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, Andrea MD	Dana-Farber Cancer Institute	Dr. Oliver studied molecular pathways conferring Tamoxifin 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, Dongjoo PhD	Memorial Sloan Kettering	Dr. Dongjoo 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 immunogenecity against a variety of
2008	Choudhury, Sibgat PhD.	Dana-Farber Cancer Institute	Dr. Choudhury looked at putative mammary precurser cells that are resistent 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 therby to improved chemotherapies
2008	Irie, Hanna Y MD, PhD.	Mount Sinai School of Medicine	Dr. Irie, a cell biologist, investigated the bais 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	Zang, 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
2010	Kochupurakki, Bose PhD	Dana-Farber Cancer Institute	Specific aims of Dr. Kochupurakki'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
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
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

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
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
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
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
2012	Jhaveri, Komal, MD	Memorial Sloan Kettering	Dr. Jhaveri is evaluating the effect of a potent class of drugs called HSP90 inhibitors in combination with the established standard-or-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
2013	Anczukow-Camarda, 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

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
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
2013	Rossetti, Stephano 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
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
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
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

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
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
2015	Pavlova, Natalya 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
2016	Albrengues, Jean PhD	Cold Spring Harbor Laboratory	Dr. Albrengues' 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. Albrengues' 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

2016	Karaayvaz, Mihriban PhD	Mass General Hospital Cancer Center	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
2016	Stover, Daniel MD	Dana-Farber Cancer Institute	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
2016	Toska, Eneda PhD	Memorial Sloan Kettering	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 show 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
2017	Li, JI PhD	Dana-Farber Cancer Institute	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

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
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

2018	Dasgupta, Arko, PhD	Fred Hutchinson Cancer Research Center	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 show to elicit responses that alter the tumor microenvironment that also contribute to chemo-resistance in other cancers such as prostate
2018	Sun, Sheng, PhD	Mass General Hospital Cancer Center	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

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.

2019	Garrido-Castro, Ana, MD	Dana-Farber Cancer Institute	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

2019	Daniels, Veerle, PhD	Dana-Farber Cancer Institute	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
2019	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

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.

2020	Guerriero, Jennifer L., PhD	Dana-Farber Cancer Institute – Harvard Medical School	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. Guerriero 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. Guerriero 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. Guerriero 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.

2020	Kabraji, Sheheryar K. BM BCh	Dana-Farber Cancer Institute – Harvard Medical School	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.

2020	Perurena, Naiara PhD, PharmD	Brigham and Women's Hospital – Harvard Medical School	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-kB 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.

2020	Remsik, Jan PhD, PharmD	Memorial Sloan Kettering Cancer Center	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.

2021	Abravanel, Daniel L. MD, PhD	Dana-Farber Cancer Institute – Harvard Medical School	Metastatic breast cancer (MBC) – breast cancer that has spread to other organs – unfortunately remains incurable. In spite of the increasing number of treatments available that can benefit patients with MBC, the disease eventually develops resistance to each therapy. As such, there is a critical need to characterize resistance in patients as insights have the potential for rapid translation to improve quality of life and survival. Most breast cancers express the estrogen receptor (ER). As these depend on estrogen, hormonal therapies are a mainstay of treatment. However, their efficacy is also limited by resistance. In fact, most breast cancer-related deaths result from ER+ MBC that develops resistance to hormonal therapy. One apparent pathway to resistance in ER+ tumors is for the cancer to become ER-negative. This phenomenon of "ER loss" impacts a substantial number of patients, limits treatment options, and is associated with worse outcomes, but remains poorly understood. In this project we aim to characterize two fundamental aspects of ER loss by combining direct evaluation of biopsy samples from patients whose tumors exhibit ER loss with mechanistic studies in breast cancer cell lines: 1) the causes of ER loss, and 2) the ways that tumors continue to progress following ER loss. The long-term goal of this work is to direct the development of more effective treatments. Identifying the mechanisms by which tumors grow following ER loss should reveal new ways to treat tumors that have lost ER and understanding the causes of ER loss could enable the development of therapeutic strategies to delay or even prevent ER loss. Dr. Abravanel received his undergraduate degree from Duke University in 2006, followed by a PhD in Cell and Molecular Biology and an MD through the University of Pennsylvania Medical Scientist Training Program. He went on to complete a residency in Internal Medicine at Brigham and Women's Hospital. He is currently a fellow in Medical Oncology in the Dana-Farber/Mass General Brigham program. In 2018 he joined the laboratories of Dr. Nikhil Wagle and Dr. Joan Brugge as a postdoctoral fellow, where his research focuses on the role of intratumor heterogeneity in metastatic breast cancer progression and therapeutic resistance.

