these receptors are the most effective treatments for hormone receptor-positive metastatic breast cancer (HR+ MBC). Unfortunately, for the vast majority of patients with hormonal therapy-refractory MBC, the mechanisms of resistance remain poorly understood. Thus, identifying new mechanisms of hormonal therapy resistance and understanding how to overcome them will have direct and immediate relevance to the therapy of patients with MBC. We have identified novel gene fusions in 14% of patients with HR+ MBC and provided strong evidence that these tumor-specific genetic rearrangements are powerful drivers of treatment resistance and poor outcomes. Successfully tracking and therapeutically targeting these fusions could thus have a major impact on patient outcomes. We hypothesize that patient-derived circulating exosomes (tiny cell-derived vesicles that circulate in the bloodstream) are likely to contain unique nucleic acids and proteins corresponding to the fusions that could potentially serve as novel biomarkers. We propose to credential these patient-specific rearrangements as blood-based markers of disease burden, clinical response and treatment outcome in MBC. This work will pave the way for effective disease monitoring that will facilitate the clinical development of targeted therapeutics to overcome treatment resistance mediated by these genetic drivers.</p>

2018

Waks, Adrienne Gropper, MD

Dana-Farber Cancer Institute

Following many important advances in treating HER2-positive breast cancer over the past two decades, a large majority of patients with non-metastatic HER2-positive tumors are cured with today's treatments. For this majority of patients who do well in the long-term, we must begin to identify ways to cure HER2-positive breast cancer with less toxic treatments. Modern treatment regimens for stage II and III non-metastatic HER2-positive breast cancer consist of multiple chemotherapy agents plus HER2-directed therapy with trastuzumab (Herceptin, H) and sometimes pertuzumab (Perjeta, P). Scaling back the number of chemotherapy agents used may allow patients to maintain better quality of life while on treatment, as well as decrease the chance of rare but serious chemotherapy complications. As a Terri Brodeur fellow, Dr. Waks plans to conduct a clinical trial investigating a new treatment approach in stage II and III HER2-positive breast cancer, with the goal of allowing select patients to receive less chemotherapy. We know that in patients who receive breast cancer treatment before breast surgery, those who have all cancer eradicated from the breast and lymph nodes at the time of surgery ("pathologic complete response") have an excellent prognosis. In our clinical trial, patients will be treated before surgery with paclitaxel, trastuzumab, and pertuzumab ("THP"), and those who achieve pathologic complete response at surgery—and have an excellent prognosis on that basis—will go on to receive further HP post-surgery, without any additional chemotherapy. Our primary goal in the trial is to assess the acceptability of this treatment approach to patients and their doctors. We hope that this trial, which is a precursor to a large international trial investigating the same approach, will be a step toward establishing HER2-positive breast cancer treatments that are highly effective for a select patient group, and also maximize patient quality of life.

Choosing the best treatments for metastatic breast cancer depends increasingly on molecular features, such as tumor subtype. Patients with hormone receptor-positive/HER2-negative breast cancer are typically treated initially with hormonal therapies, and then subsequently with chemotherapy once hormonal therapy loses its effectiveness. Loss of hormone receptor expression has been described as a mechanism of resistance to hormonal therapy. When this occurs, tumors become hormone receptor-negative and HER2-negative, i.e. triple-negative. It is unknown whether cancers that start out hormone receptor-positive and then become triple-negative (called “subtype switch”) are different than those that remain triple-negative throughout a patient’s disease course. Since treatments depend so heavily on tumor subtype, answering this question could have an immediate impact on patient care. Metastatic triple-negative breast cancer (mTNBC) remains a clinically unmet need, with a highly aggressive clinical course and shorter average survival compared to patients with other subtypes of metastatic breast cancer. Patients whose tumors are initially hormone receptor-positive/HER2-negative and then lose hormone receptor expression (i.e. become triple-negative) are typically eligible for clinical trials and standard-of-care therapies focused on mTNBC. However, comparison of tumor biology and clinical outcomes in patients whose tumors are always triple-negative and those that “switch subtype” has not been studied in detail. Preliminary results from tumor DNA analysis presented by Dr. Garrido-Castro at the 2018 San Antonio Breast Cancer Symposium suggest that primary hormone receptor-positive tumors in patients who later developed mTNBC have similar mutation and gene copy number alterations as primary triple-negative tumors. In addition, hormone receptor-positive breast cancers are generally considered ‘cold’ tumors, characterized by decreased immune cell infiltration and low responsiveness to immunotherapy. It is unclear if hormone receptor loss may induce conversion to an immunologically ‘hot’ tumor that is more susceptible to immunotherapy. This would have therapeutic implications given recent evidence supporting the combination of immune checkpoint inhibition and chemotherapy as first-line therapy in patients with mTNBC.

