CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED
MEDICAL RESEARCH PROGRAMS

# Breast Cancer Research Program

Accelerating Progress Toward Ending Breast Cancer

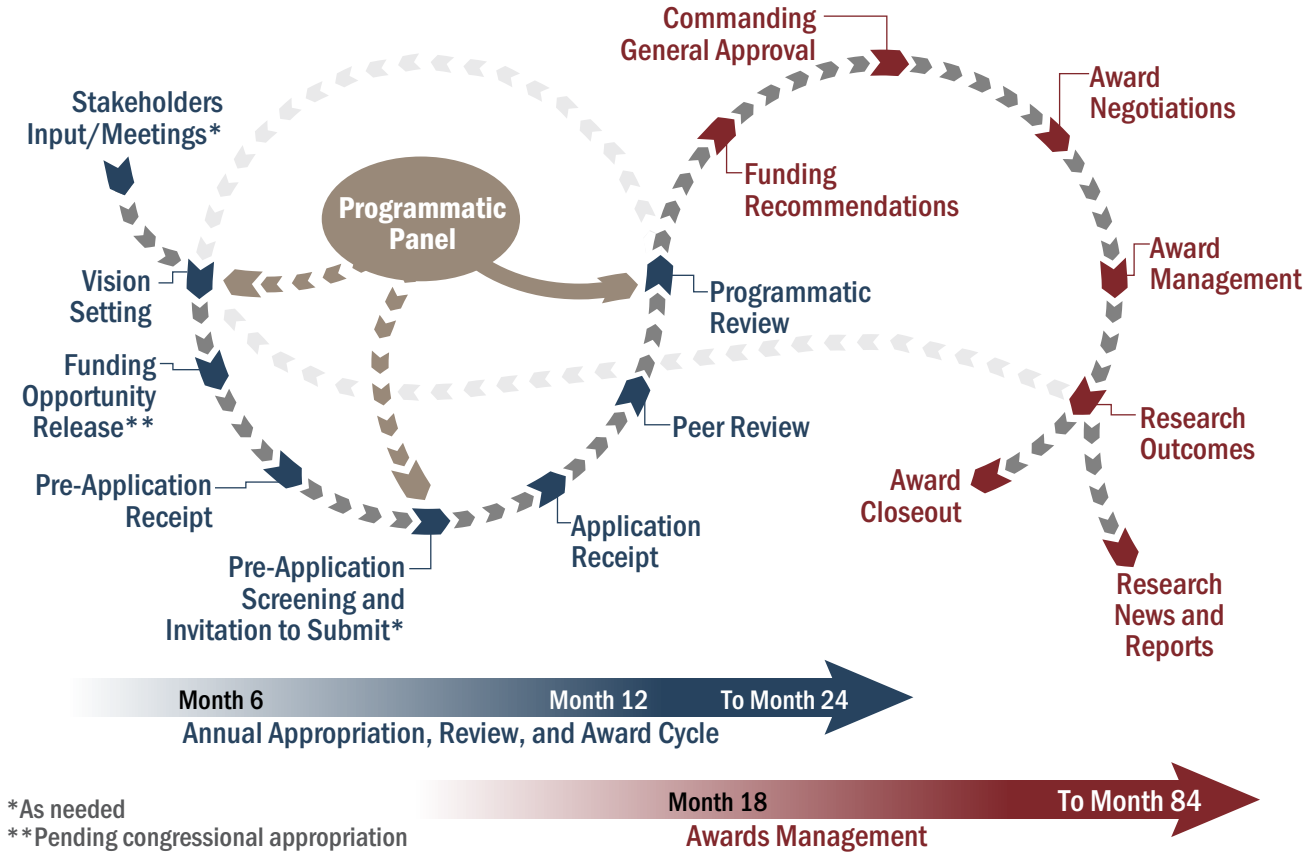
For more information, please visit
cdmrp.health.mil/bcrp

# CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

The Congressionally Directed Medical Research Programs was created in 1992 from a 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 managed over $22.3 billion in Congressional Special Interest funds from its inception through FY23. Congress provides overarching intent for each individual CDMRP program, such as the Breast Cancer Research Program, or BCRP, and specifies funding as part of the annual DOD appropriations bill.

## APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for evaluating applications that involves dynamic interaction between scientists, clinicians, consumers from advocacy communities, members of the military, and other specialists as applicable. The first tier of evaluation is a scientific peer review of applications measured against established criteria determining scientific merit. The second tier is a programmatic review conducted by the programmatic panel. At programmatic review, the programmatic panel compares the applications 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.




*CDMRP Two-Tier Review Process*

"It is exciting to know that the BCRP wants to hear from those who are living with breast cancer, including our insight on proposed research projects. Involving patient advocates in the review process helps ensure that researchers consider the day-to-day needs, concerns and challenges of people living with breast cancer. I am encouraged by the track record of therapies that have been developed with BCRP funding, and my participation in the process of reviewing proposed research makes me hopeful."

**Jamil Rivers,**
*Consumer Reviewer*

# BREAST CANCER RESEARCH PROGRAM

**VISION:** A world without breast cancer

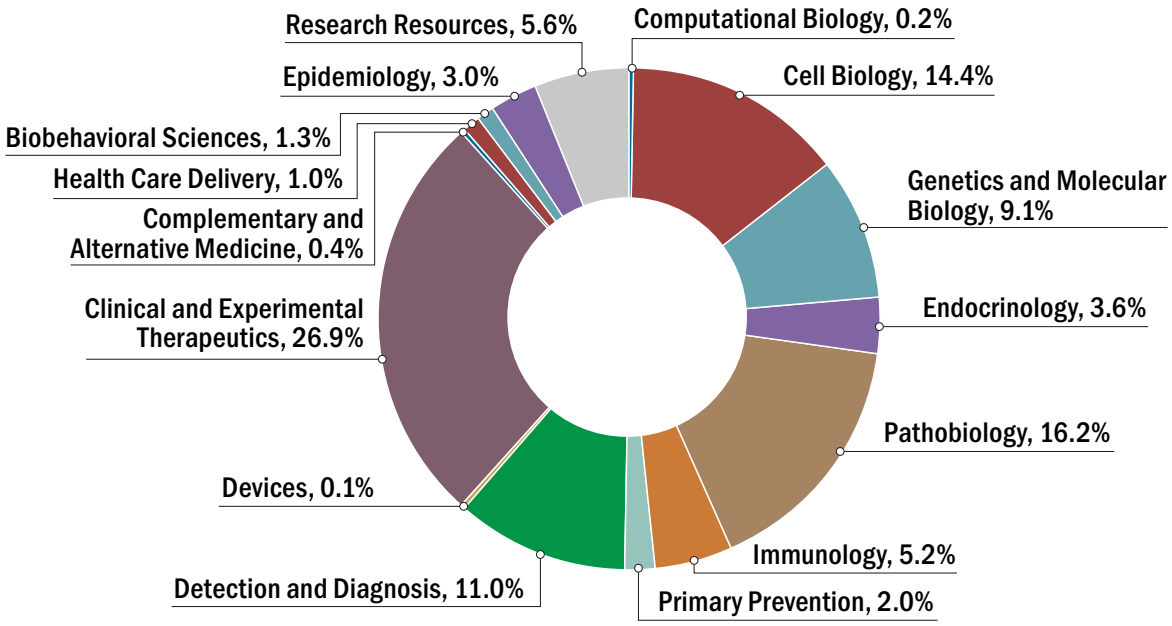
**MISSION:** To end breast cancer for Service Members and their Families, Veterans, and the general public by funding innovative, high-impact research through a partnership of scientists and consumers