2021	Malani, Rachna, MD	Memorial Sloan Kettering Cancer Center	A growing problem facing cancer patients today is metastatic disease, especially metastases to the central nervous system (CNS). As things stand today, we have large knowledge gaps in understanding why some breast cancer becomes metastatic to the CNS and how we can effectively identify CNS disease earlier. CNS disease is a serious complication of cancer and a major cause of death and well as disability. Breast cancer is the second most common cancer to spread to the CNS. Over time, this problem has been growing and we see more patients now with CNS disease than ever before. Today, this disease is typically found once patients become symptomatic and we are left to react. Part of this devasting problem, is that our understanding of why this disease occurs is lacking. In turn, this limits our ability to develop more effective treatments. Through this study, we aim to change this. We propose to create a novel approach to screening for disease in the brain and allow for the understanding of why CNS disease forms. If we can detect cancer earlier, then we have earlier opportunities for treatment. By starting treatment earlier, we may be able to more positively impact how long patients survive and their quality of life. Novel techniques have been developed to investigate the CNS through methods that avoid a surgical procedure such as a biopsy. These novel techniques including evaluating cerebrospinal fluid (CSF) for circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA). CTCs are cells which have been shed from the primary tumor and ctDNA is shedding of DNA from the primary tumor. We propose the use of these novel techniques as a form of liquid biopsy in search of a biomarker to diagnose BM earlier in patients with breast cancer and also to understand how CNS metastases form. Dr. Malani received her medical degree from University of Sheffield Medical School and completed her neurology residency at SUNY Downstate. She then did her fellowship at Memorial Sloan Kettering Cancer Center in Neuro-Oncology where she was able to undertake research in CNS metastases, including studying CSF-CTCs in patients with CNS metastases. Upon completing her fellowship in 2016, she transitioned to faculty at Memorial Sloan Kettering Cancer Center as an Assistant Attending. She focuses on taking care of patients with CNS metastases in her clinic and also undertakes clinical research in this disease area as well aimed at the understanding of disease formation in the hopes of developing better treatments.

2021	Micalizzi, Douglas MD, PhD	Massachuttes General Hospital Cancer Center	Circulating tumor cells (CTCs) are cells that are derived from a tumor, but are isolated from the blood of cancer patients. Only recently has technological advances permitted the isolation and characterization of these rare cells. CTCs offer a snapshot of the invasive cancer cells that give rise to metastatic lesions and an important model to study cancer and the stages of metastasis. The study of CTCs and the mechanisms of metastasis has the potential to catalyze the development of new treatments for breast cancer that more effectively target CTCs and prevent or suppress the development of metastasis. To investigate breast cancer CTCs and metastasis, I have generated a mouse model of breast cancer metastasis and performed a screen to identify regulators of metastasis. From this screen I identified RPL15, an integral component of the ribosome, to investigate further. I have shown that increased levels of the RPL15 enhances breast cancer spread in mice. Additionally, in breast cancer patients, CTCs with high levels of ribosome proteins correlate with more aggressive disease. The goal of this proposal is to investigate how RPL15 affects metastasis, determine whether it also contributes to drug resistance to standard breast cancer therapy and determine whether targeting the function of ribosome proteins can specifically target these aggressive breast cancer CTCs. To achieve these goals, first, I will investigate how ribosome proteins increase metastasis. Then, I will use an FDA-approved protein translation inhibitor, omacetaxine, to test its ability to reverse drug resistance to commonly used breast cancer drugs. Finally, I will use innovative new microfluidic technology to increase the number of circulating tumor cells that can be isolated from a single patient allowing for more in-depth studies of breast cancer metastasis and response to therapy. Dr. Douglas Micalizzi received his medical degree from University of Colorado School of Medicine, completed internal medicine residency at Massachusetts General Hospital and medical oncology fellowship in the Dana Farber/Partners Oncology Fellowship Program. He is currently completing his post-doctoral research in the laboratory of Dr. Daniel Haber and Dr. Shyamala Maheswaran at the Massachusetts General Cancer Center. Dr. Micalizzi is also a breast medical oncologist at Massachusetts General Hospital specializing in cancer risk assessment and hereditary cancer syndromes.