Despite recent advances in treatment options, breast cancer remains the second leading cause of cancer-related deaths in women. Triple negative breast cancer (TNBC) is a subgroup of breast cancer that is characterized by the absence of the estrogen receptor, the progesterone receptor and HER2-amplification. Because of the lack of these markers, there are at present -unlike for other subgroups of breast cancer- no targeted therapies available for TNBC. Therefore, TNBC is currently treated with conventional chemotherapy in addition to radiotherapy and surgery. Despite the often-good initial response to chemotherapy, therapy resistance is frequent in TNBC, making it one of the most severe subtypes of breast cancer. To improve the perspectives of TNBC patients, there is need for better and more targeted treatments. To address this need, Dr. Daniels aims to identify metabolic pathways that can be targeted in combination with conventional chemotherapy to increase the sensitivity of TNBC to these agents. Dr. Daniels focusses on metabolism, because the metabolic requirements of cancer cells are different than those of normal cells. Therefore, by targeting metabolism cancer cells can be weakened specifically, without affecting normal cells. To determine which metabolic features to target in cancer cells, Dr. Daniels is using a technique called "BH3-profiling". BH3-profiling was developed by the Letai laboratory to measure the proximity of the cells to dying. This novel approach allows for the identification of metabolic perturbations that push the cancer cells closer to the point of dying, even if these perturbations do not cause cell death on their own. Using a drug to induce metabolic instability in cancer cells will make them more sensitive to chemotherapy, leading to a more effective eradication of the cancer. The data generated in this project will lead to the development of better treatment regimens with a higher therapy efficacy and better clinical response. Additionally, information generated in this project can lead to the development of a targeted therapy for triple negative breast cancer. Dr. Veerle Daniels did her undergraduate studies at the department of Pharmaceutical Sciences of the KULeuven University in Belgium. In 2009, she transitioned to the department of Oncology of the KULeuven to do her Ph.D. training under the supervision of Prof. Dr. Johan Swinnen. During her Ph.D. she investigated the role of lipid metabolism in tumor development and cancer cell resistance towards chemotherapy. In 2015 she moved to the Dana-Farber Cancer Institute to start her post-doctoral training in the laboratory of Dr. Anthony Letai, M.D. PhD.

