Breast Cancer Research Program

CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

30
years of groundbreaking research

The Congressionally Directed Medical Research Programs (CDMRP) 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 $19.4 billion since its inception through fiscal year 2022 (FY22). Congress provides overarching intent for each individual CDMRP program, such as the Breast Cancer Research Program (BCRP) and specifies the funding amount as part of the annual Department of Defense (DOD) Appropriations Bill.

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for evaluating applications that involves dynamic interaction between scientists, consumers from advocacy communities, clinicians, members of the military and other specialists as applicable. The first tier of evaluation is a scientific peer review of the applications, measured against established criteria for determining scientific merit. The second tier is a programmatic review by the Programmatic Panel, which compares applications to each other and makes recommendations for funding based on scientific merit, potential impact, adherence to the intent of the award mechanism, relevance to program goals, and portfolio composition.

"Reviewing for the DOD BCRP is my absolute favorite part of my advocacy. I have learned so much from the proposals and panel members. I enjoy the challenge of reading and interpreting the information, critical thinking, knowing the right questions to ask, and learning how to listen effectively. I realize the importance of having a patient's voice present during the panel reviews. And the panel members are so gracious in clarifying information and listening to my comments. It is clear that the scientific community understands the myriad of challenges facing the breast cancer community – patient care, safety and efficacy, improving life expectancy and working to eradicate disease. I strongly feel that by participating in the DOD BCRP panel reviews, I can make a difference in ending cancer."

Lori Petitti, Consumer Reviewer

BREAST CANCER RESEARCH PROGRAM

VISION: A world without breast cancer

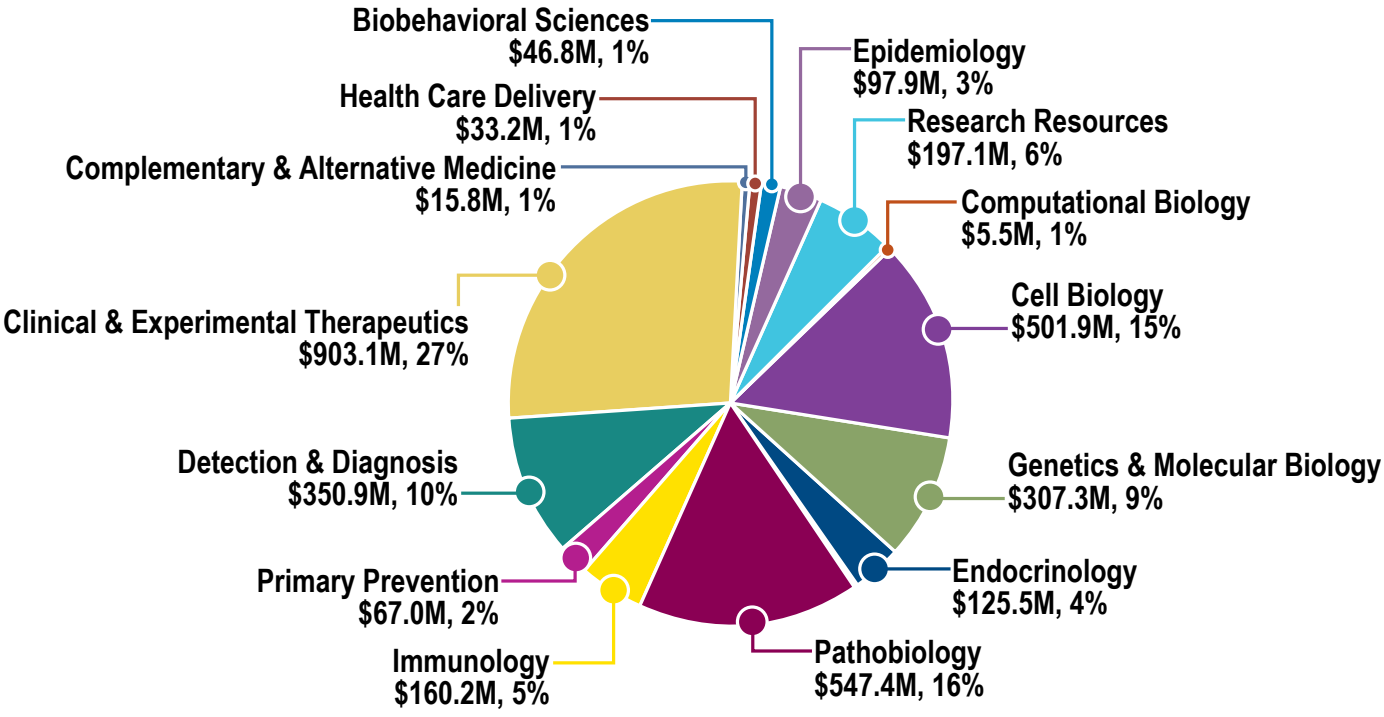
MISSION: To end breast cancer for Service Members, Veterans, and the general public by funding innovative, high-impact research through a partnership of scientists and consumers

