CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED
MEDICAL RESEARCH PROGRAMS

Breast Cancer Research Program

Accelerating Progress Toward a World Without Breast Cancer

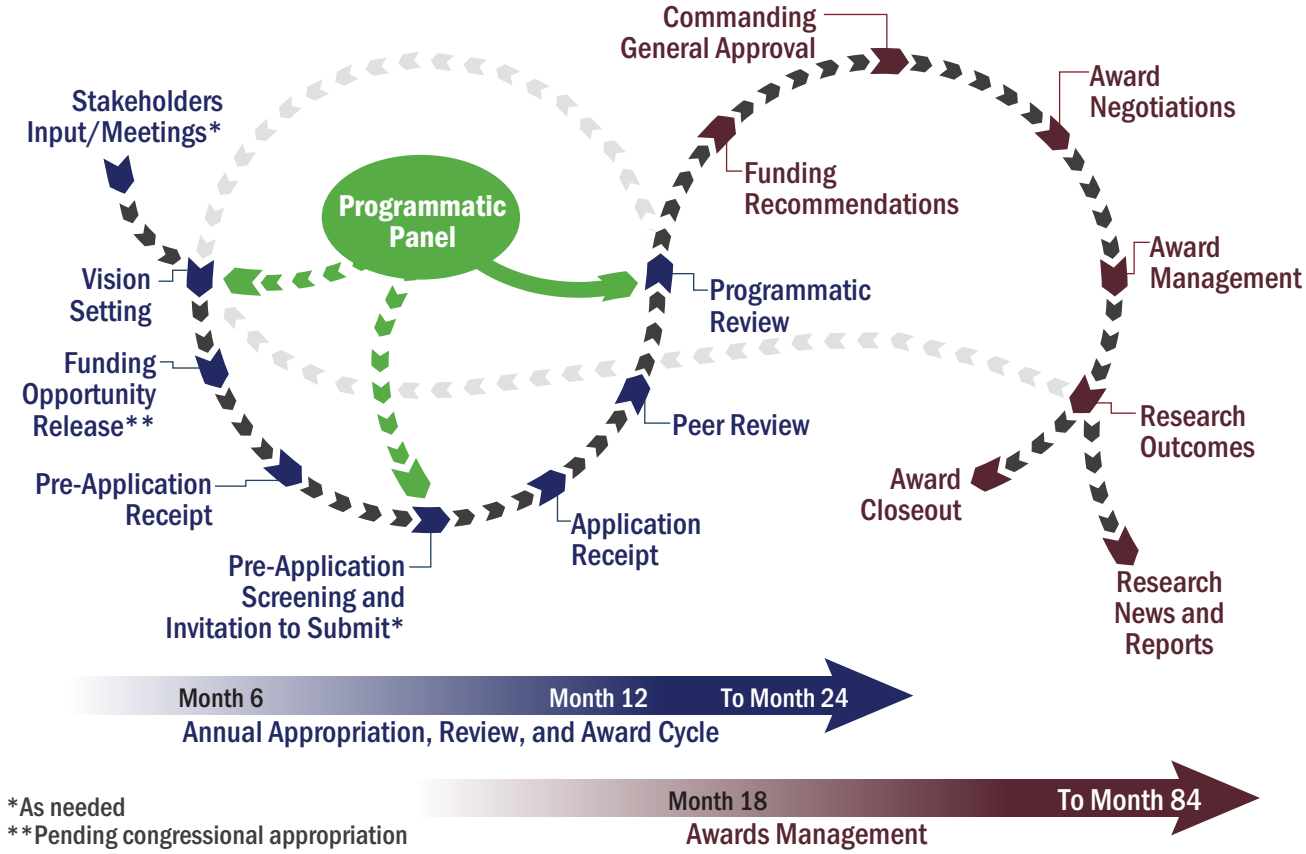
For more information, please visit
cdmrp.health.mil/bcrp

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

Congress established the Congressionally Directed Medical Research Programs in response to a grassroots effort in 1992 led by the breast cancer advocacy community. That effort resulted in a congressional appropriation of funds for breast cancer research and initiated a unique partnership among the public, Congress and the military. Since then, Congress appropriated funding for additional targeted research programs. The CDMRP managed over $19.672 billion in congressional special interest funds from inception through fiscal year 2024. Congress provides general intent for each program and specifies funding as part of the annual Department of Defense appropriations bill.

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier research application review process. This process 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 where applications with higher scientific or technical merit are evaluated for potential impact, adherence to the intent of the award mechanism, relevance to program goals and portfolio composition.



CDMRP Two-Tier Review Process

Photo provided

"Our voices and experiences are grounding for the expert panels. We have a unique perspective from which they can benefit, having actually been on the receiving end of life-saving treatments that came from earlier research. We can use that expertise to ensure others have it even better in the future... I am so impressed with the level of expertise and knowledge each panel member brought to the discussion."