Hu, Jing, PhD

Memorial Sloan Kettering Cancer Center

Metastasis is a major clinical hurdle in breast cancer treatment, with poor prognosis (5-year survival around 26.5%). Despite surgical resection of the primary tumor and systemic therapy to suppress residual disease, distant metastatic relapse may still occur within a few months to years, implying the existence of latent metastatic cells that may last for decades in the distant organs without being detected in clinic. They eventually generate overt metastasis, which is highly resistant to current therapies. Therefore, the predominant concern in the clinic is about how to prevent or treat metastatic relapse by cancer cells that had already disseminated in the distant organs at the time of diagnosis. We recently identified that NK cells suppress outgrowth of disseminated breast cancer cells. However, emergence of immune evasive clones eventually triggers aggressive outbreak. The mechanisms underlying immune evasion of metastatic outbreak are largely unknown. We discovered that breast cancer cells contain cytosolic double-stranded DNA (dsDNA), likely as a result of genomic instability. The stimulator of interferon genes (STING) pathway, triggered by cytosolic dsDNAs, is critical for initiating immune defense against pathogens. Preliminary data suggests that cancer intrinsic STING signal is reduced in immune-evasive metastatic outbreak and restoration of STING activity suppresses metastasis, possibly through immune responses. Therefore, we hypothesize that aggressive metastatic cells inhibit STING signal to evade immune surveillance. As a Terri Brodeur Fellow, Dr. Hu will apply comprehensive approaches to elucidate the mechanisms for STING-mediated metastasis suppression, to dissect determinants that inhibit STING activity during metastatic progression, and to preclinically test potential therapeutic targets that suppress metastatic outgrowth. Completion of the work will enrich the knowledge of immune responses in the metastatic microenvironment and contribute innovative ideas for treating metastatic relapse of breast cancer. Dr. Jing Hu obtained her Ph.D. in Molecular Cancer Biology Program at Duke University, under the supervision of Dr. Xiao-Fan Wang. During her Ph.D., Dr. Hu has discovered microRNA-mediated signal networks that regulate the biological properties of glioma-initiating cells (GICs) and their adaptation to the hypoxic tumor microenvironment. Dr. Hu is currently a post-doctoral fellow at Memorial Sloan Kettering Cancer Center in the lab of Dr. Joan Massagué.

2019

Spring, Laura, MD

Massachusetts General Hospital

Localized breast cancer patients with higher risk disease are often treated with chemotherapy in the neoadjuvant (before surgery) setting. However, it is difficult to predict how breast cancer will respond to treatment given in the neoadjuvant setting and we currently lack any specific blood tests to help answer this question. As a Terri Brodeur grant recipient, I plan to study a method to detect genetic material (DNA) known as circulating tumor DNA (ctDNA) that is released into the blood from some breast cancer tumor cells. One of the main goals of the study is to determine what percentage of breast cancer patients who are receiving treatment before surgery will have ctDNA detectable, as this may represent a group of patients at higher risk for recurrence. For patients with ctDNA present, we will compare the amount before treatment starts and after the first round of treatment. We believe that those with decreasing ctDNA levels will respond to treatment better with improved outcomes at the time of surgery, and ultimately have reduced risk of disease recurrence. Studies in the advanced breast cancer setting suggest that the amount and type of ctDNA in the blood can help determine the status of the tumor itself and the way it is responding to treatment. If change in ctDNA is validated as an early marker of response to different types of therapies in the preoperative setting, this could greatly improve the treatment of breast cancer by allowing more individualized treatment approaches and reducing exposure to unnecessary treatments. Dr. Spring completed her undergraduate studies at Tufts University and obtained her medical degree for the University of Massachusetts Medical School. She completed residency training in internal medicine at Brigham and Women's Hospital in Boston, MA. Following residency, she completed fellowship in medical oncology at Dana-Farber Cancer Institute and Massachusetts General Hospital. Dr. Spring is currently an attending physician in breast medical oncology at the Massachusetts General Hospital Cancer Center and an instructor in medicine at Harvard Medical School. The primary focus of her research is to develop novel therapeutic and biomarker strategies to improve the care of breast cancer patients.