2021	Rosenbluth, Jennifer MD, PhD	Dana-Farber Cancer Institute – Harvard Medical School	Currently one in eight women in the US are predicted to develop breast cancer in their lifetime, but what is unknown is how many of these cancers can be prevented through advances in precision medicine. At this time, prevention strategies focus on radiographic screening for patients above a certain age, or in those at high risk, removal of the breast tissues, a procedure that can lead to physical and mental hardship. Few chemo-preventative compounds are approved and methods for determining which patients would benefit from these agents are lacking. Thus, there is an urgent need for improved cancer prevention strategies for breast cancer. The overall goal of the research being supported by the Terri Brodeur Breast Cancer Foundation is to evaluate novel cell types present in the breast tissues of women at increased risk of breast cancer as potential targets for breast cancer prevention. In particular, we have developed a biobank of over 100 three-dimensional cultures derived from the breast tissues of patients with or without inherited mutations in breast cancer predisposition genes, including *BRCA1* and *BRCA2* , as well as patients with a personal history of breast cancer or a positive family history. Our goal is to determine the molecular pathways that are activated during the earliest stages of tumor development in specific cell subtypes, test therapeutic strategies to inhibit these pathways, and generate novel murine models that will facilitate translation of new breast cancer prevention strategies into the clinic. Dr. Jennifer Rosenbluth received her medical degree from the Vanderbilt University School of Medicine. She performed her PhD studies in the laboratory of Dr. Jennifer Pietenpol and developed a strategy for treating triple-negative breast cancer by unleashing the tumor suppressor p73 to kill cancer cells. She subsequently completed her medical residency at Massachusetts General Hospital and her oncology fellowship at Dana-Farber Cancer Institute. Her postdoctoral research studies were performed under the guidance of Dr. Joan Brugge at Harvard Medical School, where Dr. Rosenbluth developed new methods for studying premalignant breast epithelium using patient-derived three-dimensional breast organoid cultures. She is currently a medical oncologist at the Susan F. Smith Center for Women's Cancers at Dana-Farber Cancer Institute, where she performs research with the goal of understanding the molecular mechanisms of breast cancer risk and developing new personalized strategies for breast cancer prevention.

2022	Ferraro, Emanula MD	Memorial Sloan Kettering Cancer Center	The prognosis of breast cancer patients is dramatically affected by the seeding of cancer cells in the brain. The impact of brain involvement on quality of life and survival of breast cancer patients is challenging and therapeutic options are currently limited. Although new local treatment approaches in the field of surgery and radiotherapy have improved the local control brain metastases (BM), the responses are often not durable and re-treatment not always feasible. In addition, the short and long terms neurological complications of the treatment contribute to complicate the management of these subset of patients. Unlike other sites of disease spreading, most of chemotherapeutic do not help so much to block the progression in the brain. Indeed, brain is a “sanctuary” for cancer cells, and it is protected from the drugs in the bloodstream. Therefore, BM can be considered the *sword of Damocles* for breast cancer patients and new treatment approaches are urgent. A novel agent called tucatinib has been recently approved and available for patients with a specific subtype of breast cancer known as HER2-positive breast cancer, that is particularly incline to spread in the brain. Tucatinib, uniquely, is the first agent to demonstrate a significant survival benefit in patients with new or progressive BM. The aim of this project is to study biology behind the exceptional response to this agent in the brain along with mechanisms of resistance that are still unknown. This may suggest new combinations/treatment approaches to maximize the potential of this agent in a group of patients with poor prognosis. Patients who are going to receive brain surgery per clinical indication, will be treated with tucatinib preoperatively to evaluate the penetrance of this drug in the brain. Taking advantage of new technologies including whole genome sequencing, single cells transcriptomics, electron microscopy and others, this study represents an ambitious and matrixed academic effort across different departments to answer to many unsolved questions about BM in HER2-positive breast cancer. Dr. Ferraro received her medical degree from University of Roma La Sapienza and completed her Medical Oncology residency at University of Milan in 2020. She joined the Breast Medicine Service of Memorial Sloan Kettering Cancer Center in the late 2019 for a clinical research fellowship that is still ongoing. Her research directly dovetails with her clinical focus on HER2-positive breast cancer and mechanism of resistance in early and advanced stages with a special interest in brain metastases evolution.