Kara Kenan, Consumer Reviewer

BREAST CANCER RESEARCH PROGRAM

VISION: A world without breast cancer

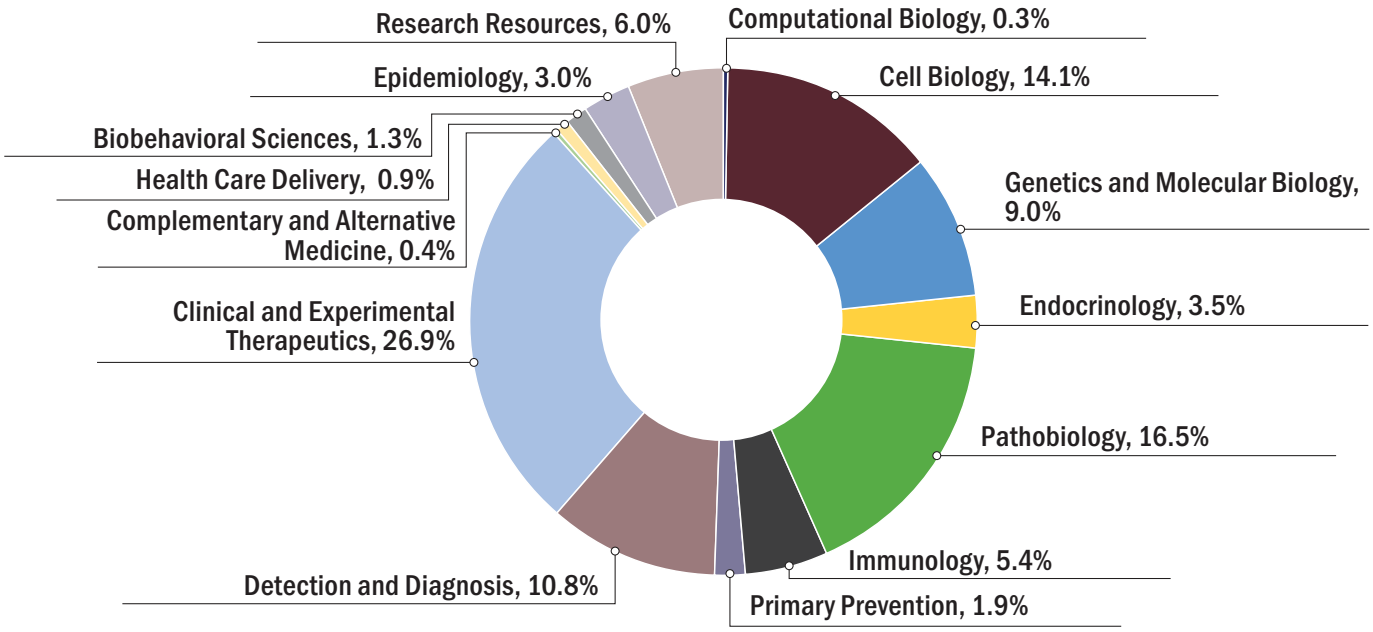
MISSION: To end breast cancer for Service Members and their Families, Veterans, and the general public by funding innovative, high-impact research through a partnership of scientists and consumers

ABOUT THE PROGRAM

The Breast Cancer Research Program, or 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 the disease. The program originated 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 $4.391 billion in congressional appropriations through FY24. 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 FY23, the BCRP funded 7,365 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 chart below, with the largest investment in clinical and experimental therapeutics.

FY92-FY23 BCRP Investment by Scientific Classification System Code



FY93-FY23 Metrics

PUBLICATIONS
19,691

PATENTS
1,383

CLINICAL TRIALS
222

THE BREAST CANCER LANDSCAPE

The BCRP outlined topics most pertinent to the program's mission of ending breast cancer in the *Breast Cancer Landscape*.[1] Some key points are:

INCIDENCE AND MORTALITY:

- Worldwide, breast cancer accounts for nearly a quarter of all cancers in women.
- In the U.S. in 2024, it is estimated that 42,250 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 age, ages at menarche and menopause, BRCA status and breast density.

RECURRENCE AND METASTASIS:

- An estimated 10% to 30% of women diagnosed with invasive breast cancer will have a recurrence.
- Treatments that permanently eradicate metastasis do not exist. There is no cure once metastatic disease has occurred.

TREATMENTS:

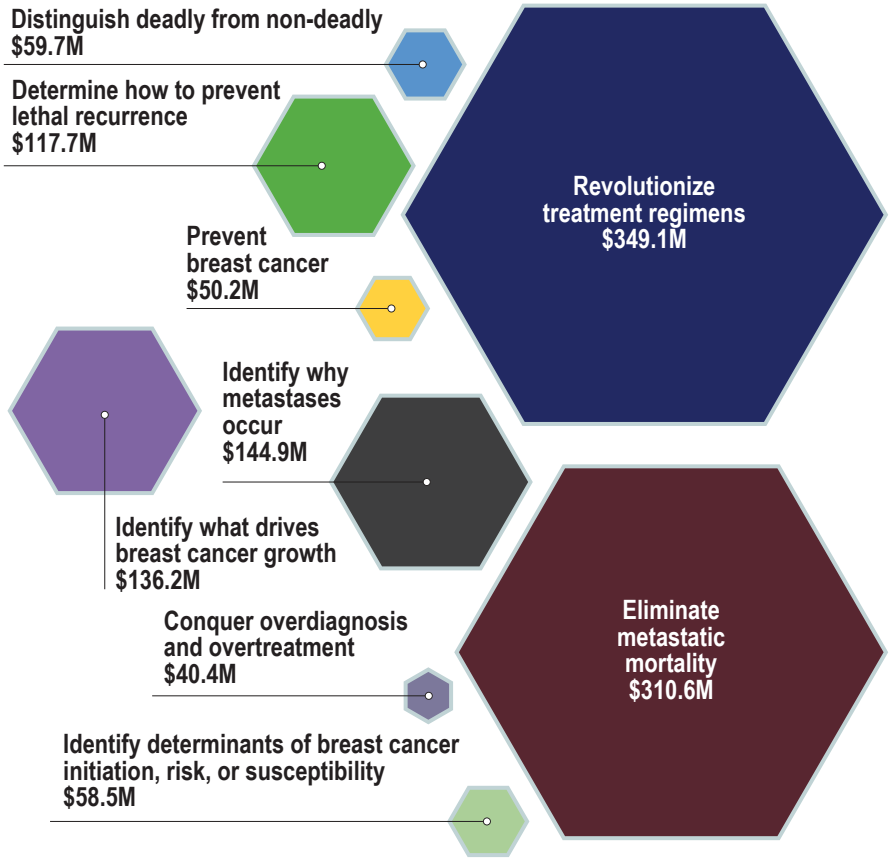
- Although breast cancers are highly heterogenous, the majority of women with breast cancer receive the same treatment, as though all breast cancers were the same within a given subtype.
- Standard adjuvant therapies have only a small impact, between 5% to 10%, on disease-specific survival.
- The cost of treating breast cancer continues to rise. Financial toxicity from both direct and indirect expenses linked to treatment is high among breast cancer patients.