## 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, resulted in more than $4.241 billion in congressional appropriations through FY23. The BCRP enables researchers to propose their best innovative ideas that address the urgency 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.

From FY92 to FY22, the BCRP funded 7,291 awards. In order to achieve its mission to end breast cancer, the BCRP invested in many different areas of scientific research as depicted in the pie chart below. The program's largest investment is in clinical and experimental therapeutics.

### FY92-FY22 BCRP Investment by Scientific Classification System Code




### FY93 to FY22 Metrics

PUBLICATIONS:
**19,415**

PATENTS:
**1,354**

CLINICAL TRIALS:
**220**

# THE BREAST CANCER LANDSCAPE

The *Breast Cancer Landscape*,[1] prepared by the BCRP, covers 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 the U.S. in 2023, it is estimated that 43,170 women and 530 men will die of breast cancer.

### RISK FACTORS

- Evidence attributes the majority of breast cancers to not only one factor, but to various physical, hormonal, environmental, and genetic factors.
- Most risk factors are not modifiable, including age, family history, reproductive history, ages at menarche/menopause, BRCA gene status, and breast density.

### RECURRENCE & METASTASIS

- An estimated 10% to 30% of women diagnosed with invasive breast cancer will experience a recurrence.
- Treatments that 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 receive the same treatment, as though all breast cancers were the same within a given 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. Financial toxicity from both direct and indirect expenses linked to treatment is high among breast cancer patients.

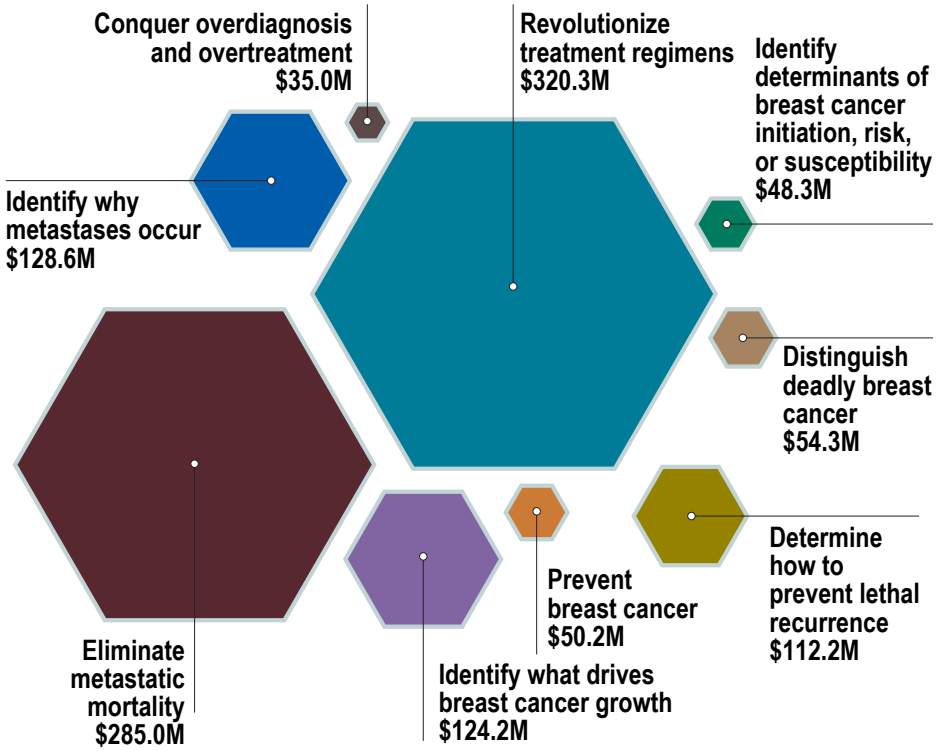
1 https://cdmrp.health.mil/bcrp/pdfs/BreastCancerLandscape2023.pdf

# BCRP OVERARCHING CHALLENGES

Considering the current *Breast Cancer Landscape* and the BCRP's mission to end breast cancer, each application must address at least one overarching challenge. The chart below indicates the program's investments in each of the following BCRP 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-FY22 BCRP Portfolio Investment by Overarching Challenge**



## RELEVANCE TO MILITARY HEALTH

- Breast cancer is the most common non-skin cancer in women and is the **deadliest cancer in females under 40**.[2,3]

- **Higher incidence rate** of breast cancer in female active-duty Service Members 40-59 years of age than in the general population.[4]

- The incident rate of breast cancer for active-duty women is **seven times higher** than the average incident rate of 15 other cancer types across all Service Members.[5]

## IMPACT IN THE MILITARY HEALTH SYSTEM

Preclinical research supported by the BCRP contributed to four FDA-approved drugs: trastuzumab, palbociclib, ribociclib, and abemaciclib. For these drugs, between 2007 through 2018 there were:

- Over **34,600** prescriptions written for more than **2,400** Military Health Service patients including active-duty Service Members and DOD beneficiaries with TRICARE coverage.[6]

[2] https://gis.cdc.gov/Cancer/USCS/#/AtAGlance/
[3] https://seer.cancer.gov/statfacts/html/aya.html
[4] https://pubmed.ncbi.nlm.nih.gov/37725334/
[5] https://pubmed.ncbi.nlm.nih.gov/27501939/
[6] Source: Defense Health Agency Pharmacy Analytics Support Section

# STRATEGIC PARTNERSHIPS: Scientists and Consumers Working Together to End Breast Cancer

*Photo provided*

"The DOD BCRP challenges the status quo and encourages new ideas, breakthroughs and collaboration. The program responds quickly to scientific advances; it is efficient and accountable to the public and focuses on research that will have a meaningful impact. It is an honor to serve, along with other committed advocates, scientists, clinicians and the DOD, as we work together to end breast cancer."