2022	Schade, Amy PhD	Brigham and Women's Hospital Harvard University	Triple Negative Breast Cancer (TNBC) is an aggressive subtype of breast cancer which represents approximately 15% of all cases. TNBC tumors frequently recur and metastatic disease is incurable. The standard of care for most TNBCs includes chemotherapy yet many tumors develop resistance. There is an urgent, unmet clinical need for effective therapeutics for advanced and metastatic TNBC. In our preliminary studies, Dr. Schade has identified a promising new therapeutic combination that is effective in a TNBC tumor model. As a Terri Brodeur Fellow, Dr. Schade plans to extensively test this combination in TNBC tumor models, deconstruct the mechanism by which it functions, and identify biomarkers to help select patients that are likely to respond. Importantly, this combination kills tumor cells (as opposed to slowing tumor growth) and has the potential to prolong treatment response and reduce chances of recurrence. This therapeutic approach is particularly exciting because this combination is comprised of clinical advanced and/or approved drugs and our preliminary data are quite compelling. Finally, these studies were designed in collaboration with clinical and pharmaceutical company colleagues so that we will be prepared able to rapidly translate these findings into clinical trials which could be developed for metastatic TNBC. Dr. Schade earned her PhD in Virology from Harvard Medical School in 2019. During her PhD, she was advised by Dr. James A. DeCaprio at Dana-Farber Cancer Institute and completed her thesis entitled, “Mechanistic Insights into DREAM and RB Control of the Cell Cycle.” She primarily studied mechanisms of cell cycle control in normal tissues and how these processes are dysregulated in cancer cells. Dr. Schade is now a Research Fellow in Medicine at Harvard Medical School and Brigham & Women’s Hospital where she is mentored by Dr. Karen Cichowksi. She focuses on understanding the mechanisms of triple negative breast cancer development, metastasis, and response to treatment. Specifically, she uses candidate-based and unbiased approaches to design novel therapies for treatment of triple negative breast cancer.

2022	Sribenja, Sirinapa PhD	Roswell Park Alliance Foundation	Breast cancer presents as several clinical subtypes that have different progression trajectories and disparate prognoses. However, there are two primary etiologic subtypes, each associated with a distinct set of risk factors and genetic profiles that essentially correspond to estrogen receptor positive (ER+) and negative (ER-) disease, and the ER status serves as an important marker for treatment options and prognosis in breast cancer patients. Compared with women diagnosed with ER+ breast cancer, those with ER- tumors generally have a poorer prognosis, partly because of their aggressive phenotype and the lack of targeted therapy. In addition, high-grade, ER- breast cancer is more common among American women of African ancestry (AA) than among those of European ancestry (EA). Presently, the underlying causes of this increased risk of ER- breast cancer in AA women are not clear, but the causes are likely multifaceted. In the last few decades, a substantial amount of research has been devoted to the identification of epigenetic and transcriptomic alterations that drive tumorigenesis. These efforts have led to an improved understanding of its mechanisms and advanced methods for targeted therapeutic strategies for cancer and its complications. However, evidence linking RNA modifications to the development, maintenance, and progression of breast cancer is still lacking. By using my expertise in molecular and cellular biology, and by taking advantage of novel, state-of-the-art high-throughput techniques in m^6A Selective Allyl Chemical labeling and sequencing (m^6A-SAC-seq) and CRISPR/Cas technology, I want to elucidate the mechanisms of action of epitranscriptomic differences in tumor progression between ER- and ER+ breast cancers and link those differences to clinical outcome disparities between women of difference races. Through this work, we have identified more than 150 candidate mRNAs that show significant differences in m^6A methylation between ER subtypes and races. I now propose to test a select group of these modifications for their effects on breast cancer progression by manipulating the fraction of m^6A methylation in breast cancer cell lines using CRISPR/Cas technology and I will identify the functional roles of m^6A RNA modifications in breast cancer cells. As an active member of the methylation research group at Roswell Park Comprehensive Cancer Center, and as a Research Associate participating in National Institutes of Health (NIH) R01 funded studies on DNA methylation profiling of breast tumors from AA and EA women as well as a currently funded R01 to study long noncoding RNAs (lncRNAs) in the same patient cohorts, I have developed a strong passion for research in the field of epigenetic regulation of cancer and will strive to become an independent investigator who conducts top-notch epigenetic research that will ultimately influence patient care. My overall long-term goal as an independent investigator is to decipher the cellular and molecular phenomena that occur in breast cancer in order to better understand breast cancer and potentially facilitate the development of novel molecular