OVERARCHING CHALLENGES

Each application, with consideration of the current breast cancer landscape and the BCRP's mission to end breast cancer, must address at least one of the following BCRP overarching challenges. The program's investments in each overarching challenge from FY13 to FY23 are shown in the chart below.

- 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-FY23 BCRP Portfolio Investment by Overarching Challenge



[1] Available at https://cdmrp.health.mil/bcrp

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]

- For females 40-59 years of age, **the incidence rate of breast cancer is higher** in Service Members compared to the general population.[4]

- The incidence rate for female Service Members is **seven times higher** than the average rate of 15 other cancer types across all components of the military.[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 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-FY25 BCRP Programmatic Panel Chair

Photo provided

"We are all working together to better understand this complicated disease. Being personally affected helps me appreciate the efforts made by all those involved. It's a privilege to have access to the science and to have worked with the scientific community striving to eradicate breast cancer. I can affirm through this experience, that it's wonderful when synergy occurs, and we are able to work together to advance this cause."

Graciela Santillan, Consumer Reviewer

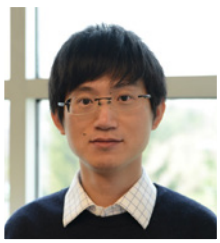


Photo provided

"My laboratory's breast cancer research would not be possible without the support of the BCRP. The Era of Hope Scholar award has enabled pioneering research on new directions including cancer immunology, gene editing, CAR-T / CAR-NK cell therapy and immune gene therapy. We hope our research will translate into the clinic to help more breast cancer patients and their families in need."

Sidi Chen, Ph.D., Yale University

RESEARCH HIGHLIGHTS

Photo provided

Mechanisms of Vascular Mimicry Impacting Tumor Progression and Response to Therapy in Breast Cancer

Gregory Hannon, Ph.D., University of Cambridge

To survive and thrive, tumor cells rely on the bloodstream to provide necessary oxygen and nutrients. Thus, tumor cells release factors to stimulate the development of new blood vessels, a process called angiogenesis.[7] While there are anti-angiogenic drugs designed to block this process, success of these drugs has been limited since tumors may also rely on alternative mechanisms. One such mechanism is called vasculogenic mimicry, or VM, a process whereby tumor cells form tubular structures that mimic blood vessels and connect the tumor to the body's vasculature.[8] With support from an fiscal year 2017 Breakthrough Award – Funding Level 2, Gregory Hannon, Ph.D., studied factors controlling VM, a poor prognostic indicator, to uncover new targets and biomarkers for treatment of breast cancer.

Anti-angiogenic drugs starve tumors of nutrients and oxygen, inducing a state of low oxygen, called hypoxia. The team found that hypoxia induces changes in tumor cells allowing them to gain VM-like characteristics, making the tumors VM-competent. Hannon and his team identified factors regulating cellular changes through the analysis of the five VM competent cell lines. His team found over 100 genes associated with VM characteristics to be commonly expressed by the cell lines. The team analyzed a subset of these genes and demonstrated that when suppressed, there was also a reduction in expression of genes commonly associated with resistance to anti-angiogenic drugs. With this, the team compared mouse models of VM-competent and noncompetent tumors treated with the anti-angiogenic drug, axitinib. The team observed a 75% volume decrease in VM noncompetent tumors treated with axitinib compared to no change in competent tumors. The team further validated these results in a mouse model implanted with patient-derived breast cancer cells, suggesting that VM promotes resistance to anti-angiogenic therapy. Finally, in a mouse model with VM-competent breast tumors, the team explored the effect of suppressing FOXC2, a protein found to control VM-promoting genes. Results indicated the suppression of FOXC2 increased the effectiveness of anti-angiogenic drugs, offering a potential therapeutic target.

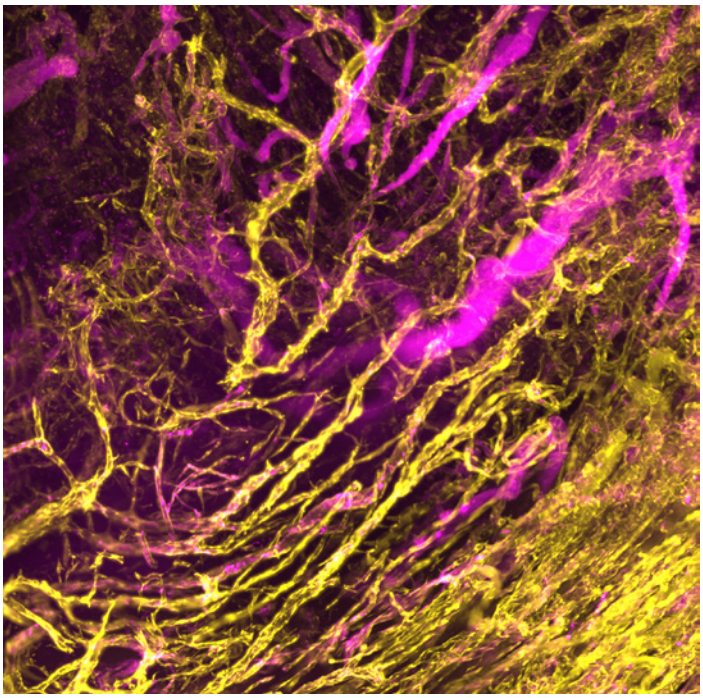


Figure 1. Imaging of vasculogenic mimicry in mouse 4T1-T tumours. Visualisation of host vasculature (CD31, yellow), fluorescent tracer introduced via the tail vein (lectin, magenta). Vasculogenic mimicry vessels are magenta (lectin positive/CD31 negative) whereas host vessels are yellow and magenta (lectin positive/CD31 positive). (Figure provided by the Principal Investigator.)

