

# Breast Cancer Research Program



Congressionally Directed Medical  
Research Programs

# CDMRP

Department of Defense



U.S. Army Medical Research  
and Development Command



# Congressionally Directed Medical Research Programs

## HISTORY

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a Congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has been responsible for managing over \$15.9 billion since its inception through fiscal year 2020 (FY20). Funds for the CDMRP are added to the Department of Defense (DoD) budget, in which support for individual programs, such as the Breast Cancer Research Program (BCRP), is allocated via specific guidance from Congress.

## APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for evaluating applications, with both tiers involving dynamic interaction between scientists and disease survivors (consumers). The first tier of evaluation is a scientific peer review of the applications, measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Programmatic Panel, which is composed of leading scientists, clinicians, and consumers.

The Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit, potential impact, adherence to the intent of the award mechanism, relevance to program goals, and portfolio composition.

# Breast Cancer Research Program

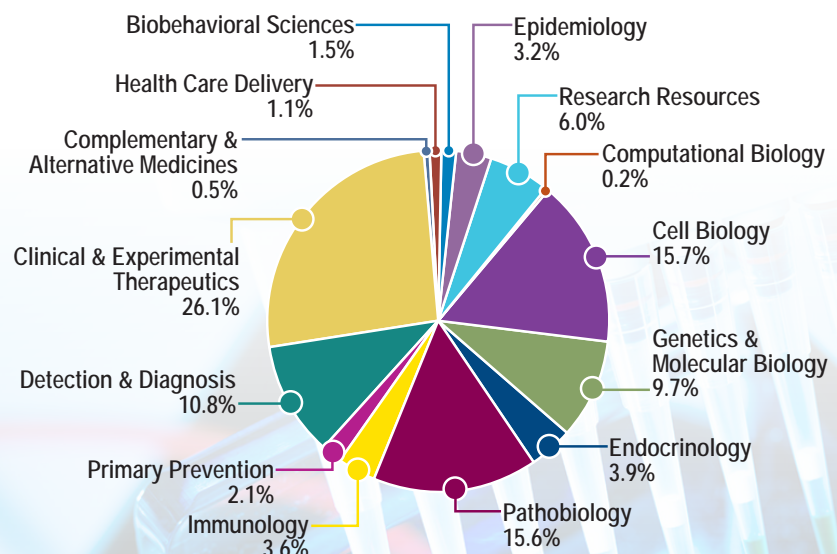
**VISION:** A world without breast cancer

**MISSION:** To end breast cancer for Service members, Veterans, and the general public by funding innovative, high-impact research through a partnership of scientists and consumers

## ABOUT THE PROGRAM

The BCRP plays a leading role in the fight against breast cancer through its innovative approaches and its focus on research that will bring an end to this disease. The program was established in 1992 as a result of the dedicated efforts of breast cancer advocates. Their continued efforts, in concert with the program's accomplishments, have resulted in more than \$3.7 billion in Congressional appropriations through FY20. The BCRP enables researchers to propose their best innovative ideas that address the urgent need to end breast cancer. The program challenges scientists to pursue high-risk, high-reward research, explore new paradigms that could lead to critical discoveries, and make an unprecedented impact on breast cancer. The BCRP also promotes synergistic collaborations across disciplines and integrates scientists and consumers in unique and meaningful research partnerships.

FY92-FY19 BCRP Portfolio

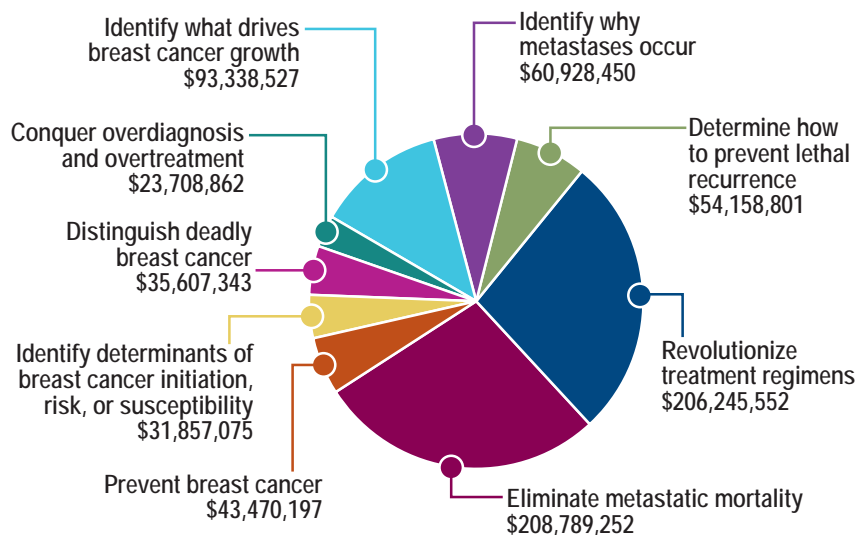


## BCRP OVERARCHING CHALLENGES

Considering the current *Breast Cancer Landscape* and the BCRP's vision to end breast cancer, each application must address at least one of the following overarching challenges:

- Prevent breast cancer (primary prevention)
- Identify determinants of breast cancer initiation, risk, or susceptibility
- Distinguish deadly from non-deadly breast cancer
- Conquer the problems of overdiagnosis and overtreatment
- Identify what drives breast cancer growth; determine how to stop it
- Identify why some breast cancers become metastatic
- Determine why/how breast cancer cells lie dormant for years and then re-emerge; determine how to prevent lethal recurrence
- Revolutionize treatment regimens by replacing them with ones that are more effective, less toxic, and impact survival
- Eliminate the mortality associated with metastatic breast cancer

FY13-FY19 BCRP Funding Invested by Overarching Challenge



## Relevance to Military Health

Breast cancer is the most common non-skin cancer in women, causing the most cancer-related deaths in women under the age of 40<sup>1</sup>. Female active duty Service members have a 20%-40% higher incidence rate of breast cancer than the general public<sup>2</sup>. The incident rate of breast cancer for active duty women is seven times higher than the average incident rate of fifteen other cancer types across all Service members<sup>3</sup>. The outcomes of BCRP-funded research will ultimately benefit military Service members, Veterans, military beneficiaries, and the general public.