2023

Barufaldi, Bruno, PhD

University of Pennsylvania

The COVID-19 pandemic has negatively affected screening practices, resulting in staffing shortages and leading to a concerning estimated deficit of 3.9 million breast cancer screenings in the US. The estimated deficit in breast cancer screening impacted by the pandemic may complicate future clinical outcomes, such as an increased number of cancers found at later stages. Women who are socially or economically disadvantaged more often miss appointments for breast cancer screening. Population modeling plays an important role in anticipating the outcomes for optimal triage strategies, especially for implementing unbiased strategies for groups who are most affected by breast cancer disparities. The Hospital of the University of Pennsylvania (HUP) seeks to actively address cancer disparities and racial biases. At HUP, almost half of the breast cancer screening population self-identifies as Black or African American. Yet, these women are under-represented at supplemental screening (e.g., abbreviated MR) because high breast density is the primary criterion for supplemental screening (after genetic and familial risk). At HUP, Black women are five times less likely to have the highest category of breast density. Instead, Black women are more likely to have anatomically complex breasts which, like high breast density, can mask patterns of cancer. Women with complex breast parenchyma are not currently offered supplemental screening. In the proposed research project, Dr. Barufaldi seeks to improve the workflow in breast imaging by developing a racially unbiased system to evaluate mask patterns of cancer efficiently and objectively. The proposed system uses artificial intelligence and computer simulations of masked cancers to prioritize same-day diagnosis of cases that require increased scrutiny by a radiologist; the remaining cases being better suited to batch (offline) reading, which has been evidenced to improve the performance of radiologists. The system uses the risk of masking, breast complexity, and socioeconomic status to determine efficiently who needs supplemental imaging.

Lipsyc-Sharf, Marla, MD	Dana-Farber Cancer Institute

Most patients with estrogen receptor-positive (ER+) breast cancer are diagnosed at early stages and receive treatment with the goal of curing breast cancer. However, some breast cancers recur, meaning the cancer returns in the breast or spreads to a different part of the body after the original tumor has been removed. When breast cancer spreads to a different part of the body, it is a treatable, but typically no longer curable. Therefore, reducing the risk of recurrence, is critical. Patients with ER+ breast cancer, the most common kind of breast cancer, are at risk of recurrence for many years, even decades. This problem of recurrence is particularly challenging in young women, who not only have longer life expectancy, but also develop more aggressive breast cancers. This challenge may become even more pronounced in the coming years given the increasing incidence of ER+ breast cancer in young women. For patients with breast cancer, there is currently no recommended blood test administered during or after treatment to predict breast cancer recurrence. However, personalized “liquid biopsies” are being developed for this purpose. These blood tests look for signs of cancer in the blood by detecting “circulating tumor DNA” (ctDNA). To find the very small amounts of ctDNA expected in early-stage breast cancer, a very powerful or “ultrasensitive” ctDNA test is needed. In this project, we will determine how well ultrasensitive ctDNA testing predicts breast cancer recurrences in young women with ER+ breast cancer, and we will explore whether ultrasensitive ctDNA detection correlates with known risk factors for recurrence. We will assess ultrasensitive ctDNA testing in participants with ER+ breast cancer in the Dana-Farber Young Women’s Breast Cancer study who previously donated tumor and blood samples for research. We will apply ctDNA tests to blood tests from forty-four of these patients that have had breast cancer recurrence and forty-four matched control patients that have not had a breast cancer recurrence. We will test whether a positive ultrasensitive ctDNA test was able to predict recurrences in this group so that this method for ctDNA detection can be studied in future clinical trials aimed at reducing the risk of breast cancer recurrence in this population.