With this significant groundwork defining the mechanisms associated with anti-angiogenic therapies, hypoxia and VM, Hannon will continue his research with support from a fiscal year 2023 Expansion Award. In the follow-on study, the team seeks to better understand the mechanism of hypoxia that drives VM. If successful, this work could lead to the identification of new breast cancer biomarkers and drug targets specific for VM.

Publication:

Cannell, Ian G et al. "FOXC2 promotes vasculogenic mimicry and resistance to anti-angiogenic therapy." Cell reports vol. 42,8 (2023): 112791. doi:10.1016/j.celrep.2023.112791

[7] National Cancer Institute Dictionaries (https://www.cancer.gov/publications/dictionaries/cancer-terms/def/angiogenesis accessed October 2024)

[8] Yang, J P et al. "Tumor vasculogenic mimicry predicts poor prognosis in cancer patients: a meta-analysis." Angiogenesis vol. 19,2 (2016): 191-200. doi:10.1007/s10456-016-9500-2

Photos provided

Overcoming Immunotherapy Resistance in Breast Cancer Using Radiation Therapy-Mediated Immunomodulation

Stephen Shiao, M.D., Ph.D. and Simon Knott, Ph.D., Cedars-Sinai Medical Center

Triple-negative breast cancer is an aggressive, difficult to treat subtype of breast cancer. Immunotherapy, a type of treatment that works by adjusting a patient's immune system so their body can mount an anti-tumor response, has shown limited promise in treating triple-negative breast cancer despite its success in other cancer types. One type of immunotherapy, immune checkpoint inhibitors, block signals that normally prevent an immune response to a tumor. By inhibiting these signals, the immune system can recognize and kill cancer cells.[9] Emerging evidence indicates radiation therapy may alter the environment around a tumor increasing responsiveness to immunotherapy such as immune checkpoint inhibitors.[10] With a fiscal year 2018 Breakthrough Award – Funding Level 3 – Clinical Trial – Partnering Principal Investigator Option, Dr. Stephen Shiao and Simon Knott, Ph.D. investigated the role of neoadjuvant administration of radiation in combination with immune checkpoint inhibitors and conducted a phase 1/2 clinical trial to determine the efficacy of neoadjuvant radiation with immune checkpoint inhibitors.

In a mouse model of breast cancer, radiation therapy acted as a catalyst to fight tumor cells through activation of various immune cell populations. Radiation therapy with subsequent immune checkpoint inhibitor dosing resulted in significant tumor shrinkage and a 100% survival rate in mice receiving the combination treatment, compared to either therapy alone. In a phase 1/2 clinical trial, the safety and efficacy of the treatment combination was evaluated in patients with early-stage triple-negative breast cancer in a neoadjuvant setting. Results indicated three distinct populations of patients: those who appeared to respond to the immune checkpoint inhibitor alone; those who required the combination for a response; and those with no response to treatment. Tumor characteristics from each group were used to develop a highly accurate algorithm to assist in prediction of treatment response. With support of an fiscal year 2022 Clinical Research Extension Award, the investigators will assess the long-term impact of neoadjuvant radiation therapy and immune checkpoint inhibitors, and also conduct additional analyses of the circulating immune cells collected during the trial.

This work began to elucidate the mechanism of action for the combination therapy. Additionally, this study could provide a new treatment strategy for triple-negative breast cancer and offers a prediction method that could assist clinicians in determining an optimal treatment approach.

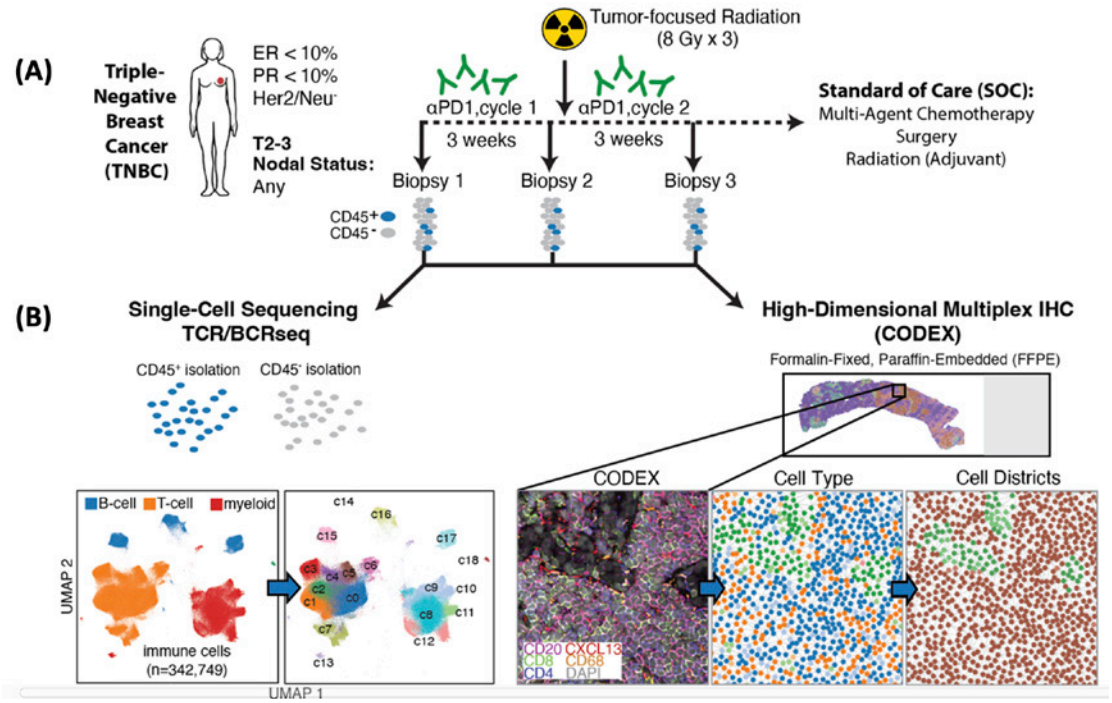


Figure 2. (A) Clinical trial design: TNBC patients were enrolled in a clinical trial of pre-surgical PD-1 directed therapy and Radiation Therapy (RT) with three separate biopsies collected after each treatment prior to patients receiving standard of care treatment. Biopsies were sent for analysis (B) by either single-cell sequencing or high-dimensional multiplex immunohistochemistry (IHC). Sample analysis results are depicted. (Figure provided by Principal Investigators.)