ABOUT THE PROGRAM

The BCRP plays a leading role in the fight against breast cancer through its innovative approaches and its focus on research that will bring an end to this disease. The program was established in 1992 as a result of the dedicated efforts of breast cancer advocates. Their continued efforts, in concert with the program's accomplishments, have resulted in more than $4 billion in congressional appropriations through FY22. The BCRP enables researchers to propose their best innovative ideas that address the urgent need to end breast cancer. The program challenges scientists to pursue high-risk, high-reward research, explore new paradigms that could lead to critical discoveries, and make an unprecedented impact on breast cancer. The BCRP also promotes synergistic collaborations across disciplines and integrates scientists and consumers in unique and meaningful research partnerships.

From FY92–FY21, the BCRP funded 7,213 awards. In order to achieve its mission to end breast cancer, the BCRP has 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-FY21 BCRP Investment by Research Type



THE BREAST CANCER LANDSCAPE

The BCRP has prepared an overview of the *Breast Cancer Landscape,*[1] covering topics most pertinent to the program's mission of ending breast cancer. Some key points from the *Breast Cancer Landscape*:

INCIDENCE & MORTALITY

- Worldwide, breast cancer accounts for nearly a quarter of all cancers in women.
- In 2020, there were 684,996 breast cancer deaths globally.

RISK FACTORS

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

RECURRENCE & METASTASIS

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

TREATMENTS

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

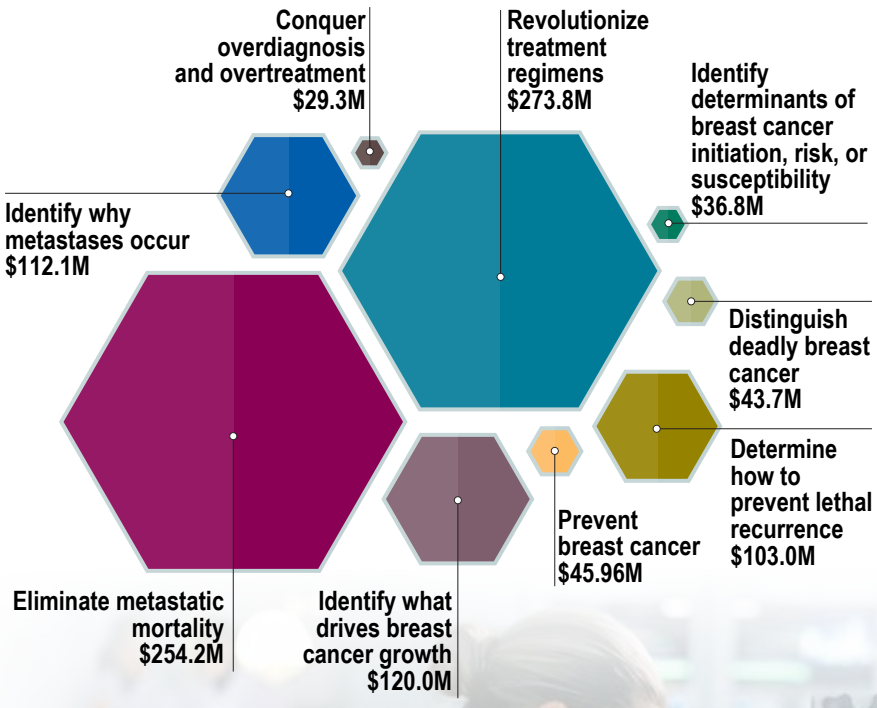
[1] https://cdmrp.health.mil/bcrp/pdfs/BreastCancerLandscape2022.pdf