***Pat Haugen, FY24 BCRP Programmatic Panel Chair***

*Photo provided*

"Working as a consumer reviewer for the BCRP has been an absolute honor. I consider it a privilege to work on panels with other scientists, experts and peers with a common goal in mind, making an impactful difference in the lives of breast cancer patients by ensuring adequate and efficient treatments."

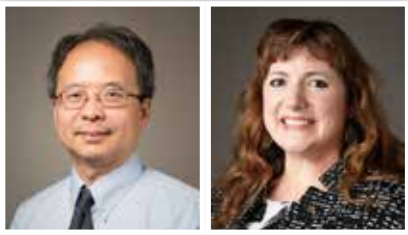
***Krystle Hensley, Consumer Reviewer***

*Photo provided*

"The DOD BCRP Breakthrough Award is a unique mechanism that funds projects with particularly high potential to impact the lives of breast cancer patients. Support from our Breakthrough Award - Level 4 allowed us to initiate the clinical testing of our new therapeutic vaccines that use patients' own dendritic cells to treat advanced breast cancer which has spread to the brain. These patients typically do not respond to immune checkpoint inhibitors used as single agents and currently lack effective treatment options. Based on our preliminary data, we have high expectations for the anticipated findings from our two recently started trials."

***Pawel Kalinski, M.D., Ph.D., Roswell Park Comprehensive Cancer Center***

# RESEARCH HIGHLIGHTS



*Photos provided. Photos by Caleb Jia, University of Tennessee Health Science Center Communications and Marketing Department*

## A Novel Tubulin Inhibitor to Overcome Taxane Resistance in Metastatic Breast Cancer

**Wei Li, Ph.D., and Tiffany Seagroves, Ph.D., University of Tennessee Health Science Center**

Triple-negative breast cancer, or TNBC, is a particularly aggressive subtype of breast cancer associated with early recurrence and a high rate of metastasis. Treatment for TNBC commonly includes tubulin inhibitors, or taxane drugs, which target the proteins essential for the division and proliferation of both cancer and healthy cells. However, there are limitations associated with prolonged use of these drugs, including development of chemotherapy resistance and dose-limiting toxicities. To overcome these challenges, Wei Li, Ph.D., and Tiffany Seagroves, Ph.D., at the University of Tennessee Health Science Center identified a novel class of tubulin inhibitors that appears to overcome mechanisms of taxane resistance and have lower toxicity, based on preclinical studies. In animal models of TNBC, the lead compound, sabizabulin, inhibited primary tumor growth and metastasis and also inhibited the growth of established metastases present before treatment initiation. With BCRP support, Li and Seagroves aim to develop new analogs of sabizabulin for potential use in treating metastatic breast cancer, including in patients whose cancer progresses on taxane drugs. Through structure-based optimization of sabizabulin, the researchers identified and evaluated an analog called CH-2-77 for anticancer activity in TNBC models. When tested in a panel of TNBC cell lines, nanomolar concentrations of CH-2-77 inhibited cellular proliferation and overcame taxane resistance. The team also observed that CH-2-77 disrupted microtubule assembly, inhibited migration and invasion, and induced cell death pathways. Additionally, when studied in an animal model of TNBC, CH-2-77 significantly inhibited primary tumor growth and lung metastases with no obvious signs of toxicity. Findings from the work of Li and Seagroves support the further development of CH-2-77 and similar compounds to address current clinical challenges in treating patients with TNBC.

**Publication:**

Deng S, Krutilina RI, Hartman KL, et al. 2022. Colchicine-Binding Site Agent CH-2-77 as a Potent Tubulin Inhibitor Suppressing Triple-Negative Breast Cancer. *Molecular Cancer Therapeutics* 21(7):1103-1114. https://doi.org/10.1158/1535-7163.mct-21-0899

*Photo provided*

## Programmable Probiotics for Targeted Breast Cancer Therapy

**Tal Danino, Ph.D., Columbia University**

Researchers continue to investigate probiotic bacteria as a potential therapeutic strategy for treating a variety of cancers, including breast cancer. This is an attractive strategy for several reasons, including the prospect of engineering probiotic bacteria to deliver genetically encoded anti-tumor agents. Despite the potential advantages, host toxicity from the bacteria has been shown to limit the tolerated dose and the effectiveness of the therapy. With BCRP support, Tal Danino, Ph.D., and his team developed genetically engineered bacteria that enable the programmable expression of surface molecules that protect microbes, called capsular polysaccharides, or CAP, to promote immune evasion and enhance tumor colonization and drug delivery while improving patient safety. The team studied CAP in *Escherichia coli* strain Nissle 1917, or EcN, and created a novel inducible CAP system. Bacteria carrying their CAP system are termed EcN iCAP. Danino's team demonstrated that the encapsulating iCAP system enhanced bacterial survival in blood through protection from the immune system. In mice, the maximum tolerated dose of transiently induced EcN iCAP was about 10 times higher than the wild-type EcN or the CAP knockout strain. Furthermore, when researchers tested bacteria engineered to produce an anti-tumor agent in a preclinical breast cancer model, the toxin-producing EcN iCAP suppressed tumor growth more so than an unengineered control EcN. Finally, the researchers demonstrated activation of CAP after injection of EcN iCAP into a tumor, with subsequent trafficking of the bacteria to other tumors. This suggests the potential utility of the iCAP system as an alternate route of bacterial delivery to inaccessible tumors. Danino's study demonstrated that the tunable expression of CAP in engineered bacteria improved the maximum tolerated dose and anti-tumor effects in a model of breast cancer. Further investigation may accelerate the translation of engineered bacteria-based breast cancer therapies, with the potential to improve patient outcomes.