<sup>1</sup> [www.cdc.gov/cancer/dataviz](http://www.cdc.gov/cancer/dataviz)

<sup>2</sup> Zhu K, Devesa SS, Wu H, et al. 2009. Cancer incidence in the U.S. military population: comparison with rates from the SEER program. *Cancer Epidemiology, Biomarkers and Prevention* 18(6):1740-1745

<sup>3</sup> Lee T, Williams VF, and Clark LL. 2016. Incident diagnoses of cancers in the active component and cancer-related deaths in the active and reserve components, U.S. Armed Forces, 2005-2014. *Medical Surveillance Monthly Report* 23(7):23-31

## THE BREAST CANCER LANDSCAPE

The BCRP has prepared an overview of the *Breast Cancer Landscape*<sup>4</sup>, covering topics most pertinent to the program's mission of ending breast cancer. Some key points from the *Breast Cancer Landscape*:

### INCIDENCE & MORTALITY

- Worldwide, breast cancer accounts for nearly a quarter of all cancers in women.
- In 2018, there were 626,679 breast cancer deaths globally.

### RISK FACTORS

- Evidence attributes the majority of breast cancers not to one factor but various physical, environmental, and genetic factors.
- Most risk factors are not modifiable, including age, family history, BRCA mutation status, and breast density.

### RECURRENCE & METASTASIS

- An estimated 20%-30% of women diagnosed with invasive breast cancer will have a recurrence.
- Treatments to permanently eradicate metastasis do not exist. There is no cure once metastatic disease has occurred.

### TREATMENTS

- Although breast cancers are highly heterogeneous, the majority of women with breast cancer still receive the same treatment, as though all breast cancers were the same within that subtype.
- Standard adjuvant therapies have only a small (5% to 10%) impact on disease-specific survival.
- The cost of treating breast cancer continues to rise. The total national costs for medical services and oral prescription drug costs for 2015 were highest for female breast cancer (\$26 billion).

<sup>4</sup> <https://cdmrip.army.mil/bcrp/pdfs/Breast%20Cancer%20Landscape2020.pdf>

# Strategic Partnerships

SCIENTISTS AND CONSUMERS WORKING TOGETHER TO END BREAST CANCER

“It is an honor and a privilege to be a part of the BCRP programmatic panel. Working together collaboratively, members of the panel play a vital role in crafting and implementing the unique vision of this program. The BCRP is distinguished by its encouragement of high-risk, high-reward, innovative applications that are most likely to have a high impact. It is inspiring to be a part of selecting proposals that have the highest potential for breakthrough discovery in the mission of ending breast cancer.”

*Sara Hurvitz, M.D., FY21 Programmatic Panel Chair*



The DoD BCRP is a place where breast cancer survivors and researchers are on the same team. We all have different backgrounds and expertise, but we come together to fund the best research. We are all deeply committed to the work and goal of ending breast cancer. The researchers have personal reasons for doing the work as well as scientific expertise, so they come to discussions highly engaged. I have experience and expertise in the real world of breast cancer, which is an important voice and not something truly understood without living with the disease. My perspective includes an understanding of what may or may not work for patients and what breakthrough research really means. I attend with the intention of fighting for everyone dying for a cure, and for those not yet diagnosed.”

*Michelle McGree, Consumer Reviewer*

“My husband and I were raised within the DoD. We feel a deep and continuing obligation to support our military and my serving as a DoD BCRP consumer reviewer is one small way for me to give back. In 2020, we live in a time of great uncertainty so knowing that the DoD BCRP is working towards ending breast cancer is a comfort. Based on the breast cancer researchers I have met over the years, their commitment to ultimately ending breast cancer is total. It is a joy to meet new scientists who have worked in labs but never met a breast cancer survivor. Without exception they express a renewed commitment to their work on our behalf.”

*Carol McWilliams, Consumer Reviewer*



“For the past 30 years, consumer advocates have educated me on the side of medicine that doctors don’t learn in medical school. They have communicated their diverse experience of the disease, conveyed their specific needs and transmitted their passion and commitment to eradicating breast cancer for all. Through their example and generosity, they have made me a better doctor and a better person.”

*Silvia Formenti, M.D., Weill Cornell Medical College*

# Research Highlights



## **Fasting-Mimicking Diet (FMD) Induces Breast Cancer Regression Through Enhanced Effectiveness of Hormone Therapy**

**Valter Longo, Ph.D.**, University of Southern California, and **Alessio Nencioni, Ph.D.**, (pictured) University of Genoa

*FY16 Breakthrough Award – Funding Level 2*

For hormone receptor positive (HR+) breast cancers, resistance to anti-estrogen therapies (e.g., tamoxifen and fulvestrant) remains a problem for patients, and disease progression often occurs. Fasting or FMDs (i.e., diets that are plant-based, low-calorie, high-fat, sugar- and protein-restricted) reduce the level of pro-tumorigenic circulating growth factors (e.g., insulin, insulin-like growth factor 1 [IGF1], and leptin; collectively termed fasting-reduced factors [FRFs]) that enhance estrogen receptor activity within tumor cells. Drs. Longo and Nencioni determined that weekly cycles of fasting or FMD alone or in combination with tamoxifen or fulvestrant reduced the levels of endogenous insulin production and FRFs in HR+ mouse models. When the researchers treated mice bearing HR+ tumors with fulvestrant plus FMD, reintroduction of FRFs resulted in increased tumor growth and drug resistance; FRF withdrawal reversed this outcome. Combining FMD, palbociclib (an inhibitor of cyclin-dependent kinase (CDK) 4/6), and fulvestrant prevented tumor growth for >160 days, and led to slow but steady tumor shrinkage. Mouse tumors previously resistant to fulvestrant plus palbociclib treatment could be re-sensitized to this combination treatment after periodic cycles of FMD. Importantly, in 36 HR+ breast cancer patients receiving anti-estrogen therapy (NCT03595540 and NCT03340935), periodic FMD led to long-lasting metabolic changes analogous to those observed in the mouse experiments. These results provide rationale for larger clinical trials of FMD as an adjuvant to anti-estrogen therapy to improve clinical outcomes in patients with HR+ breast cancers.