BCRP OVERARCHING CHALLENGES

Considering the current Breast Cancer Landscape and the BCRP's vision to end breast cancer, each application must address at least one overarching challenge. The pie 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–FY21 BCRP Funding Invested by Overarching Challenge



RELEVANCE TO MILITARY HEALTH

- Breast cancer is the most common non-skin cancer in women, causing the **most cancer-related deaths in women under the age of 40**.[2,3]

- Female active-duty Service Members have a **20%-40% higher incidence rate** of breast cancer than females 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 U.S. Food and Drug Administration (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] PMID: 19505907
[5] PMID: 27501939.
[6] Source: DHA Pharmacy Analytics Support Section

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

"The DOD BCRP is a unique collaboration of patients living with the diagnosis of breast cancer, scientists across all disciplines, and translational oncologists which envisions a world without breast cancer as an achievable goal. It is a collaboration on equal footing in which the paradigm for research funding is reworked by the reality of living with breast cancer to eliminate the common barriers to the rapid translation of innovative concepts for treatment and prevention. The breast cancer research community that has grown with the support of this program has accomplished some remarkable things that have increased knowledge and improved patient outcomes. The opportunity to work with this community as FY23 Programmatic Panel Chair in completing our mission to eradicate breast cancer is an honor and a privilege."

Dr. Frank Calzone, FY23 BCRP Programmatic Panel Chair

"The DOD BCRP plays a huge role in change for breast cancer by looking at the community as a whole, from early- to late-stage breast cancer. Each new research proposal is looked at individually and time is spent understanding each application and how it will affect the community. The consumer reviewers' opinions are weighed heavily as they are the ones living with the disease, the treatments, and the side effects of those treatments."

Leslie Falduto, Consumer Reviewer

"I am very appreciative of the DOD BRCP award mechanism which allowed our team to conduct a large randomized controlled trial. We were able to answer a question that has been of great interest to patients and clinicians for many years. The DOD BCRP award mechanism is important because it takes chances on risky but important questions such as ours that would not be of interest to industry funders."

Dr. Michelle Holmes, Harvard University

RESEARCH HIGHLIGHTS

Jean Zhao (left) and Nancy Lin

Overcoming HER2-Based Therapy Resistance in Breast Cancer Brain Metastases through CDK4/6 Inhibition