**Publication:**

Harimoto T, Hahn J, et al. 2022. A Programmable Encapsulation System Improves Delivery of Therapeutic Bacteria in Mice. *Nature Biotechnology* 40(8):1259-1269. https://doi.org/10.1038/s41587-022-01244-y

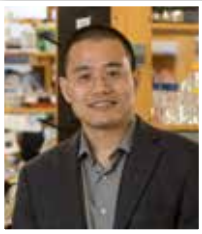



*Photo provided. Photo by Denise Applewhite, Princeton University*

*Photo provided*

## Functional Mechanism and Targeting of Metadherin in Breast Cancer

**Yibin Kang, Ph.D., Princeton University and Yongna Xing, Ph.D., University of Wisconsin-Madision**

Most breast cancer deaths result from metastatic disease, underscoring the urgent need for effective therapeutics to treat metastatic breast cancer. Two important challenges associated with metastatic breast cancer are the development of therapeutic resistance and the ability of tumors to circumvent the body's natural immune detection and elimination strategies. Yibin Kang, Ph.D., and Yongna Xing, Ph.D., previously demonstrated that metadherin, or MTDH, plays a critical role in cancer progression and chemotherapy resistance by creating a protein complex with Staphylococcal nuclease domain containing 1, or SND1. Mutations in certain portions of the MTDH protein prevent MTDH-SND1 interactions, thereby eliminating the tumor-initiating effects normally mediated by MTDH. With BCRP support, the team built on their previous research to identify novel compounds that target the MTDH-SND1 complex to suppress tumor growth and metastasis. The team found that methyltriazolopyridinamine, or C26-A6, blocked the interaction of MTDH and SND1, inhibiting tumor growth and metastasis in a preclinical model of TNBC. Additionally, combination treatment with C26-A6 and the chemotherapy drug paclitaxel further reduced primary tumor growth and metastasis. Using preclinical models, Kang's team investigated the mechanisms underlying the role of MTDH in breast cancer, demonstrating that MTDH-SND1 complexes inhibit antigen presentation in cancer cells, and high levels of MTDH lead to poor cytotoxic T cell infiltration and activation. In animals with metastatic tumors, treatment with C26-A6 increased antigen presentation as well as T cell infiltration and activation. C26-A6 treatment combined with an anti-PD-1 drug currently used as a cancer immune checkpoint blockade therapy resulted in increased inhibition of tumor growth and metastasis, compared to treatment with anti-PD-1 therapy alone. Results from Kang and Xing's BCRP-funded research support the potential for novel therapeutics to inhibit breast cancer progression and metastasis. Additionally, their findings show that targeting MTDH can sensitize tumors to therapies currently used to treat metastatic disease. Taken together, these findings could improve outcomes for metastatic breast cancer patients.

**Publications:**

Shen M, Smith HA, Wei Y, et al. 2022. Pharmacological disruption of the MTDH-SND1 complex enhances tumor antigen presentation and synergizes with anti-PD-1 therapy in metastatic breast cancer. *Nature Cancer* 3(1):60-74. https://doi.org/10.1038/s43018-021-00280-y

Shen M, Wei Y, Hahn K, et al. 2022. Small-Molecule Inhibitors That Disrupt the MTDH-SND1 Complex Suppress Breast Cancer Progression and Metastasis. *Nature Cancer* 3(1):43-59. https://doi.org/10.1038/s43018-021-00279-5

*Photo provided*

## Pathway to the Clinic: A Novel Automated Liquid Biopsy Biomarker Assay for Metastatic Breast Cancer

**Saraswati Sukumar, Ph.D., Johns Hopkins University**

Treatment regimens for some cancers are guided in part by tests that quantify biomarkers in the blood; these tests help evaluate how a patient is responding to treatment and assist clinicians in making informed decisions about which treatment to choose or when to try other options. Currently, no such molecular tests to predict disease progression in patients undergoing treatment for metastatic breast cancer exist. Thus, many patients continue taking treatments with unfavorable side effects, only to find that their disease has not responded and is still progressing. To address this need, Saraswati Sukumar, Ph.D., and her team previously developed a novel automated liquid biopsy assay for measuring biomarkers in the blood and predicting disease progression in women with metastatic breast cancer. Their assay quantifies circulating tumor DNA by measuring methylation, a surface modification of DNA, at genes known to be modified in breast cancer tumors. With BCRP support, the team adapted their assay for automated clinical application and developed the Liquid Biopsy-Breast Cancer Methylation, or LBx-BCM, prototype assay. After confirming in laboratory studies that it reliably detected methylated breast cancer tumor DNA in serum samples, the team conducted a prospective clinical study with patients beginning a treatment regimen for metastatic breast cancer. They paired the LBx-BCM assay measurements with participant data and developed a preliminary risk model that effectively predicted 3-, 6-, and 9-month disease progression. In another study recently funded by the BCRP, Sukumar is conducting research to improve the sensitivity of the test and evaluate its utility for monitoring disease response and predicting breast cancer recurrence in patients with localized disease undergoing neoadjuvant therapy. Should this assay reach the clinic, it has the potential to enhance disease monitoring and enable earlier replacement of ineffective treatments with more suitable options, thereby improving patient care and outcomes.

**Publication:**

Visvanathan K, Cope L, Fackler MJ, et al. 2023. Evaluation of a Liquid Biopsy-Breast Cancer Methylation (LBx-BCM) Cartridge Assay for Predicting Early Disease Progression and Survival: TBCRC 005 Prospective Trial. *Clinical Cancer Research* 29(4):784-790. https://doi.org/10.1158/1078-0432.CCR-22-2128