### **Publication:**

Caffa I, Spagnolo V, Vernieri C, et al. 2020. Fasting-mimicking diet and hormone therapy induce breast cancer regression. *Nature* 583(7817):620-624.

## **De-Escalating Treatment in Human Epidermal Growth Factor Receptor 2 Positive (HER2+) Breast Cancer: Establishing Effective and Less Toxic Therapy Based on Predictive Biomarkers**



The Baylor College of Medicine research team. Dr. Rimawi (left) and Dr. Schiff (middle), the principal investigators on the project, and Dr. Veeraraghavan (right), a team member and first author in the *Annals of Oncology* publication.

they receive HER2-targeted treatments plus additional chemotherapy. Drs. Rimawi and Schiff evaluated HER2-overexpressing patient breast tumors for biomarkers that correlated with clinical response after 12 weeks of trastuzumab + lapatinib therapy. They observed that 65% of patients harbored phosphoinositol-3-kinase (PI3K) pathway irregularities; if the PI3K pathway was deregulated, only 4% of patients had pCR. Moreover, tumors initially classified as HER2-enriched (HER2-E) with the highest baseline expression of HER2 mRNA exhibited a higher probability of pCR following trastuzumab + lapatinib therapy compared to HER2-E tumors with lower baseline HER2 mRNA levels or tumors from non-HER2-E disease. Analysis of baseline tumor PI3K pathway activity and/or HER2 mRNA levels could help identify patients responsive to anti-HER2 therapy alone, allowing for a de-escalation of patient exposure to chemotherapy.

### **Publications:**

Veeraraghavan J, De Angelis C, Mao R, et al. 2019. A combinatorial biomarker predicts pathologic complete response to neoadjuvant lapatinib and trastuzumab without chemotherapy in patients with HER2+ breast cancer. *Annals of Oncology* 30(6):927-933.

Prat A, Pascual T, De Angelis C, et al. 2020. HER2-enriched subtype and ERBB2 expression in HER2-positive breast cancer treated with dual HER2 blockade. *Journal of the National Cancer Institute* 112(1):36-44.

**Mothaffar F. Rimawi, M.D.**, and **Rachel Schiff, Ph.D.**, Baylor College of Medicine

*FY16 Breakthrough Award – Funding Level 3 – Clinical Trial – Partnering PI Option*

Genetic amplification or overexpression of the HER2 oncogene drives HER2+ breast cancer. Dual HER2-blockade, such as trastuzumab + lapatinib, without chemotherapy results in pathologic complete response (pCR) approximately 25% of the time. The remaining 75% of patients have improved clinical outcomes when



## New Diagnostic and Therapeutic Approaches to Eradicating Recurrent Breast Cancer

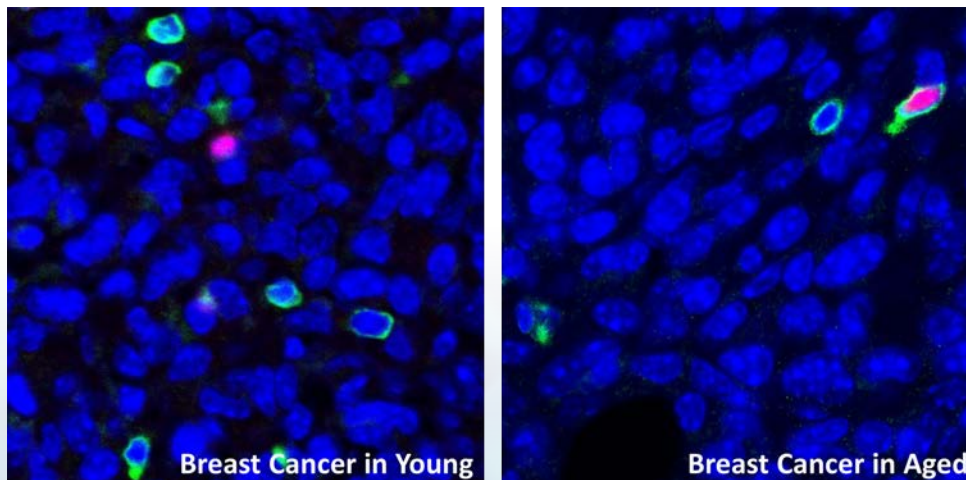
Sandra McAllister, Ph.D., Brigham and Women's Hospital

FY13 Era of Hope Scholar Award

Age-related changes to immunity could affect the efficacy of immune checkpoint blockade (ICB) therapy for the treatment of triple-negative breast cancer (TNBC). While TNBC affects women of all ages equally, older patients are typically excluded from or underrepresented in trials evaluating ICB in TNBC, and the impact of age-related immune dysfunction on the response to therapy remains unknown. Dr. McAllister sought to define age- and ICB-related changes to the TNBC tumor microenvironment (TME) and determine whether these changes affect the efficacy of ICB therapy. In ICB-treated mouse models of TNBC, young tumor-bearing mice exhibited significantly decreased tumor growth and increased overall survival compared to aged mice. The tumors from aged mice exhibited an increased emergence of an immunologically “cold” TME, characterized by absence of tumor killing tumor-infiltrating lymphocytes and decreased signaling of the antitumor interferon (IFN) signaling pathways. The age-dependent differences in treatment outcomes were attributed to enriched baseline (i.e., before ICB treatment) expression of IFN gene sets in tumors from young mice compared to aged mice, an observation that was consistent with baseline genomic data from TNBC patients that were  $\leq 40$  years or  $\geq 65$  years of age. The group next discovered that, while stimulation of IFN signaling with the IFN pathway agonist DMXAA (5,6-dimethylxanthenone-4-acetic acid) was ineffective in improving survival of aged mice, the combination of DMXAA + ICB significantly reduced tumor growth and improved overall survival only in the aged mice. These results suggest that ICB coupled with IFN pathway agonists can activate the immune system within the immunologically “cold” TME commonly observed in older TNBC patients, thus identifying a new potential treatment regimen. Dr. McAllister received a FY19 BCRP Expansion Award, to continue to evaluate the efficacy of ICB combined with IFN pathway agonists for the treatment of TNBC in older patients.