Publication:

Shiao, Stephen L et al. "Single-cell and spatial profiling identify three response trajectories to pembrolizumab and radiation therapy in triple negative breast cancer." Cancer cell vol. 42,1 (2024): 70-84.e8. doi:10.1016/j.ccell.2023.12.012

[9] Kwa Maryann J., and Sylvia, Adams. "Checkpoint Inhibitors in Triple-Negative Breast Cancer (TNBC): Where to Go From Here." *Cancer* 124, 10 (2018): 2086-2103. doi:10.1002/cnrc.31272

[10] Ko, Eric C, and Silvia C Formenti. "Radiation therapy to enhance tumor immunotherapy: a novel application for an established modality." International journal of radiation biology vol. 95,7 (2019): 936-939. doi:10.1080/09553002.2019.1623429

Photo provided

Disrupting a Vital Complex Involved in Tumor Regeneration in Triple-Negative Breast Cancer

Ofer Reizes, Ph.D., Cleveland Clinic

Triple-negative breast cancer is an aggressive disease that is associated with high rates of recurrence and metastasis. Among factors that may contribute to metastasis are therapy-resistant cancer stem cells associated with triple-negative breast cancer.[11] Since cancer stem cells often use similar cellular pathways that normal stem cells use to carry out their physiological function, they have historically been difficult to target without causing off-target toxicity to normal stem cells. It is therefore critical to understand how cancer stem cells use these pathways in order to develop new therapeutics that directly target them. Prior research identified a protein assembly complex involved in cancer stem cell self-renewal called the Cx26/NANOG/FAK complex. One component, Connexin 26, or Cx26, offered researchers a potential target due to elevated levels in triple-negative cell lines and patient-derived xenograft models.[12] Cx26 interacts with the other constituents of the complex, NANOG and focal adhesion kinase, or FAK, and controls the growth and progression of cancer stem cells, particularly their self-renewal capabilities. With a fiscal year 2018 Breakthrough Award – Funding Level 2, Ofer Reizes, Ph.D., investigated whether disrupting the Cx26/NANOG/FAK complex with a Cx26 peptide mimetic could reduce cancer stem cell self-renewal and tumor growth in triple-negative breast cancer models.

To disrupt the complex, Reizes' research team generated a small peptide mimicking a portion of Cx26 protein, called aCx26-pep, that binds to NANOG and FAK. The team confirmed that aCx26-pep could enter cancer cells and disrupts cancer stem cell self-renewal in cellular models of triple-negative breast cancer. In contrast, the effect was not observed in the luminal subtype breast cancer cells. Reizes and the collaborators tested the peptide mimetic in a mouse model of triple-negative breast cancer. Results indicated that mice treated with aCx26-pep had smaller tumors with more dead cells compared to the controls. These findings provide proof of concept that a peptide mimetic could be a viable targeted therapeutic approach for triple-negative breast cancer. In addition, results from this study show early evidence that it is possible to specifically target the self-renewal capabilities of cancer stem cells. While additional research is needed, this study on aCx26-pep offers the possibility of a future treatment modality for patients with triple-negative breast cancer.

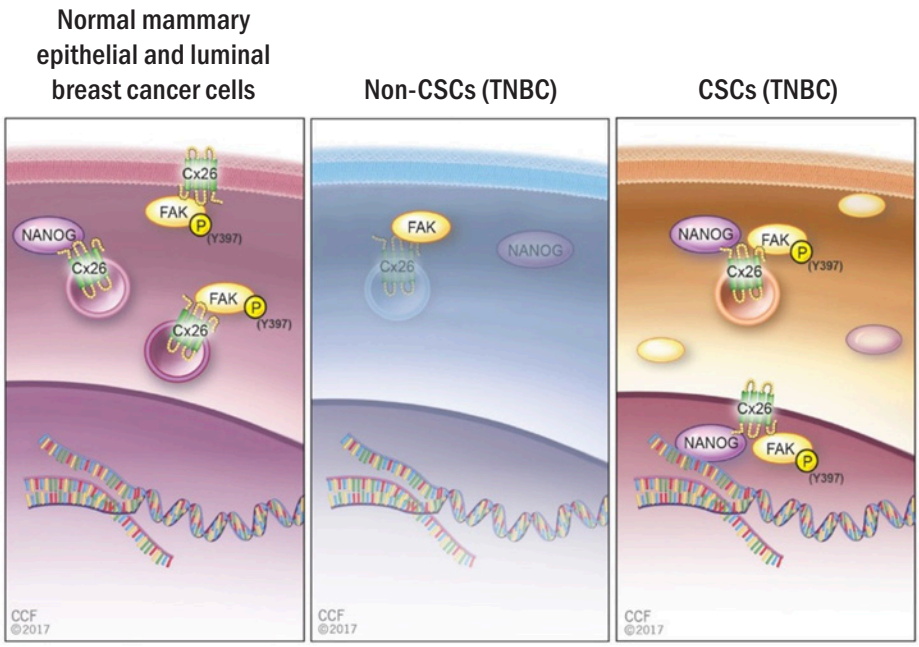


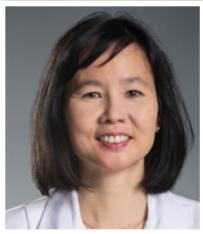
Figure 3. Model of Cx26, NANOG, and FAK interaction in normal mammary epithelium, luminal breast cancer, and triple-negative breast cancer (TNBC) cells. In normal mammary epithelium and luminal breast cancer cells, Cx26 interacts with FAK and NANOG individually. In contrast, in TNBC, the CX26/NANOG/FAK complex forms and drives cancer stem cell self-renewal. The research focuses on disrupting the complex in TNBC. (Figure provided by the Principal Investigator.)