*Photo provided*

# Identification of Actionable Networks Promoting Breast Cancer Progression and Brain Metastasis

**Ann Marie Pendergast, Ph.D., Duke University School of Medicine**

Patients with HER2+ breast cancer experience metastasis at higher rates than other patients, and brain metastasis in particular is a devastating complication. Historically, HER2-targeted therapies have been unsuccessful in treating brain metastases due to poor blood-brain barrier, or BBB, penetrance and drug resistance. Previous research showed that the Abelson, or ABL, family kinases ABL1 and ABL2 play a role in the function and signaling of cell-surface receptors like HER2. With BCRP support, Ann Marie Pendergast, Ph.D., and her team studied ABL kinase inhibition and its effect on breast cancer progression and metastasis. In mice treated with an inhibitor of ABL kinase, there was an 80% decrease in ABL kinase activity, a decrease in metastasis to the brain, and an increase in overall survival compared to controls. The team evaluated HER2 protein levels in HER2+ brain metastatic cell lines and observed that the inhibition of ABL kinase reduced HER2 protein levels. The team tested whether ABL kinase inhibition altered transcription of the gene *ERBB2* that encodes HER2, HER2 protein stability, and translation of corresponding messenger RNA, or mRNA, into protein. They found that the decline in HER2 protein levels resulted from decreased interaction between the *HER2/ERBB2* mRNA and an RNA binding protein called Y-box-binding protein, or YB-1, which plays a role in regulating protein synthesis. In addition, loss of YB-1 expression in HER2+ brain metastatic cells decreased HER2 protein levels and impaired brain metastatic outgrowth, leading to improved survival in preclinical models. Finally, the team showed that ABL-mediated phosphorylation of YB-1 is required to promote HER2 protein synthesis. Overall, the research team's findings unveiled the mechanism of ABL-YB-1 signaling and its effects on the HER2 protein. The finding that cancer cells expressing HER2 can be targeted by BBB-permeable inhibitors of the ABL kinases suggests that these drugs might be effective in treating patients with HER2+ breast cancer brain metastasis. Continued research on the ABL-YB-1 pathway and its regulation of HER2 may improve breast cancer treatment and decrease the development of metastasis, thereby improving patient outcomes.

**Publication:**

McKernan CM, Khatri A, Hannigan M, et al. 2022. ABL Kinases Regulate Translation in HER2+ Cells Through Y-Box-Binding Protein 1 to Facilitate Colonization of the Brain. *Cell Reports* 40(9):111268. https://doi: 10.1016/j.celrep.2022.111268

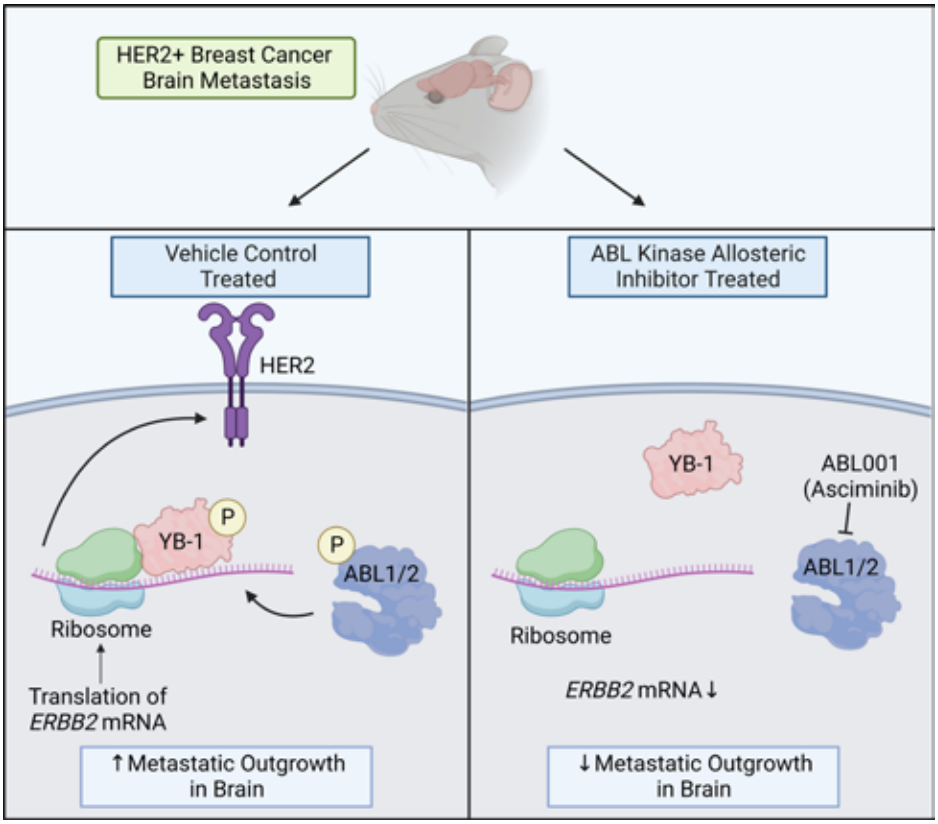
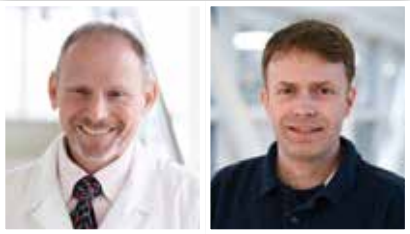



*Figure 1. Model diagram illustrating the role of the ABL-YB-1 signaling axis in the regulation of HER2 translation and the effectiveness of ABL kinase inhibitor treatment in decreasing HER2 translation and impairing outgrowth of metastatic HER2+ breast cancer cells in the brain. (Figure provided by the Principal Investigator.)*



*Photos provided*

# Inhibition of Myeloid-Derived Suppressor Cell Biogenesis to Improve the Efficacy of Immune Checkpoint Inhibitors in Models of Triple-Negative Breast Cancer

**Scott Abrams, Ph.D., and Michael Nemeth, Ph.D., Roswell Park Comprehensive Cancer Center**

TNBC is a difficult-to-treat cancer that often spreads faster than other breast cancers and has higher rates of recurrence, leading to poorer outcomes. Immune checkpoint inhibitors, or ICIs, are drugs that prevent immune checkpoint proteins from suppressing immune function, thereby boosting antitumor activity. TNBC tumors, however, may negate the effects of ICIs by inducing the development of myeloid-derived suppressor cells, or MDSCs. MDSCs are derived from immature bone marrow cells, known as myeloid progenitors. While MDSCs normally exist only briefly to turn off the immune response after an acute injury or cellular damage, TNBC tumors induce persistent accumulation of MDSCs, which leads to immune suppression potentially limiting the efficacy of ICIs. With BCRP support, Scott Abrams, Ph.D., and Michael Nemeth, Ph.D., aim to improve the efficacy of ICIs in TNBC by preventing MDSC development, also known as biogenesis. Using a bone marrow culture system, the team first showed that a compound called brequinar, or BRQ, significantly reduced the prevalence of MDSCs and consequently limited their suppression of T cells, which play an integral role in the antitumor response. They also demonstrated that BRQ reduced the expression of multiple genes involved in immune suppression and increased the expression of a gene known to dampen MDSC development. When tested in mouse models of TNBC, MDSCs collected from BRQ-treated mice showed signs of greater maturation, suggesting that BRQ promoted the differentiation of myeloid progenitors as a potential reason for their reduced immune suppressive activity. The team next used the same preclinical models of TNBC to test BRQ in combination with anti-PD-1, an antibody that inhibits the immune checkpoint protein PD-1 on T cells. Anti-PD-1 antibodies, such as pembrolizumab, are FDA-approved for the treatment of TNBC and other cancers. The team showed that neither BRQ nor anti-PD-1 alone exerted substantial antitumor effects in these preclinical models. However, when combined, these treatments acted synergistically to reduce the growth of TNBC tumors. BRQ alone and combined with anti-PD-1 also reduced metastases in the lung, a common site for metastatic spread of TNBC. Additional experiments demonstrated that BRQ treatment inhibited the ability of myeloid progenitors in the bone marrow to develop into MDSCs. Therapies for TNBC are limited, driving the need for new treatment options or improving existing treatments. Through their research, Abrams and Nemeth demonstrated that adding BRQ improved the efficacy of existing ICIs, and this may translate to effective clinical applications in patients with TNBC or other cancer types where MDSCs may pose a barrier to therapeutic efficacy.