### Publication:

Sceney J, Goreczny GJ, Wilson K, et al. 2019. Interferon signaling is diminished with age and is associated with immune checkpoint blockade efficacy in triple-negative breast cancer. *Cancer Discovery* 9(9):1208-1227.



*Old Stay Cold.* Triple-negative breast cancer (TNBC) tumors in young mice (left) show signs of an activated “hot” immune system while the TNBC tumors in aged mice (right) have an attenuated “cold” immune response. After treatment with immune checkpoint blockade therapy, the immune response in the tumors of young mice becomes even more active while the immune response in tumors from aged mice stays cold. In the images, cells that are exclusively blue are TNBC tumor cells (DAPI+), cells that are both green and blue are T lymphocytes (CD3+), and cells that are labeled both green and pink are T-regulatory cells (Foxp3+/CD3).



## Death Effector Domain-Containing Protein (DEDD) Vulnerability to Cell Cycle Inhibition in Triple-Negative Breast Cancer (TNBC)

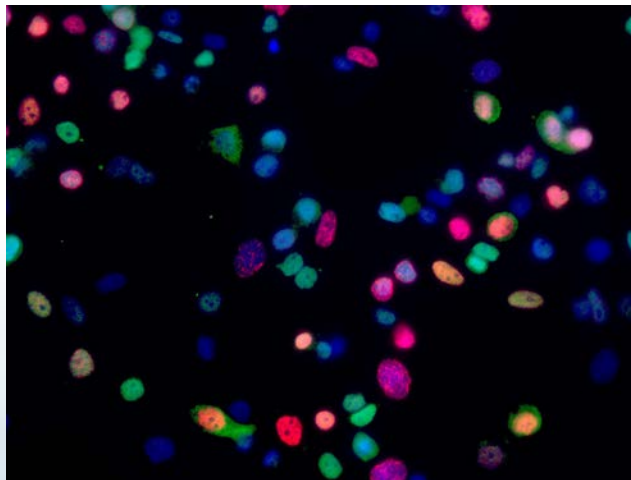
**Siyuan Zhang, Ph.D.**, University of Notre Dame

*FY17 Breakthrough Award – Funding Level 2*

There is an urgent need for therapeutically targetable biomarkers for the treatment of TNBC to improve patient outcomes for this aggressive subtype of breast cancer. Although a large percentage of TNBCs express epidermal growth factor receptor (EGFR), clinical trials using EGFR inhibitors, such as lapatinib, have not shown promise in patients diagnosed with TNBC. Dr. Zhang's laboratory determined that the nuclear-to-cytosolic transition and overexpression of DEDD, a protein normally localized to the nucleus of cells that promotes the activation of cell death pathways, contributes to TNBC cell cycle progression by promoting the degradation of the retinoblastoma (Rb) tumor suppressor protein via the cyclin-dependent kinase 4 (CDK4)/CDK6/Rb pathway. Targeting CDK4/6 in combination with lapatinib in DEDD-overexpressed TNBC cells significantly and synergistically inhibited cell proliferation in vitro, and the synergistic response was independent of Rb expression levels. The team examined both cell line- and patient-derived xenograft mouse models of TNBC. Initial tumor immunohistochemistry analyses showed DEDD predominantly localized to the cytoplasm of tumor cells. Compared to single agent therapy, treating TNBC mouse tumors with the combination of lapatinib and CDK4/6 inhibitors led to significant reductions in size and proliferation index of tumors across all models. Importantly, TNBC tumors that were resistant to either single agent treatment were sensitive to combination treatment. This research challenges current dogma that CDK4/6 inhibitors are only effective in breast cancer tumors expressing wild-type Rb protein, and provides preclinical rationale for initiation of clinical trials testing the efficacy of CDK4/6 inhibitors in TNBC patients using cytoplasmic DEDD expression as a patient selection guideline.

**Publication:**

Ni Y, Schmidt KR, Werner BA, et al. 2019. Death effector domain-containing protein induces vulnerability to cell cycle inhibition in triple-negative breast cancer. *Nature Communications* 10(1):2860.



*The researchers used immunofluorescence (IF) staining to assess DEDD intracellular location and its association with cell cycle progression. Cell proliferation is indicated by EdU (Red) incorporation into the nucleus (blue). DEDD expression was detected anti-DEDD IF staining (green)*



## Characterization of Clustered CTCs to Eliminate Breast Cancer Metastasis

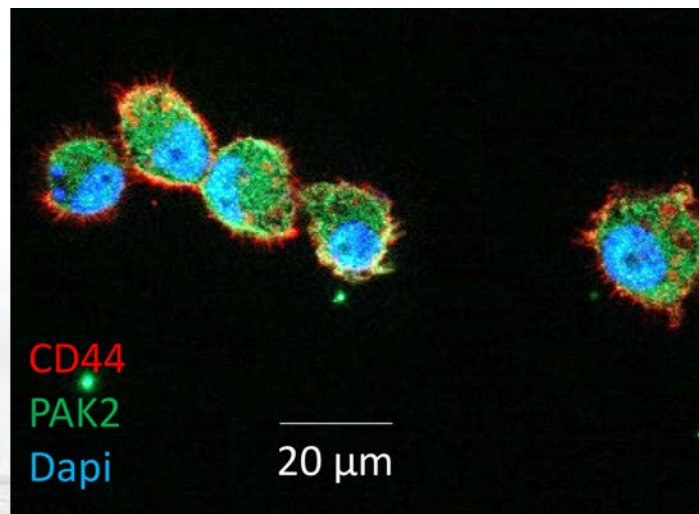
Huiping Liu, M.D., Ph.D., Northwestern University