Publication:

Mulkearns-Hubert, Erin E., et al. 2024. "Targeting NANOG and FAK via Cx26-Derived Cell-Penetrating Peptides in Triple-Negative Breast Cancer." *Molecular Cancer Therapeutics* 23 (1):56-67.

[11] Idowu, Michael O et al. "CD44(+)/CD24(-/low) cancer stem/progenitor cells are more abundant in triple-negative invasive breast carcinoma phenotype and are associated with poor outcome." Human pathology vol. 43,3 (2012): 364-73. doi:10.1016/j.humpath.2011.05.005

[12] Thiagarajan, Praveena S et al. "Cx26 drives self-renewal in triple-negative breast cancer via interaction with NANOG and focal adhesion kinase." Nature communications vol. 9,1 (2018): 578. doi:10.1038/s41467-018-02938-1




Photos provided

Investigating Aspirin for the Treatment of Breast Cancer

Wendy Chen, M.D., Dana-Farber Cancer Institute* and Michelle Holmes, M.D., Brigham and Women's Hospital

To prevent breast cancer recurrence and metastasis, patients may benefit from adjuvant treatment options. Unfortunately, some individuals stop adjuvant treatments early due to side effects and high costs. Among efforts to identify new treatment options, researchers showed interest in aspirin as a potential adjuvant therapy. Previously, investigators from multiple observational studies reported improved breast cancer survival with regular aspirin use.[13] In a 2012 analysis of data from five clinical trials that assessed aspirin use for heart disease prevention, researchers reported a reduced risk of metastatic cancer for those taking the medication.[14] Based on these studies, and with the knowledge that aspirin targets cellular processes implicated in breast cancer progression, researchers were encouraged to further investigate aspirin as a potential adjuvant treatment. With a fiscal year 2014 Breakthrough Award – Funding Level 4 – Clinical Trial – Partnering Principal Investigator Option, Drs. Wendy Chen and Michelle Holmes conducted a phase 3 clinical trial to test the efficacy of aspirin in preventing recurrence and metastasis of breast cancer.

The team enrolled 3,020 patients with high-risk, HER2-negative breast cancer and randomly assigned each to receive either 300 milligrams of aspirin or a placebo once daily for five years. The team followed up with patients every six-months for history and physical examination and assessments of study adherence. The primary endpoint of the trial was: invasive disease-free survival defined as the time from randomization to the development of recurrence, ipsilateral or contralateral breast cancer; or a second primary (non-breast) invasive cancer; or death from any cause. At a predefined interim analysis, it was found to be statistically unlikely that aspirin would be beneficial, so the trial was stopped. With a median patient follow-up of 33.8 months, the researchers observed a total of 141 and 112 invasive disease-free survival events and 63 and 62 deaths in the aspirin and placebo groups, respectively. Overall, the team concluded that 300 milligrams of aspirin daily did not reduce the risk of developing a breast cancer recurrence or improve survival in early follow-up.

In conjunction with the clinical trial, investigators collected biospecimens of tumor samples, blood and urine, and lifestyle questionnaires from a subset of participants. The team established a biorepository of these valuable resources and biospecimens with matched clinical data for utilization in future correlative studies, the results of which could impact patients at risk for breast cancer recurrence and metastasis.

* Eric Winer, M.D., served as the original Principal Investigator at Dana-Farber Cancer Institute

Publication:

Chen, Wendy Y et al. "Aspirin vs Placebo as Adjuvant Therapy for Breast Cancer: The Alliance A011502 Randomized Trial." JAMA vol. 331,20 (2024): 1714-1721. doi:10.1001/jama.2024.4840

[13] Chen, Wendy Y, and Michelle D Holmes. "Role of Aspirin in Breast Cancer Survival." Current oncology reports vol. 19,7 (2017): 48. doi:10.1007/s11912-017-0605-6

[14] Rothwell, Peter M et al. "Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials." Lancet (London, England) vol. 379,9826 (2012): 1591-601. doi:10.1016/S0140-6736(12)60209-8

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 1/2	Phase 3
NeuVax™: Constantin Ioannides and Elizabeth Mittendorf *An immunogenic peptide-based vaccine to prevent or delay breast cancer recurrence.*	BCRP	BCRP	Other
HER2 Intracellular Domain, or ICD, Vaccine: Mary (Nora) L. Disis *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.*	BCRP	BCRP	
STEMVAC: Mary (Nora) L. Disis *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.*	BCRP	BCRP	
Mammaglobin-A cDNA Vaccine: William Gillanders *A mammaglobin-A DNA vaccine to induce antitumor immunity in breast cancer patients undergoing neoadjuvant endocrine therapy or chemotherapy.*	Previous	BCRP	
Folate Receptor Alpha Vaccine: Keith Knutson, Edith Perez, and Saranya Chumsri *A vaccine targeting the folate receptor alpha in patients with TNBC to prevent or delay recurrence.*	Previous	BCRP	
HER2 Bi-Armed Activated T Cells, or HER2 BATs: Lawrence G. Lum *A therapy that induces the development of "memory" antigen-specific cytotoxic T cells directed at HER2 to treat patients with HER2+ metastatic breast cancer.*	BCRP	Other	
TRC105: Ben Seon *A monoclonal antibody that targets endoglin to suppress the growth of both established and new breast tumors.*	BCRP	Other	
Mesothelin-Targeted T Cell Therapy: Michel Sadelain, Prasad Adusumilli, and Shanu Modi *A mesothelin-targeted chimeric antigen receptor, or CAR, T cell therapy to treat patients with treatment-refractory metastatic TNBC.*	BCRP	BCRP	
AVX901 HER2 Vaccine, also called VRP-HER2: H. Kim Lyerly *A vaccine composed of an alphaviral vector expressing the human HER2 gene to treat patients with HER2+ metastatic breast cancer.*	BCRP	BCRP	
P10s-PADRE with Standard Neoadjuvant Chemotherapy: Thomas Kieber-Emmons *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.*	BCRP	BCRP	
Combination Vaccine for HER2+ Metastatic Breast Cancer: Leisha Emens *Combining trastuzumab, cyclophosphamide, and an allogeneic granulocyte-macrophage colony stimulating factor-secreting breast tumor vaccine to treat HER2+ metastatic breast cancer.*	BCRP	BCRP	
Alpha-Lactalbumin Vaccine: G. Thomas Budd, Vincent Tuohy, and Thaddeus Stappenbeck *A vaccine for TNBC patients recovering from current standard of care therapy or administered to healthy individuals to prevent the development of breast cancer.*	Previous	BCRP	
NY-ESO-1-Specific T Cell Receptor-Engineered T Cells: Rongfu Wang *A therapy using T cell receptors engineered to recognize the NY-ESO-1 cancer antigen to treat locally advanced or metastatic TNBC.*	BCRP	BCRP	
HER2-Specific Helper T Cell Epitope Vaccine: Keith Knutson and Amy Degnim *A HER2/neu subdominant epitope-based vaccine to enhance HER2-specific CD4 T cell immunity in patients with ductal carcinoma in situ.*	BCRP	BCRP	
Multivalent Th1 DNA Vaccine with HER2-Pulsed IL-12 Secreting DC1 Vaccine: Brian Czerniecki *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.*	Previous	BCRP	