Jean Zhao, Ph.D., and Nancy Lin, M.D., Dana-Farber Cancer Institute

Breast cancer brain metastases (BCBMs) are a major concern for patients with metastatic human epidermal growth factor receptor 2 positive (HER2+) breast cancer, with brain metastases developing in up to 50% of cases. BCBMs are a significant cause of patient morbidity and mortality since effective therapies remain limited due to treatment resistance and challenges targeting the brain. Drs. Zhao and Lin previously established predictive animal models of BCBM using patient-derived tissues which demonstrated that cyclin-dependent kinase 4 and 6 (CDK4/6), proteins which regulate cancer cell replication, are involved in resistance to HER2-targeted therapies. The tumor suppressor protein $p16^{INK4A}$ binds to and inhibits CDK4/6; however, it is often impaired in metastatic tumors. In this study, the researchers investigated the effects of combined CDK4/6 and HER2 inhibition, based on $p16^{INK4A}$ expression, in their animal models. Genomic profiling revealed that $p16^{INK4A}$ expression was low or undetectable for the majority of the HER2+ models. When tested in models of $p16^{INK4A}$ - negative HER2+ BCBM, combination treatment with CDK4/6 and HER2 inhibitors produced a more robust response (compared to either CDK4/6 or HER2 inhibitor alone), as demonstrated by prolonged survival and marked tumor regression due to stimulation of anti-cancer mechanisms. They also found evidence suggesting that the loss of p16INK4A expression contributes to HER2-targeted therapy resistance in BCBMs, suggesting that $p16^{INK4A}$ may serve as a potential biomarker to identify patients likely to respond to combined CDK4/6 and HER2 inhibitor treatment. This important research provides preliminary evidence that may pave the way for a future $p16^{INK4A}$ biomarker-driven clinical trial of combined CDK4/6 and HER2 inhibition in patients with HER2+ BCBMs aimed at optimizing patient outcomes.

Publication: Ni J, Kabraji S, Xie S, et al. 2022. p16INK4A-deficiency predicts response to combined HER2 and CDK4/6 inhibition in HER2+ breast cancer brain metastases. *Nature Communications* (13): 1473.

E. Premkumar Reddy

Hanna Irie

Targeting Drug Resistance in Triple-Negative Breast Cancer

E. Premkumar Reddy, Ph.D., and Hanna Irie, M.D., Ph.D., Icahn School of Medicine at Mount Sinai

Chemotherapy resistance is a significant issue for patients with triple-negative breast cancer (TNBC), a particularly aggressive subtype of this disease. Breast cancer stem cells (BCSCs), a subpopulation of cells that resides within the tumor itself, represent a potential therapeutic target against TNBC since they are relatively resistant to standard chemotherapy and have the ability to self-renew and initiate tumor development. Drs. Reddy and Irie previously identified the multi-kinase inhibitor molecule 108600 through a screen for compounds that would preferentially induce death in BCSCs. In this study, they investigated 108660 as a novel, potential treatment option for TNBC by examining which pathways are involved and studying effects on BCSCs using preclinical models. The team found that 108600 showed remarkable activity against cell line derived BCSC populations and TNBC cell lines. Furthermore, 108600 inhibited multiple signaling pathways important for BCSC survival: the casein kinase II (CK2) pathway, the TRAF2 and NCK interacting kinases (TNIK) pathway, and the dual-specificity tyrosine phosphorylation-regulated kinase (DYRK) pathway. These pathways are robustly expressed in most TNBC cell lines and BCSCs, with relatively lower expression in normal cells, suggesting that 108600 may target BCSCs with minimal effect on normal cells. Through cell assays and animal models, the team determined that 108600 enhances sensitivity to chemotherapy to inhibit growth of chemotherapy-resistant metastatic TNBC. Importantly, although 108600 inhibits multiple kinases, it did not induce death of normal cells or cause side effects in the animal models. Overall, this research supports clinical translation of 108600, as it could lead to dramatic improvements in TNBC patient outcomes.

Publication: Sato K, Padgaonkar A, Baker S, et al. 2021. Simultaneous CK2/TNIK/DYRK1 inhibition by 108600 suppresses triple negative breast cancer stem cells and chemotherapy-resistant disease. *Nature Communications* 12(1):4671.