FY15 Breakthrough Award – Funding Level 2 – Partnering PI Option

Circulating tumor cells (CTCs) are cancer cells that disseminated from a solid primary tumor, are detectable in the blood, and may lead to metastases. Detection of clustered CTCs in the blood, as opposed to single CTCs, is associated with a worse prognosis. However, the mechanisms by which CTCs form clusters and promote the establishment of metastatic lesions remain unclear. Using a patient-derived xenograft (PDX) lung-metastatic mouse model of breast cancer as a replication of human metastatic disease, a team led by Dr. Liu examined peripheral blood and lung tissue of mice bearing multiple primary tumors derived from tumor cells that were genetically modified to express different (i.e., red or green) fluorescent proteins. Both single-color and dual-color CTC clusters were detectable in blood, as well as in lung metastatic colonies, demonstrating the potential for CTC clusters to form from single CTCs while in circulation. Moreover, implantation of CTC clusters in tumor-free mice drastically increased tumorigenesis compared to implantation of single CTCs. Comparing single and clustered CTCs from mouse PDX and human tumor samples, the team observed that CTC clusters have enhanced expression and bonding of CD44 at the interface of two neighboring cells. CD44 is a protein located on the surface of cancer stem cells that plays a role in migration, adhesion, and invasion to other tissues. Importantly, metastatic breast cancer patients with CTCs that did not cluster or express high levels of CD44 exhibited longer overall survival. These results provide compelling evidence that CTC clusters and CD44 expression have a negative impact on patient outcomes, and offer new strategies for anti-CD44 therapies that specifically target CD44 cell-cell bonding and reduce the metastatic potential of CTCs.

### Publications:

Liu X, Taftaf R, Kawaguchi M, et al. 2019. Homophilic CD44 interactions mediate tumor cell aggregation and polyclonal metastasis in patient-derived breast cancer models. *Cancer Discovery* 9(1):96-113.  
Kawaguchi M, Dashzeveg N, Cao Y, et al. 2020. Extracellular domains I and II of cell-surface glycoprotein CD44 mediate its trans-homophilic dimerization and tumor cluster aggregation. *Journal of Biological Chemistry* 295(9):2640-2649.



Trans-dimerization of CD44 (red) at the surface of individual breast tumor cells (blue) drives the formation of a four-cell cluster (left) in suspension.



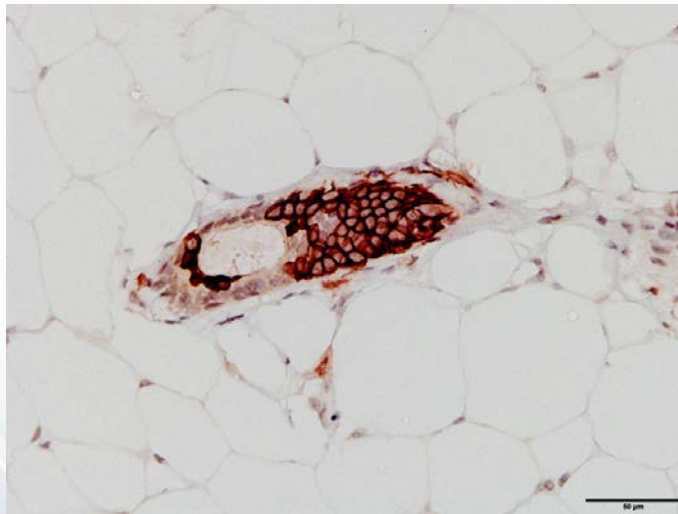


## Ruxolitinib for the Prevention of Breast Cancer

Yi Li, Ph.D., Baylor College of Medicine

*FY98 Postdoctoral Traineeship Award; FY03 and FY07 Idea Awards; FY11 Idea Expansion Award; FY19 Breakthrough Award – Level 2 – Population Science and Prevention*

Annually in the United States, an estimated 10% of breast biopsies result in a diagnosis of atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH), two types of benign breast lesions that carry a 30% chance of developing into breast cancer within 25 years of diagnosis. The side effects and duration of preventative treatment for ADH and ALH, which includes a 5-year course of antiestrogen therapy, lead many women to forego or discontinue their therapy prematurely, indicating a need for a new preventative treatment that would be widely accepted by these high-risk women. Toward this end, Dr. Li first developed a viral gene transfer system that allowed his team to dissect the genetic pathways involved in breast tumor development, and then leveraged that technology for the development of a novel breast cancer mouse model that recapitulated the natural progression of human disease. Using his viral gene transfer system and mouse model, Dr. Li not only identified activation of signal transducer and activator of transcription 5 (STAT5) in the Janus kinase 2 (JAK2)/STAT5 pathway as essential for the progression of atypical hyperplasia to breast tumor formation, but also determined that mouse mammary epithelial cells that activated STAT5 had lower levels of apoptosis. Importantly, genetic and pharmacological inhibition of STAT5 with the JAK1/2 inhibitor, ruxolitinib, induced apoptosis and caused early lesions to regress. The strong preclinical data from Dr. Li's mouse studies convinced Incyte, the company that makes ruxolitinib, to support a multi-center window-of-opportunity clinical trial (Translational Breast Cancer Research Consortium [TBCRC 042]; NCT02928978) examining whether prophylactic treatment with ruxolitinib inhibits activation of STAT5 in precancerous lesions, including ALH and ADH. Dr. Li plans to use mouse models of human ADH, as well as patient samples of ADH lesions collected as part of TBCRC 042, to determine the impact and effectiveness of ruxolitinib on restoring the apoptosis anti-cancer barrier for the prevention of disease progression. If successful, results from Dr. Li's work and TBCRC 042 will provide the initial evidence needed to support the clinical use of ruxolitinib as a breast cancer prevention strategy.