* 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 1/2	Phase 3
Trastuzumab Emtansine/Pertuzumab with HER2 HLA-DR Vaccine Therapy: Keith Knutson and Saranya Chumsri *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.*		BCRP-funded*	
Regional Oncolytic Poliovirus Immunotherapy: Smita Nair *Oncolytic poliovirus PVSRIPO to eradicate tumors in patients with TNBC.*	BCRP-funded*	BCRP-funded*	
Radiotherapy-Mediated Immunomodulation: Stephen Shiao and Simon Knott *Using preoperative focal radiation combined with pembrolizumab to generate antitumor immune responses in patients diagnosed with early-stage operable TNBC or ER+ breast cancers.*		BCRP-funded*	
Dendritic Cell Vaccines: Pawel Kalinski and Brian Czerniecki *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.*	BCRP-funded*	BCRP-funded*	
HER2-Specific Helper T Cell Epitope Vaccine, also called H2NVAC: Keith Knutson and Amy Degnim *A HER2/neu subdominant-epitope-based vaccine to enhance HER2-specific CD4 T cell immunity in patients with ductal carcinoma in situ.*	BCRP-funded*	BCRP-funded*	
Anti-HLA-A2/NY-ESO-1 TCR-Transduced Autologous T Lymphocytes: Rongfu Wang *A2-ESO-1 TCR-T cells to treat patients with relapsed/refractory locally advanced or metastatic TNBC that overexpresses NY-ESO-1.*	BCRP-funded*	BCRP-funded*	
ESR1 Peptide Vaccine plus GM-CSF and Montanide ISA: Zachary Hartman *A vaccine that targets five neoepitopes of estrogen receptor alpha, or ESR1, in combination with GM-CSF and Montanide ISA to treat patients with ER+ breast cancer.*	BCRP-funded*	Current phase supported by other sources	
DIAGNOSTICS AND IMAGING	**Pre-IND****	**Phase 1/2**	**Phase 3**
Targeted HER2 Radiotracer: Gary Ulaner *89Zr-pertuzumab to determine the proportion of patients with HER2- primary breast cancer who develop imageable HER2+ metastases.*	BCRP-funded*	BCRP-funded*	
Polycationic Peptides for Fluorescence-Guided Surgery: Roger Tsien *Protease-activatable fluorescent peptide, pegloprastide, or AVB-620, injected prior to surgery to enable surgeons to identify critical cancer margins for tumor resection and examine lymph nodes for invasive disease.*	BCRP-funded*	Current phase supported by other sources	
TrackDOI: Darren Roblyer *A new optical metabolic scanning technology, TrackDOI, to monitor breast cancer patient tumor response to neoadjuvant chemotherapy in real time.*	BCRP-funded*	Current phase supported by other sources	