**Publication:**

Colligan SH, Amitrano AM, Zollo RA, et al. 2022. Inhibiting the Biogenesis of Myeloid-Derived Suppressor Cells Enhances Immunotherapy Efficacy Against Mammary Tumor Progression. *The Journal of Clinical Investigation* 132(23):e158661. https://doi.org/10.1172/JCI158661

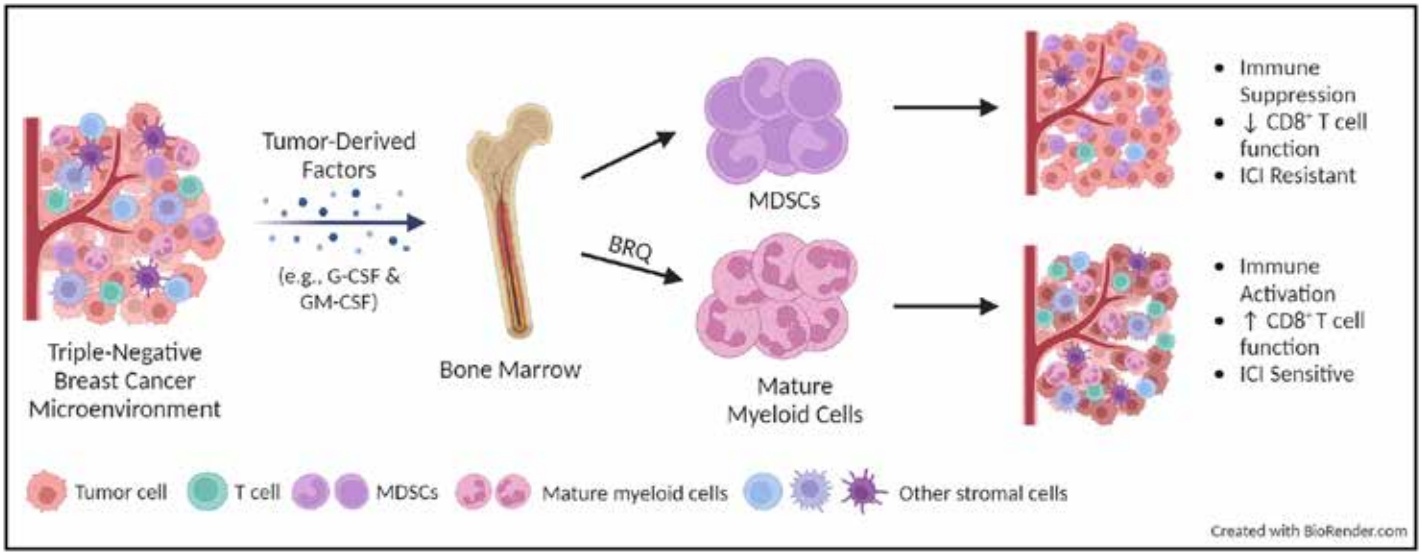



*Figure 2. This figure illustrates the impact of the drug BRQ on MDSC biogenesis and immune checkpoint inhibitor therapy on the antitumor response. (Figure provided by the Principal Investigator.) (Image generated with BioRender under license.)*

# 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 are underway or are in preparation.

*BCRP-funded** *Current phase supported by other sources* *Previous phase supported by other sources*

| VACCINES AND IMMUNOTHERAPIES | Pre-IND** | Phase I/II | Phase III |
|---|---|---|---|
| **NeuVax™ -** Constantin Ioannides and Elizabeth Mittendorf<br>*An immunogenic peptide-based vaccine to prevent or delay breast cancer recurrence.* | | | |
| **HER2 Intracellular Domain, or ICD, Vaccine -** Mary (Nora) L. Disis<br>*A cancer vaccine encoding the HER2 ICD to treat breast cancer by stimulating the immune system-mediated destruction of remaining cancer cells after primary cancer therapy.* | | | |
| **STEMVAC -** Mary (Nora) L. Disis<br>*A multi-antigen vaccine comprised of Th1 epitopes derived from five breast cancer stem cell/epithelial-to-mesenchymal transition immunogenic proteins to inhibit tumor growth.* | | | |
| **Mammaglobin-A cDNA Vaccine -** William Gillanders<br>*A mammaglobin-A DNA vaccine to induce antitumor immunity in breast cancer patients undergoing neoadjuvant endocrine therapy or chemotherapy.* | | | |
| **Folate Receptor Alpha Vaccine -** Keith Knutson, Edith Perez, and Saranya Chumsri<br>*A vaccine targeting the folate receptor alpha in patients with TNBC to prevent or delay recurrence.* | | | |
| **HER2 Bi-Armed Activated T Cells, or HER2 BATs -** Lawrence G. Lum<br>*A therapy that induces the development of "memory" antigen-specific cytotoxic T-cells directed at HER2 to treat patients with HER2+ metastatic breast cancer.* | | | |
| **TRC105 -** Ben Seon<br>*A monoclonal antibody that targets endoglin to suppress the growth of both established and new breast tumors.* | | | |
| **Mesothelin-Targeted T Cell Therapy -** Michel Sadelain, Prasad Adusumilli, and Shanu Modi<br>*A mesothelin-targeted chimeric antigen receptor, or CAR, T cell therapy to treat patients with treatment-refractory metastatic TNBC.* | | | |
| **AVX901 HER2 Vaccine, also called VRP-HER2 -** H. Kim Lyerly<br>*A vaccine composed of an alphaviral vector expressing the human HER2 gene to treat patients with HER2+ metastatic breast cancer.* | | | |
| **P10s-PADRE with Standard Neoadjuvant Chemotherapy -** Thomas Kieber-Emmons<br>*A carbohydrate mimetic peptide vaccine that targets tumor-associated carbohydrate antigens in combination with standard neoadjuvant chemotherapy to treat patients with TNBC and ER+/HER2- breast cancer.* | | | |
| **Combination Vaccine for HER2+ Metastatic Breast Cancer -** Leisha Emens<br>*Combining trastuzumab, cyclophosphamide, and an allogeneic granulocyte-macrophage colony stimulating factor-secreting breast tumor vaccine to treat HER2+ metastatic breast cancer.* | | | |
| **Alpha-Lactalbumin Vaccine -** G. Thomas Budd, Vincent Tuohy, and Thaddeus Stappenbeck<br>*A vaccine for TNBC patients recovering from current standard-of-care therapy or administered to healthy individuals to prevent the development of breast cancer.* | | | |