*Human ADH cells grown in mice as highlighted by a human cell specific marker Cytokeratin 19.*

# In the Clinical Pipeline

The BCRP has invested in the discovery and development of multiple therapies and diagnostic tools, many of which have continued to advance through the clinical pipeline. The BCRP is also currently funding several projects with clinical trials that have been initiated or are in preparation.

BCRP-funded
  Current phase supported by other sources
  Prior phase supported by other sources

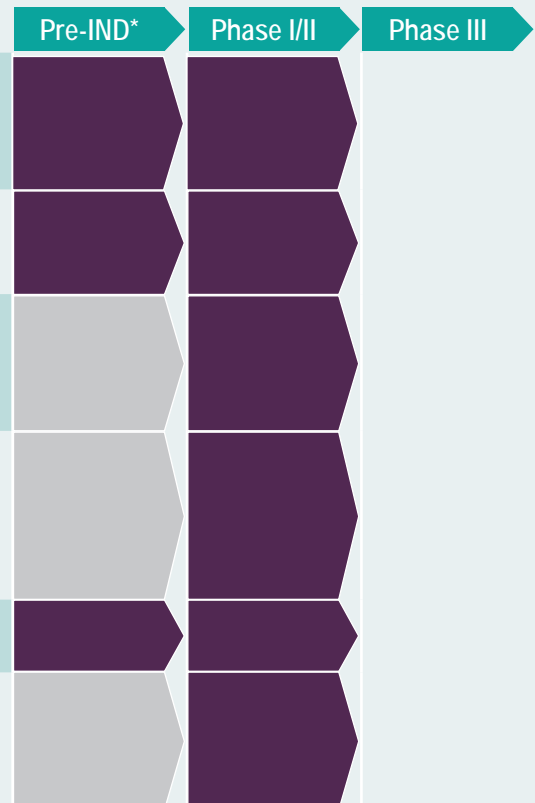
## Vaccines and Immunotherapies

	Pre-IND*	Phase I/II	Phase III
<p><b>NeuVax™</b> — <i>Constantin Ioannides and Elizabeth Mittendorf</i> An immunogenic peptide-based vaccine to prevent or delay breast cancer recurrence.</p>			
<p><b>HER2 Peptide-Based Vaccine</b> — <i>Mary (Nora) L. Disis</i> A HER2 intercellular domain peptide-based vaccine designed to treat breast cancer by stimulating the immune system-mediated destruction of remaining cancer cells after primary cancer therapy.</p>			
<p><b>STEMVAC</b> — <i>Mary (Nora) L. Disis</i> A multi-antigen vaccine comprised of Th1 epitopes derived from five breast cancer stem cell/epithelial-mesenchymal transition immunogenic proteins to inhibit tumor growth.</p>			
<p><b>Mammaglobin cDNA Vaccine</b> — <i>William Gillanders</i> A mammaglobin-A DNA vaccine that induces specific IFN-γ-secreting CD8 T cells and results in longer progression-free survival for patients.</p>			
<p><b>Folate Receptor Alpha Vaccines</b> — <i>Keith Knutson and Edith Perez</i> A vaccine targeting the folate receptor alpha in patients with TNBC to prevent or delay recurrence.</p>			
<p><b>HER2 Bi-Armed Activated T Cells (HER2 BATs)</b> — <i>Lawrence G. Lum</i> Therapy that induces the development of “memory” antigen-specific cytotoxic T cells directed at HER2 to treat women with HER2+ metastatic breast cancer.</p>			
<p><b>TRC105</b> — <i>Ben Seon</i> A monoclonal antibody that targets endoglin, inhibits angiogenesis, and was found in preclinical models to suppress the growth of both established and new tumors.</p>			
<p><b>Mesothelin-Targeted T-Cell Therapy for Metastatic Breast Cancer</b> — <i>Michel Sadelain and Shanu Modi</i> A mesothelin (MSLN) targeted chimeric antigen receptor (CAR) T-cell therapy for patients with treatment-refractory, metastatic TNBC.</p>			
<p><b>AVX901 HER2 Vaccine</b> — <i>H. Kim Lyerly</i> A vaccine composed of adenoviral and alphaviral vectors expressing the human HER2 gene.</p>			
<p><b>P10s-PADRE</b> — <i>Thomas Kieber-Emmons</i> A carbohydrate mimetic peptide vaccine that targets tumor-associated carbohydrate antigens.</p>			
<p><b>Combination Vaccine for HER2+ Metastatic Breast Cancer</b> — <i>Leisha Emens</i> Combining trastuzumab, cyclophosphamide, and an allogeneic granulocyte-macrophage colony-stimulating factor-secreting breast tumor vaccine for HER2+ metastatic breast cancer.</p>			
<p><b>Alpha-Lactalbumin Vaccine for Triple-Negative Breast Cancer</b> — <i>Vincent Tuohy and George Budd</i> A vaccine for TNBC patients that have recovered from current standard-of-care therapy with potential use in a prophylactic setting.</p>			

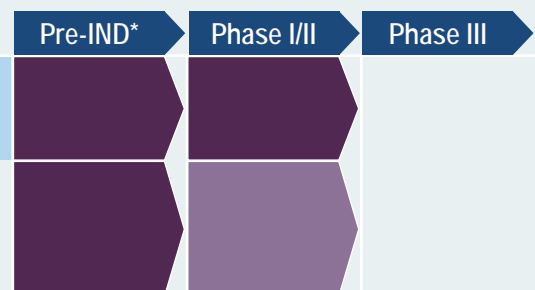
# In the Clinical Pipeline (cont.)