* 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 1/2	Phase 3
Fatty Acid Synthase Inhibitor: Ruth Lupu and Tufia Haddad *Combining the fatty acid synthase inhibitor, TVB-2640, with paclitaxel and trastuzumab to treat patients with taxane-resistant metastatic HER2+ breast cancer.*		BCRP-funded*	
Temozolomide Combined with T-DM1: Patricia Steeg *Treatment of HER2+ breast cancer with T-DM1 and temozolomide to prevent formation of new metastases in the brain.*	BCRP-funded*	Current phase supported by other sources	
Radiation with Pembrolizumab and/or Tremelimumab: Andy Minn *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.*	BCRP-funded*	BCRP-funded*	
Anastrozole with Saracatinib: Joyce Slingerland and Isabel Chu *Anastrazole, an aromatase inhibitor that stops estrogen production, combined with a Src inhibitor, saracatinib, or AZD0530, to test tolerability and efficacy in post-menopausal women with ER+ breast cancer.*	BCRP-funded*	Current phase supported by other sources	
5-Fluoro-2'deoxycytidine (FdCyd): Edward Newman *Combining FdCyd with tetrahydrouridine to reverse DNA methylation in several genes expressed by breast cancer cells and control tumor growth.*	BCRP-funded*	Current phase supported by other sources	
Enzalutamide + Fulvestrant: Anthony Elias and Jennifer Richer *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.*	BCRP-funded*	BCRP-funded*	
Meclofenamate: Joan Massague *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.*	BCRP-funded*	BCRP-funded*	
Aspirin as Adjuvant Therapy: Eric Winer, Wendy Chen, and Michelle Holmes *Long-term aspirin to reduce breast cancer recurrence and improve survival in patients with node-positive breast cancer.*			BCRP-funded*
Molecular Triage Therapy Approach: Mothaffar Rimawi and Rachel Schiff *A molecular classifier, based on detection of resistance-associated genomic alterations, to identify patients who may benefit from anti-HER2 therapy without added chemotherapy.*	BCRP-funded*	BCRP-funded*	
BMS-777607/ASLAN002: Alana Welm *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.*	BCRP-funded*	Current phase supported by other sources	
Talazoparib: Dennis Slamon *Combining the novel PARP inhibitor talazoparib with other therapies to treat non-BRCA mutant TNBC.*	BCRP-funded*	Current phase supported by other sources	Current phase supported by other sources
Denosumab (XGEVA®): Josef Penninger, Judy Garber, and Christian Singer *Prophylactic administration of denosumab to prevent the development of breast cancer in women with BRCA1 germline mutations.*			BCRP-funded*
Biomarker-Driven Targeted Therapy: Christina Curtis, George Sledge, and Jennifer Caswell-Jin *Therapeutics targeting driver gene amplifications present in integrative clusters (IC1, IC2, and IC6) to treat high-risk ER+/HER2- breast cancer.*		BCRP-funded*	
Neoadjuvant Endocrine Therapy, or NET, with Radiotherapy: Silvia Formenti and Sandra Demaria *Treating HR+ breast cancer with a combination of focal radiotherapy and letrozole NET to enable a response to immunotherapies.*	BCRP-funded*	BCRP-funded*	
Functional Precision Oncology - Patient Derived Breast Tumor Grafts: Christos Vaklavas and Alana Welm *Patient derived breast tumor grafts to predict, prevent, and inform treatment of recurrence in patients with HR-low/HER2- or TNBC.*	BCRP-funded*	BCRP-funded*	
Ruxolitinib: Yi Li *Ruxolitinib for prevention of breast cancer in patients with high risk and precancerous breast conditions.*	BCRP-funded*	Current phase supported by other sources	

* 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 1/2	Phase 3
Enobosarm: Theresa Hickey *Treating AR+ breast cancer with a selective androgen receptor targeting agonist, enobosarm.*	■	■	■
AOH1996: Robert Hickey and John Perry *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 *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 *Combining abemaciclib, a CDK4/6 inhibitor, with pembrolizumab, a PD-1 inhibitor, to treat HR+, HER2- breast cancer.*	■	■	
PLX3397 and Eribulin: Lisa Coussens *Eribulin in combination with PLX3397, a novel CSF1 inhibitor, to treat patients with metastatic breast cancer.*	■	■	
Ivermectin with Balstilimab: Peter Lee *Combining ivermectin with balstilimab (PD-1 inhibitor) for the treatment of metastatic TNBC.*	■	■	
Zunsemetinib with Capecitabine: Sheila Stewart and Cynthia Ma *A MAPK-activated protein kinase 2 inhibitor, zunsemetinib, or ATI-450, combined with capecitabine to treat HR+/HER2- breast cancer patients with bone metastases.*	■	■	
MBQ-167: Jose Rodriguez *MBQ-167, a dual Rac and Cdc42 inhibitor, to treat patients with advanced breast cancer where standard of care has failed or has proven intolerable.*	■	■	
Preoperative Chemotherapy with Bevacizumab: Rakesh Jain *A vascular endothelial growth factor inhibitor, bevacizumab, combined with standard preoperative chemotherapeutic regimens to treat patients with ER+ and/or PR+, HER2- operable breast cancer.*	■	■	
TTI-101 with Palbociclib: Nicole Kettner *A STAT3 inhibitor, TTI-101, combined with palbociclib and aromatase inhibitor or fulvestrant to treat patients with HR+, HER2- palbociclib-resistant breast cancer.*	■	■	
Omeprazole and Standard Neoadjuvant Chemotherapy: Jian-Ting Zhang *A proton pump inhibitor, omeprazole, to improve pathologic complete response in TNBC patients whose tumors express fatty acid synthase.*	■	■	
Dinaciclib with Pembrolizumab: Andrei Goga *A cyclin dependent kinase 1 inhibitor, dinaciclib, combined with the PD-1 inhibitor, pembrolizumab, to target MYC-driven tumors in women with metastatic or locally advanced and unresectable TNBC.*	■	■	
NB004: Andrei Goga *An orally available PIM kinase inhibitor, NB004, to treat advanced breast cancers in patients where standard treatments are ineffective.*	■	■	
Neratinib and Trastuzumab Deruxtecan: Ron Bose and Cynthia Ma *A potent pan-HER2 inhibitor, neratinib, combined with an antibody drug conjugate to target HER2, trastuzumab deruxtecan, to treat patients with tumors that have HER2 amplification.*	■	■	
Tocilizumab with and without Carboplatin: Harikrishna Nakshatri *Carboplatin as a single agent versus carboplatin combined with the interleukin 6 receptor inhibitor, tocilizumab, to treat patients with metastatic triple-negative or ER-low breast cancer.*	■	■	
AT-0174: Jennifer Richer *A dual inhibitor of tryptophan-2,3-dioxygenase, AT-0174, to inhibit tryptophan metabolism in breast cancer to reduce tumor growth and alleviate antitumor immunity in patients with advanced disease.*	■	■	

* May also be supported by non-BCRP sources

** Investigational New Drug (IND)

PRODUCTS MAKING AN IMPACT

TREATMENTS

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. It is also approved in combination with an aromatase inhibitor for adjuvant treatment of some patients with high-risk early-stage HR-positive, HER2-negative breast cancer.

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 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 provides counseling and risk analysis to individuals with a family history of breast or ovarian cancer.

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

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.

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.

nCounter® Myeloid Innate Immunity Panel - *Lisa Coussens*
This commercially available research tool has utility for basic and translational immuno-oncology research.

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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