Tesch, Megan , MD	Dana-Farber Cancer Institute	The optimization of systemic therapy for young women with early-stage hormone receptor-positive (HR+)/HER2-negative remains a significant challenge, particularly in terms of predicting chemotherapy responsiveness. This is exemplified by recent gene expression profile-driven adjuvant therapy trials, in which premenopausal patients with low-to-intermediate genomic risk HR+ tumors derived a survival advantage from chemotherapy, but not their postmenopausal counterparts. Critical questions have arisen as to whether this chemotherapy benefit stems from induction of ovarian function suppression, with consequent downregulation of estrogen receptor activity, or whether there are intrinsic differences in the biology of young women's tumors, particularly tumor-immune microenvironment, that render them more susceptible to the cytotoxic effects of chemotherapy. Systemic therapy strategies for young women with HR+ breast cancer could differ considerably on the basis of these alternative hypotheses, ranging from chemotherapy-sparing/hormonal-based approaches to escalated chemotherapy regimens incorporating agents such as immune checkpoint inhibitors.The objective of this project is to determine the impact of chemotherapy on estrogen receptor activity and tumor-immune microenvironment in young women with HR+ breast cancer, by examining changes in the expression of pertinent genes in response to chemotherapy. In doing so, this project aims to elucidate key mechanisms by which chemotherapy exerts a differential benefit in young women with HR+ breast cancer. Tumor specimens will be derived from a prospective multicenter cohort study of women diagnosed with breast cancer at age 40 years or younger, enabling correlation of chemotherapy-mediated estrogen receptor- and immune-related gene expression changes with patient characteristics, treatment response, and survival outcomes. This will help to establish the clinical significance of these chemotherapeutic effects in young women with HR+ breast cancer, and accordingly, could provide a strong rationale for future tumor biology-guided clinical trials within this disparate population in need of more tailored systemic therapy options.

Will, Marie, MD, PhD	Memorial Sloan Kettering Cancer Cent	Genomic studies of breast cancer have dramatically transformed the field over the last few decades. Key oncogenic drivers identified in these studies have not only shed light on breast cancer biology but also paved the way for clinical tumor profiling and targeted therapy. Several recent large-scale analyses have identified *GATA3* as one of the most commonly mutated genes in breast cancer; however, little is known about the mechanism by which *GATA3* mutations modify breast cancer phenotypes. This represents a major gap in our scientific understanding of the disease and a missed opportunities for targeted therapeutics in patients with these mutations. GATA3 has long been known as a critical factor in mammary development, where it is required for the activation and maintenance of the mammary luminal differentiation program. In addition, GATA3 regulates estrogen receptor (ER) signaling and is crucial in the biology of ER+ breast cancer. We hypothesize that (1) *GATA3* mutations modify breast cancer phenotypes by directing lineage transitions and modulating the ER transcriptome, and that (2) these modifications have important ramifications for breast tumor biology and therapy. Studies of breast cancer drivers thus far have largely focused on oncogenes or tumor suppressors with well-defined downstream substrates, such as kinases and phosphatases. Attempts to investigate epigenetic drivers such as GATA3, which may exert an impact on lineage phenotypes, have been hampered by a lack of experimental models that can recapitulate these transitions. We recently developed a novel ER+ mammary organoid system that combines the ease of genetic modification with the ability to study subpopulations. We now propose a detailed investigation of how *GATA3* mutations affects ER activity and breast tumor lineage. Results will not only fill a major knowledge gap in the functional and biologic consequences of *GATA3* mutations in breast cancer but also guide the development of novel therapeutic strategies.

Wu, Bogan, PhD	Massachusetts General Hospital	Triple negative breast cancer (TNBC) accounts for 10% to 20% of all breast cancers and is associated with the worst prognosis among all breast cancer subtypes. TNBC is characterized by a limited response to standard chemotherapy and few options for targeted therapies, and therefore represents a major unmet clinical need. While the immune system plays an important role in fighting cancer and in response to anticancer treatment, TNBCs are often “immune-cold”, characterized as lack of immune cell infiltration. Understanding the immune-suppressive mechanisms of TNBCs and developing conceptually new therapeutic approaches will be essential to providing patients with more effective therapies that impact survival. In preliminary studies, Dr. Wu has identified a previously unappreciated mechanism of immune evasion utilized by TNBC. With the support from The Terri Brodeur Breast Cancer Foundation, Dr. Wu plans to systematically dissect novel mechanisms that function to suppress antitumor immunity in TNBC and to test the synergism between existing and emerging therapeutic regimens including immune modulatory agents. The proposed studies also incorporate molecular profiling of patient specimens as well as hypothesis-driven high-throughput genetic screening approaches. Furthermore, close collaboration with the clinical research team brought together by this fellowship award will greatly facilitate a timely transition of our laboratory findings into potentially novel clinical practice including patient stratification and innovative combinatory therapies.