BCRP-funded
  Current phase supported by other sources
  Prior phase supported by other sources

## Vaccines and Immunotherapies (cont.)



## Diagnostics and Imaging



# In the Clinical Pipeline (cont.)

BCRP-funded
  Current phase supported by other sources
  Prior phase supported by other sources

## Therapeutics

	Pre-IND*	Phase I/II	Phase III
<p><b>Fatty Acid Synthase Inhibitor</b> — Ruth Lupu and Tufia Haddad</p> <p>Treatment of taxane-resistant metastatic HER2+ breast cancer with the fatty acid synthase inhibitor, TVB-2640 (3-V Biosciences), in combination with paclitaxel and trastuzumab.</p>			
<p><b>Temozolomide Combined with T-DM1</b> — Patricia Steeg</p> <p>Treatment of HER2+ breast cancer with T-DM1 and temozolomide to prevent formation of new metastases in the brain.</p>			
<p><b>Pembrolizumab and Tremelimumab for Treatment of Oligometastasis</b> — Andy Minn</p> <p>Radiation to metastatic lesions in combination with the immune checkpoint inhibitor pembrolizumab (PD-1 inhibitor) for patients with metastatic cancers for which anti-PD-1 therapy has failed. Radiation in combination with dual immune checkpoint blockade using tremelimumab (anti-CTLA-4) and MED14736 (anti-PDL1) to treat metastatic breast cancer and other cancers.</p>			
<p><b>Combining Aromatase and Src Inhibitors</b> — Joyce Slingerland and Isabel Chu</p> <p>Combination therapy using anastrozole, an aromatase inhibitor that stops estrogen production with Src inhibitor AZD0530 in postmenopausal women with ER+ breast cancer.</p>			
<p><b>5-Fluoro-2'deoxyctidine (FdCyd)</b> — Edward Newman</p> <p>Reversal of DNA methylation in several genes expressed by breast cancer cells with FdCyd and tetrahydrouridine.</p>			
<p><b>Anti-Androgen Therapy (Enzalutamide)</b> — Anthony Elias and Jennifer Richer</p> <p>Combining enzalutamide with fulvestrant to limit signaling through androgen receptors expressed on ER+ breast cancers that are resistant to anti-estrogen therapy.</p>			
<p><b>Meclofenamate for Brain Metastasis</b> — Joan Massague</p> <p>An FDA-approved non-aspirin, non-steroidal anti-inflammatory drug to prevent new brain metastases in patients with recurrent or progressive brain metastasis from a solid primary tumor.</p>			
<p><b>Aspirin as Adjuvant Therapy for Node-Positive Breast Cancer</b> — Eric Winer and Michelle Holmes</p> <p>Long-term aspirin use to reduce breast cancer recurrence and improve survival in patients with node-positive breast cancer.</p>			
<p><b>Molecular Triage Approach for a More Effective and Less Toxic Therapy for HER2+ Breast Cancer</b> — Mothaffar Rimawi and Rachel Schiff</p> <p>A molecular classifier, based on detection of resistance-associated genomic alterations, used to identify patients who may benefit from anti-HER2 therapy without added chemotherapy.</p>			
<p><b>A Novel Druggable Pathway That Prevents Bone Loss in Breast Cancer Patients</b> — Alana Welm</p> <p>Using the RON kinase inhibitor, BMS-777607/ASLAN002 in metastatic cancer patients to decrease osteolysis and promote bone repair.</p>			

# In the Clinical Pipeline (cont.)

BCRP-funded
  Current phase supported by other sources
  Prior phase supported by other sources

## Therapeutics (cont.)

### **Talazoparib** — Dennis Slamon

The novel PARP inhibitor talazoparib used in combination with other therapies to treat non-BRCA mutant TNBC.

### **Denosumab (XGEVA®)** — Josef Penninger, Judy Garber, and Christian Singer

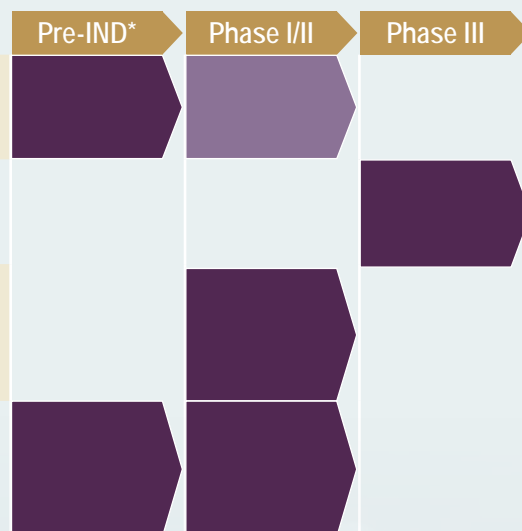
Prophylactic administration to reduce the risk of breast cancer in women with BRCA1 mutations.

### **Biomarker-Driven Targeted Therapy for Late-Recurring ER-Positive Breast Cancer** — Christina Curtis and George Sledge

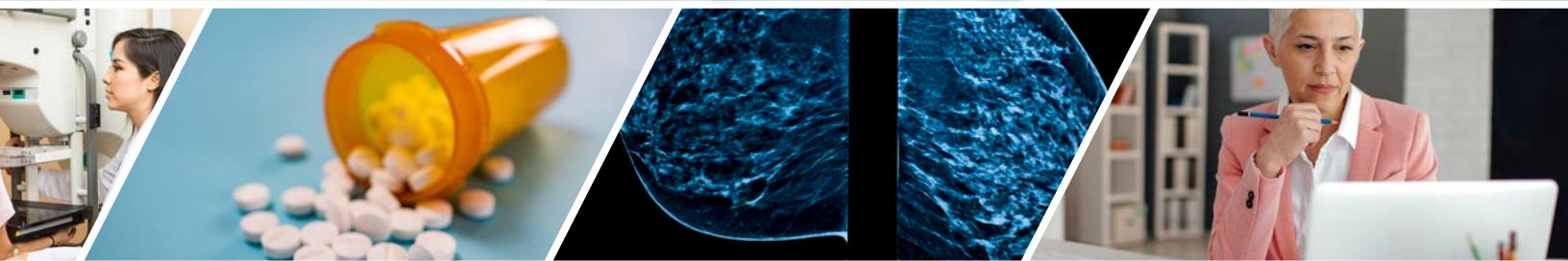
Targeting driver gene amplifications present in integrative clusters (IC1, IC2, and IC6) in high-risk ER+/HER2- breast cancer.