Modulating the immune system as an anti-cancer strategy has shown great promise in some types of cancer, however there has been limited responses in breast cancer. While the main focus of immunotherapy has been on the adaptive immune system, namely T cells, harnessing innate immune cells such as tumor associated macrophages (TAMs) offers a novel strategy to induce breast tumor regression. Breast tumors are highly infiltrated with suppressive TAMs and clinically, a high number of TAMs in breast tumors correlate with a worse overall prognosis and increased metastasis. Therefore, the proposed research focuses on understanding how TAMs contribute to the suppressive tumor microenvironment. A major goal of the project funded through the Terri Brodeur Breast Cancer Foundation is to reveal novel signaling pathways in TAMs that can be targeted therapeutically. The unique and novel clinical focus of harnessing macrophages has the potential to have a considerable impact in the treatment of breast cancer. Dr. Guerrero received her bachelor's degree in Biochemistry from Northeastern University and has a PhD in Molecular and Cellular Biology and Immunology and Pathology from Stony Brook University where she trained under Dr. Wei-Xing Zong and completed her thesis entitled, "A study of cell death pathways and innate immunity in cancer chemotherapy". Dr. Guerrero completed her postdoctoral training in the laboratory of Dr. Anthony Letai at Dana-Farber Cancer Institute where she investigated the role of tumor macrophages in breast cancer and identified novel mechanisms to target pro-tumor macrophages to an anti-tumor phenotype to induce tumor regression. Dr. Guerrero is now an Instructor in Medicine at Harvard Medical School and is the Director of the Breast Tumor Immunology Laboratory at Dana-Farber Cancer-Institute. Her main focus is to bridge basic and translational breast cancer research and immunology with clinical science. She focuses on translating basic knowledge of how macrophages in the breast tumor microenvironment induce apoptosis of cancer cells, as well as identify how macrophages regulate their phenotype at a molecular level. A major goal is to harnessing the anti-tumor potential of tumor-associated macrophages for anti-cancer therapy in breast cancer.

While effective HER2-targeting drugs have greatly improved outcomes for patients with HER2-positive (HER2+) breast cancer, relapse and recurrence still occur. When HER2+ breast cancer returns after treatment, it is because some cancer cells survive killing, and are known as minimal residual disease (MRD). To study the biology of MRD we have developed a mouse model of HER2+ breast cancer (t-HER2) where we can turn on and turn off tumor formation at will. This model also has an intact immune system, making it ideal to study tumor-immune interactions. When we turn off tumors, we model the scenario in patients where tumors shrink with effective therapy. However, like in some patients, tumors recur spontaneously in our model. Using the t-HER2 model we found that MRD is comprised of rare 'sleeping', or quiescent, cancer cells surrounded by signs of a suppressed anti-tumor immune response. We hypothesize that MRD after anti-HER2 treatment occurs because drug-resistant quiescent cancer cells dampen the anti-tumor response. Our objective is to eliminate MRD after HER2 therapy by stimulating an anti-tumor immune response. To achieve this goal, we will first investigate the immune changes seen when tumors shrink to MRD in the t-HER2 model. Next, we will study how the AKTlow quiescent cancer cell (QCC) suppresses the anti-tumor immune response in the setting of MRD. Finally, we will test whether using immunotherapy can prevent tumors from recurring after they shrink with HER2 inhibition. This study will suggest new ways to identify patients at risk for MRD and help understand how rare, quiescent cancer cells contribute to tumor drug-resistance. Our results could be readily translated into a novel clinical trial using a QCC-targeting drug + immunotherapy to prevent relapse and recurrence in patients with HER2+ breast cancer. Dr Sheheryar Kabraji received his medical degree from Oxford University Medical School and completed internal medicine residency at Massachusetts General Hospital. As a medical oncology fellow in the Dana Farber/Partners Hematology/Oncology Fellowship Program, he undertook post-doctoral research in the laboratory of Sridhar Ramaswamy at the Mass General Cancer Center where he demonstrated that AKTlow quiescent cancer cells can be found in residual breast tumors after neoadjuvant chemotherapy. Dr Kabraji is a breast medical oncologist at the Susan F. Smith Center for Women's Cancers, Dana Farber Cancer Institute, and Instructor in Medicine at Harvard Medical School. Dr Kabraji's research in the Zhao Laboratory at Dana Farber Cancer Institute focuses on cancer cell quiescence as a mechanism of tumor drug resistance in localized and metastatic breast cancer.