* May also be supported by non-BCRP sources

** Investigational New Drug (IND)

# IN THE CLINICAL PIPELINE (cont.)

*BCRP-funded** *Current phase supported by other sources* *Previous phase supported by other sources*

| VACCINES AND IMMUNOTHERAPIES | Pre-IND** | Phase I/II | Phase III |
|---|---|---|---|
| **NY-ESO-1-Specific T Cell Receptor-Engineered T Cells -** Rongfu Wang<br>*A therapy using T-cell receptors engineered to recognize the NY-ESO-1 cancer antigen to treat locally advanced or metastatic TNBC.* | | | |
| **HER2-Specific Helper T Cell Epitope Vaccine -** Keith Knutson and Amy Degnim<br>*A HER2/neu subdominant epitope-based vaccine to enhance HER2-specific CD4 T cell immunity in patients with ductal carcinoma in situ.* | | | |
| **Multivalent Th1 DNA Vaccine with HER2-pulsed IL-12 secreting DC1 Vaccine -** Brian Czerniecki<br>*Combining a multivalent Th1 epitope anti-oncodriver DNA vaccine and HER2-pulsed IL-12 secreting dendritic cell 1, or DC1, vaccine to improve complete pathologic response rates and prevent recurrence in HER2+ breast cancer.* | | | |
| **Trastuzumab Emtansine/Pertuzumab with HER2 HLA-DR Vaccine Therapy -** Keith Knutson and Saranya Chumsri<br>*A multi-epitope HER2 vaccine administered during anti-HER2 maintenance therapy in patients with residual disease post-neoadjuvant chemotherapy to block disease recurrence and metastasis.* | | | |
| **Regional Oncolytic Poliovirus Immunotherapy -** Smita Nair<br>*Oncolytic poliovirus PVSRIPO to eradicate tumors in patients with TNBC.* | | | |
| **Overcoming Immunotherapy Resistance Using Radiotherapy Mediated Immunomodulation -** Stephen Shiao and Simon Knott<br>*Using preoperative focal radiation combined with pembrolizumab to generate antitumor immune responses in patients diagnosed with early-stage operable TNBC or ER+ breast cancers.* | | | |
| **Novel Immunotherapy for Brain-Metastatic Breast Cancer -** Pawel Kalinski and Brian Czerniecki<br>*Dendritic cell vaccines against HER2/HER3 combined with pembrolizumab to treat patients with brain metastasis from TNBC or HER2+ breast cancer. Dendritic cell vaccine to treat patients with leptomeningeal disease from TNBC or HER2+ breast cancer.* | | | |
| **B7-H3 Specific CAR T Cell Immunotherapy -** Marcela Maus, Soldano Ferrone, and Steven Isakoff<br>*A B7-H3 specific CAR T cell with a safety switch to treat patients with metastatic TNBC.* | | | |
| **DIAGNOSTICS AND IMAGING** | **Pre-IND**** | **Phase I/II** | **Phase III** |
| **Targeted HER2 Radiotracer -** Gary Ulaner<br>*89Zr-trastuzumab to determine the proportion of patients with HER2- primary breast cancer who develop imageable HER2+ metastases.* | | | |
| **Polycationic Peptides for Fluorescence-Guided Surgery -** Roger Tsien<br>*Protease-activatable fluorescent peptide, AVB-620, injected prior to surgery to enable surgeons to identify critical cancer margins for tumor resection and examine lymph nodes for invasive disease.* | | | |
| **TrackDOI -** Darren Roblyer<br>*A new optical metabolic scanning technology, TrackDOI, to monitor breast cancer patient tumor response to neoadjuvant chemotherapy in real time.* | | | |

* May also be supported by non-BCRP sources

** Investigational New Drug (IND)

# IN THE CLINICAL PIPELINE (cont.)

*BCRP-funded** *Current phase supported by other sources* *Previous phase supported by other sources*