### **Neoadjuvant Endocrine Therapy (NET) + Radiotherapy** — Silvia Formenti and Sandra Demaria

Treatment of HR+ breast cancer with a combination of focal radiotherapy and letrozole NET to enable a response to immunotherapies.



# Products Making an Impact



## THERAPEUTICS

### ***Trastuzumab (Herceptin®)***

***Dennis Slamon***

This monoclonal antibody that targets the HER2 receptor revolutionized breast cancer treatment and the field of targeted therapeutics for HER2+ early-stage and metastatic breast cancers.

### ***ATLAS Clinical Trial***

***Richard Peto***

The ATLAS trial indicated reduced risk of recurrence or death from breast cancer in women who took tamoxifen for 10 years versus 5 years, changing clinical practice for premenopausal women with ER+ breast cancer.

### ***Prone Radiotherapy***

***Silvia Formenti***

Treating DCIS patients in the prone position with an accelerated, hypofractionated, whole breast radiation therapy resulted in reduced unnecessary radiation exposure of the heart and lungs.

### ***Palbociclib (Ibrance®)***

***Dennis Slamon***

This small molecule CDK inhibitor is FDA-approved to treat metastatic HR-positive, HER2-negative breast cancer in combination with letrozole or fulvestrant.

### ***Ribociclib (Kisquali®)***

***Dennis Slamon***

This small molecule CDK inhibitor is FDA-approved to treat metastatic HR-positive, HER2-negative breast cancer in combination with letrozole or fulvestrant.

### ***Abemaciclib (Verzenio™)***

***Dennis Slamon***

This small molecule CDK inhibitor is FDA-approved to treat metastatic HR-positive, HER2-negative breast cancer as a monotherapy or in combination with an aromatase inhibitor or fulvestrant.

## DIAGNOSTICS

### ***Sentinel Lymph Node Biopsy***

***Douglas Reintgen and Kathryn Verbanac***

This diagnostic/prognostic technique enables clinicians to determine both tumor staging and the extent to which more extensive lymph node surgery is necessary.

### ***Molecular Breast Imaging***

***Carrie Hruska***

This FDA-approved, commercially available nuclear medicine technique uses high resolution dual-head gamma cameras to detect the functional uptake of a radiotracer in the breast.

### ***Digital Mammography and Breast Tomosynthesis***

***Laurie Fajardo and Daniel Kopans***

This 3-D digital mammography tool improved sensitivity for detection of breast cancer in women with dense breast tissue and is FDA-approved and commercially available.

## PATIENT RESOURCES AND REGISTRIES

### ***BreastCancerTrials.org***

***Laura Esserman***

This online resource informs patients about breast cancer clinical trials and matches them with appropriate trials.

### ***Carolina Mammography Registry***

***Bonnie Yankaskas***

This population-based mammography registry became a member site of the National Cancer Institute Breast Cancer Surveillance Consortium, a national registry that provides a resource for researchers to study mammography screening on a national level.

### ***Dyson Family Risk Assessment Program***

***Mary Daly***

This program, which serves Philadelphia and its surrounding communities, provides a range of risk assessment, screening, and preventive services.

### ***BrainMetsBC.org***

***Patricia Steeg***

Breast cancer advocates led the efforts to develop this online resource that provides updates in both English and Spanish on current research, treatments, and clinical trials on brain metastases, as well as personal experiences written by patients.



## RISK ASSESSMENT

### ***BRCA2 617delT Mutation***

***David Goldgar and Susan Neuhausen***

One of the founder BRCA1/2 mutations that occurs in Ashkenazi Jews, a population with increased likelihood of BRCA1/2 mutations, is now part of a commercialized test for this risk group.

### ***OncoVue®***

***Eldon Jupe***

This commercially available genetic-based breast cancer risk test enables clinicians to identify high-risk patients and individualize breast cancer screening and monitoring.

### ***PTEN***

***Michael Wigler***

A test is commercially available to confirm PTEN mutations for clinical and prenatal diagnoses and identification of at-risk family members.

### ***PALB2 Mutations***

***Bing Xia***

Mutations in the PALB2 gene increase breast cancer susceptibility two-fold; a commercialized PALB2 genetic test is available for those with familial breast cancer.

### ***BROCA Cancer Risk Panel***

***Tomas Walsh and Mary-Claire King***

A comprehensive test that enables assessment of all known breast cancer genes and mutation types in a single assay.

## PROGNOSTICS

### ***Breast Cancer Index***

***Dennis Sgroi***

A commercialized test that evaluates the likelihood of recurrence and benefit from extended endocrine therapy.

### ***MetaSite Breast™***

***John Condeelis and Allison Harney***

Clinical Laboratory Improvement Amendments-certified and publicly available test measuring Tumor Microenvironment of Metastasis (TMEM) levels to predict the metastatic potential of the primary tumor.

### ***MenaCalc™***

***John Condeelis and Jeanine Pignatelli***

This test has been clinically validated for use in cancer treatment decision making and as an independent prognostic factor and predictor of metastasis.

## RESEARCH RESOURCES

### ***Expression Arrest™ shRNA Libraries***

***Gregory Hannon and Stephen Elledge***

This commercially available research tool provides ready-to-use, rapid RNAi screens for the entire human and mouse genomes to study gene regulation and identify new therapeutic targets in many diseases and conditions, including cancer.

### ***Three-Dimensional Culture Systems***

***Mina Bissell***

3-D culture models are currently utilized across academic laboratories and by drug companies as screening assays to test for therapeutic response.

### ***Novel Models for Breast Tumor Growth and Metastasis***

***Alana Welm***

Publicly available, patient-centric tumor graft mouse models that replicate the diversity of human breast cancer and enhance the study of tumor growth, metastasis, drug efficacy, and prognosis.



For more information, please visit

<https://cdmrp.army.mil>

or contact us at:

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12/2020

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