Rahul Jandial

Targeting GM-CSF to Inhibit Development of Leptomeningeal Disease from Breast Cancer

Rahul Jandial, Ph.D., City of Hope Beckman Research Institute

Leptomeningeal carcinomatosis (LC) is an aggressive disease that develops when cancer cells spread to the cerebrospinal fluid-containing leptomeninges (tissues that surround the brain and spinal cord). Metastatic HER2+ breast cancer remains the most common origin of LC and, to date, clinically validated and effective treatments are scarce. Dr. Jandial and his team developed novel HER2+ LC patient-derived cell lines ("Lepto" cell lines) to investigate the role of various central nervous system cell types involved in the development of LC for identification of potential therapeutic targets. Using their uniquely developed models of HER2+ LC, the researchers found that granulocyte-macrophage colony-stimulating factor (GM-CSF) is a significant promoter of Lepto cell growth through autocrine signaling, a form of self-sustaining growth. They determined that the OPC-derived protein TPP1 induced apoptosis and decreased viability of the Lepto cells by degradation of GM-CSF, prompting investigation of GM-CSF as a potential target. Through further investigations, the team identified a pan-Aurora kinase compound that inhibited Lepto cell viability and induced apoptosis. Additionally, animals given combination treatment of the identified pan-Aurora kinase inhibitor and anti-GM-CSF neutralizing antibodies had significantly decreased tumor progression, compared to the controls or individual treatments, due to synergistic inhibition of GM-CSF. Overall, the results demonstrate that the GM-CSF pathway may potentially be exploited for targeted therapy to inhibit growth of LC from HER2+ BC and ultimately improve patient quality of life and survival.

Publication: Ansari KI, Arunoday B, Saotome M, et al. 2021. Autocrine GMCSF Signaling Contributes to Growth of HER2+ Breast Leptomeningeal Carcinomatosis. *Cancer Research*. (81)18:4723-4735.

Tohru Yamada

Tumor-Specific Fluorescence-Guided Surgery for Breast Cancer

Tohru Yamada, Ph.D., University of Illinois Chicago

For many patients with early-stage breast cancer, breast-conserving surgery (BCS) is a key component of their treatment plan, though achieving complete tumor removal with clean margins represents a challenge. Intraoperative (i.e., real-time) imaging technologies used to discriminate between malignant and normal tissues, and thus guide surgeons in real time, have potential to reduce local recurrence and metastases for breast cancer patients undergoing BCS. Indocyanine green (ICG) is a near-infrared fluorescent probe used clinically for other imaging applications, but its lack of target specificity limits use for intraoperative tumor localization. Dr. Yamada previously demonstrated that the *Pseudomonas aeruginosa*-secreted protein azurin contains a peptide (p28) which exhibits preferential entry into cancer cells and anti-cancer properties. Thus, he aimed to conjugate ICG with p28 as a novel, targeted intraoperative imaging agent and investigate its performance in preclinical models for breast cancer. In animal models, rapid tissue uptake and localization at the tumors was observed following injection of ICG-p28. Kinetic parameters and biodistribution analyses following systemic injection of ICG-p28 were comparable among all breast cancer cell lines, suggesting that ICG-p28 may be suitable for a range of breast cancer types. When tested as an intraoperative imaging agent using an animal model of breast cancer, there was targeted delivery of ICG-p28 and a clear contrast of the mammary tumor relative to normal tissue. The rate of tumor recurrence in animals where ICG-p28 was used to guide surgical removal of tumors was significantly decreased compared to the controls. These findings support the potential use of ICG-p28 as an intraoperative imaging agent in patients undergoing BCS, and may aid in the transition of this agent to early phase clinical trials.

(Image provided by Principal Investigator)

Publication: Naffouje SA, Goto M, Coward LU, et al. 2022. Nontoxic tumor-targeting optical agents for intraoperative breast tumor imaging. *Journal of Medicinal Chemistry* (65)10:7371-7379.