| THERAPEUTICS | Pre-IND** | Phase I/II | Phase III |
|---|---|---|---|
| **Fatty Acid Synthase Inhibitor -** Ruth Lupu and Tufia Haddad<br>*Combining the fatty acid synthase inhibitor, TVB-2640 (Sagimet Biosciences), with paclitaxel and trastuzumab to treat patients with taxane-resistant metastatic HER2+ breast cancer.* | | | |
| **Temozolomide Combined with T-DM1 -** Patricia Steeg<br>*Treatment of HER2+ breast cancer with T-DM1 and temozolomide to prevent formation of new metastases in the brain.* | | | |
| **Radiation with Pembrolizumab and/or Tremelimumab -** Andy Minn<br>*Administering radiation therapy to metastatic lesions in combination with pembrolizumab (PD-1 inhibitor) to treat patients with metastatic cancers that did not initially respond to anti-PD-1 therapy. Radiation combined with dual immune checkpoint blockade using tremelimumab (anti-CTLA-4) and MED14736 (anti-PD-L1) to treat metastatic breast cancer.* | | | |
| **Anastrozole with AZD0530 -** Joyce Slingerland and Isabel Chu<br>*Combining anastrazole, an aromatase inhibitor that stops estrogen production, with a Src inhibitor, AZD0530, to test tolerability and efficacy in post-menopausal women with ER+ breast cancer.* | | | |
| **5-Fluoro-2'deoxycytidine (FdCyd) -** Edward Newman<br>*Combining FdCyd with tetrahydrouridine to reverse DNA methylation in several genes expressed by breast cancer cells and control tumor growth.* | | | |
| **Enzalutamide + Fulvestrant -** Anthony Elias and Jennifer Richer<br>*Combining enzalutamide with fulvestrant to limit signaling through androgen receptors expressed on advanced ER+ breast cancers that are resistant to anti-estrogen therapy. Preoperative fulvestrant with or without enzalutamide to reduce tumor growth prior to surgery in ER+ breast cancer patients with locally advanced disease.* | | | |
| **Meclofenamate for Brain Metastasis -** Joan Massague<br>*An FDA-approved non-steroidal, anti-inflammatory drug, meclofenamate, to prevent new brain metastases in patients with recurrent or progressive brain metastasis from a solid primary tumor.* | | | |
| **Aspirin as Adjuvant Therapy for Node-Positive Breast Cancer -** Eric Winer, Wendy Chen, and Michelle Holmes<br>*Long-term aspirin to reduce breast cancer recurrence and improve survival in patients with node-positive breast cancer.* | | | |
| **Molecular Triage Approach for a More Effective and Less Toxic Therapy for HER2+ Breast Cancer -** Mothaffar Rimawi and Rachel Schiff<br>*A molecular classifier, based on detection of resistance-associated genomic alterations, to identify patients who may benefit from anti-HER2 therapy without added chemotherapy.* | | | |
| **BMS-777607/ASLAN002 -** Alana Welm<br>*The novel RON kinase inhibitor, BMS-777607/ASLAN002, to prevent bone metastasis formation by decreasing bone loss and promoting bone repair in metastatic breast cancer patients.* | | | |

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** Investigational New Drug (IND)

# IN THE CLINICAL PIPELINE (cont.)

*BCRP-funded** *Current phase supported by other sources* *Previous phase supported by other sources*

| THERAPEUTICS | Pre-IND** | Phase I/II | Phase III |
|---|---|---|---|
| **Talazoparib -** Dennis Slamon<br>*Combining the novel PARP inhibitor talazoparib with other therapies to treat non-BRCA mutant TNBC.* | | | |
| **Denosumab (XGEVA®) -** Josef Penninger, Judy Garber, and Christian Singer<br>*Prophylactic administration of denosumab to prevent the development of breast cancer in women with BRCA1 germline mutations.* | | | |
| **Biomarker-Driven Targeted Therapy for Late-Recurring ER-Positive Breast Cancer**<br>Christina Curtis, George Sledge, and Jennifer Caswell-Jin<br>*Therapeutics targeting driver gene amplifications present in integrative clusters (IC1, IC2, and IC6) to treat high-risk ER+/HER2- breast cancer.* | | | |
| **Neoadjuvant Endocrine Therapy (NET) + Radiotherapy -** Silvia Formenti and Sandra Demaria<br>*Treating HR+ breast cancer with a combination of focal radiotherapy and letrozole NET to enable a response to immunotherapies.* | | | |
| **Functional Precision Oncology - Patient Derived Breast Tumor Grafts -** Christos Vaklavas and Alana Welm<br>*Patient derived breast tumor grafts to predict, prevent, and inform treatment of recurrence in patients with HR-low/HER2- or TNBC.* | | | |
| **Ruxolitinib -** Yi Li<br>*Ruxolitinib for prevention of breast cancer in patients with high risk and precancerous breast conditions* | | | |
| **Enobosarm -** Theresa Hickey<br>*Treating AR+ breast cancer with a selective androgen receptor targeting agonist, enobosarm.* | | | |
| **AOH1996 -** Robert Hickey and John Perry<br>*A novel inhibitor of the cancer-associated proliferating cell nuclear antigen (caPCNA) protein, AOH1996, to treat refractory solid tumors including breast tumors.* | | | |
| **Fulvestrant and Binimetinib -** Eric Chang, Bora Lim, and Matthew Ellis<br>*Combining fulvestrant with the mitogen-activated protein kinase inhibitor, binimetinib, to treat ER+ metastatic breast cancers expressing mutated neurofibromatosis 1.* | | | |
| **Abemaciclib and Pembrolizumab -** Sandra McAllister<br>*Combining abemaciclib, a CDK4/6 inhibitor, with pembrolizumab, a PD-1 inhibitor, to treat HR+, HER2- breast cancer.* | | | |
| **PLX3397 and Eribulin -** Lisa Coussens<br>*Eribulin in combination with PLX3397, a novel CSF1 inhibitor, to treat patients with metastatic breast cancer.* | | | |
| **Ivermectin and Balstilimab -** Peter Lee<br>*Combining ivermectin with balstilimab (PD-1 inhibitor) for the treatment of metastatic TNBC.* | | | |

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** Investigational New Drug (IND)

# 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 ductal carcinoma in situ 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 cyclin-dependent kinase, or CDK, inhibitor is FDA-approved to treat HR+, HER2- advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant.

**Ribociclib (Kisqali®) -** ***Dennis Slamon***
This small molecule CDK inhibitor is FDA-approved to treat HR+, HER2- advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant.

**Abemaciclib (Verzenio®) -** ***Dennis Slamon***
This small-molecule CDK inhibitor is FDA-approved to treat HR+, HER2- advanced or metastatic breast cancer as a monotherapy or in combination with an aromatase inhibitor or fulvestrant. It is also approved in combination with endocrine therapy for adjuvant treatment of some patients with high-risk early-stage HR-positive, HER2-negative breast cancer.

## DIAGNOSTICS AND PROGNOSTICS

**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 three-dimensional digital mammography tool improved sensitivity for detection of breast cancer in women with dense breast tissue and is FDA-approved and commercially available.

**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 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.

# 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 gene 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 twofold; 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.

# PATIENT RESOURCES AND REGISTRIES

### Dyson Family Risk Assessment Program
*Mary Daly*
This program, which serves Philadelphia, Pennsylvania, and its surrounding communities, provides a range of risk assessment, screening, and preventive services.

### 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.

### BreastCancerTrials.org
*Laura Esserman*
This online resource informs patients about breast cancer clinical trials and matches them with appropriate trials.

# RESEARCH RESOURCES

### Expression Arrest™ shRNA Libraries
*Gregory Hannon and Stephen Elledge*
This commercially available research tool provides ready-to-use, rapid RNA interference 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*
Three-dimensional 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.health.mil***
**or contact us at:**
***usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@health.mil***

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