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Perurena, Naiara PhD, PharmD

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Around 15-20% of breast cancers are characterized by the amplification or overexpression of the receptor tyrosine kinase HER2 and are therefore classified as HER2-positive. In these tumors, HER2 drives tumor formation and progression by activating an oncogenic signaling cascade. Fortunately, the development of therapeutic agents that directly target HER2 has substantially improved the clinical outcome of individuals with HER2-positive breast cancer. Nevertheless, resistance to HER2 inhibitors remains a major challenge, especially in the metastatic setting. Currently, there are no cures for metastatic breast cancer. In addition, while many individuals with localized disease initially respond to HER2-directed therapies, a subset of patients with no overt signs of metastasis may still relapse. Therefore, there is an urgent need to 1) understand the mechanisms that underlie resistance to current treatments, 2) identify robust biomarkers of therapeutic resistance, and 3) develop improved, and more importantly, curative therapies. As a Terri Brodeur Fellow, Dr. Perurena aims to define the role of two new tumor suppressor RasGAPs in anti-HER2 resistance. We have previously shown that the loss of these RasGAPs promotes primary tumor growth and metastasis through the activation of AKT, ERK and NF- κ B signaling pathways. Interestingly, all three of these pathways have been implicated in resistance to anti-HER2 therapies. Therefore, we hypothesized that the loss of these RasGAPs might not only drive metastasis but also induce resistance to anti-HER2 therapies in breast cancer. Our preliminary data support this hypothesis. The overall goals of the project are to: 1) determine how the loss of these proteins precisely promotes resistance to anti-HER2 therapies and 2) identify new targets in these RasGAP-deficient tumors so that we may develop more effective combination therapies. Dr. Perurena obtained her Pharm.D. in 2010 from the University of Navarra (Pamplona, Spain) after completing an internship at St. George's Hospital (London, UK). She completed her Ph.D. in 2015 under the supervision of Dr. Lecanda at the Center for Applied Medical Research (Pamplona, Spain). During her Ph.D. she studied molecular mechanisms of metastasis and received a fellowship to join Dr. Egeblad's laboratory at Cold Spring Harbor Laboratory as a visiting student. Since 2016, Dr. Perurena is a postdoctoral research fellow in the laboratory of Dr. Cichowski at Brigham and Women's Hospital/Harvard Medical School.

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Leptomeningeal metastasis (LM), or the spread of tumor cells into the cerebrospinal fluid, is an increasingly common complication of cancer that results in rapid neurologic disability and death. Colonization of leptomeningeal space by cancer cells can take years or even decades after primary cancer diagnosis. The molecular basis of this devastating process remains virtually unknown. In the proposed project, we plan to investigate why some breast cancers become metastatic and lead to LM, how therapy contributes to the dormancy and re-emergence of these cells, and ultimately, which genes are involved in lethal recurrence. Working from our observations from patient samples and unique experimental mouse models, we will dissect the mechanism of cancer cell entry to the spinal fluid using cutting-edge technologies. Moreover, the presence of a functional immune system in our novel syngeneic mouse models enables us to target immune pathways essential for the development of LM. Due to the routine clinical management of breast cancer patients with LM at MSKCC, we have access to a unique collection of fully annotated spinal fluid samples. This gives us the opportunity to validate findings from mouse studies in human disease. We aim to identify molecules that promote the colonization of leptomeninges by breast cancer cells. We will then identify breast cancer patients with high risk of LM development and target these essential genes with FDA-approved and experimental drugs in mice. Dr. Remsik obtained his Ph.D. in Biology at Masaryk University in the Czech Republic under the supervision of Dr. Karel Soucek. During his graduate studies, Dr. Remsik studied intratumoral heterogeneity in breast and prostate cancer, focusing on the role of epithelial-to-mesenchymal transition on the cell surfaceome. Jan is currently a postdoctoral fellow at the MSKCC's Human Oncology & Pathogenesis Program in the lab of Dr. Adrienne Boire.