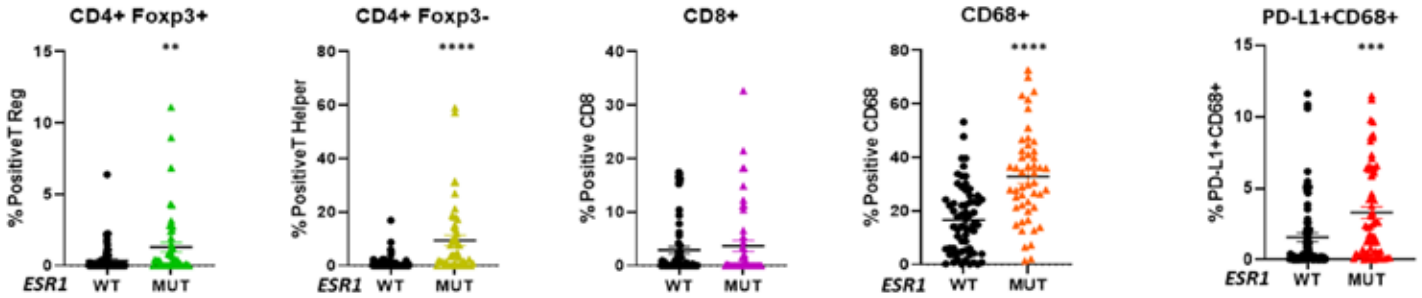
Jason Gertz

Jennifer Richer

Investigating Estrogen Receptor Mutations in Breast Cancer to Guide New Therapeutic Strategies

Jason Gertz, Ph.D., University of Utah, and Jennifer Richer, Ph.D., University of Colorado Anschutz Medical Campus

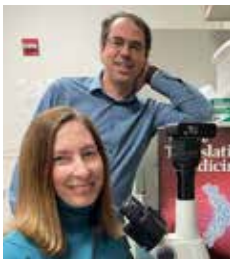
Two-thirds of all primary breast cancers are estrogen receptor alpha (ER)-positive. Aromatase inhibitors (AIs), which suppress estrogen production, are the first line of treatment for most ER-positive patients. However, virtually all recurrent metastatic breast cancers are AI-resistant, with about 40% carrying mutations in the gene encoding ER alpha, ESR1. Drs. Gertz and Richer sought to investigate the biological consequences of ER mutations and determine whether the mutations, or associated pathways, represent potential therapeutic targets for treatment of AI-resistant metastatic breast cancer. Using biopsies from patients with ER-positive metastatic breast cancer resistant to AI therapy (NCT02953860), they found that metastases with ER mutations expressed similar levels of androgen receptor (AR) as tumors with wild-type ER, indicating a potential role for AR in metastasis irrespective of ER mutational status. To investigate the role of AR, the team utilized ER mutant breast cancer models and found that following long-term estrogen-deprivation to mimic AI therapy (the situation under which ER mutations arise), AR was markedly upregulated. Growing cells in conditions to test survival advantage and metastatic potential, AR protein was increased, particularly in ER mutant cells, and this survival advantage could be inhibited by enzalutamide, an AR antagonist. Additionally, there was a significantly higher lung metastatic burden in animals with mutant ER breast cancer cells compared to those with wild-type ER. Pathway analysis found that the AR-regulated immunomodulatory secreted protein Chitinase-3-like protein 1 (CHI3L1) was elevated in mutant ER cells, particularly in the absence of estrogen, and when blocked, the ER mutant cells lost metastatic capacity. Furthermore, they determined that interferon-induced transmembrane 3 (IFITM3), which plays a role in AI resistance, was upregulated in ER mutant cell lines and ER mutant biopsies from patients with metastatic breast cancer. Since mutant ER cell lines showed enhanced innate immune pathway activation, the team examined tumor-infiltrating immune cells in patient biopsies. Metastatic biopsies with mutant ER had higher levels of pro-tumor T regulatory cells and macrophages (see accompanying figure). Macrophages expressing programmed cell death-ligand 1 (PD-L1), a checkpoint protein that suppresses the immune system, were also significantly higher in ER mutant metastases. Overall, these results suggest that acquired differences in AR, CHI3L1, and IFITM3 and macrophage PD-L1 expression in mutant ER breast cancer support survival and metastasis, and thus, therapies targeting these proteins may represent new therapeutic approaches.



*Sections of metastatic breast cancer biopsies that have estrogen receptor mutations (ESR1 Mut) or do not have estrogen receptor mutation (WT) were evaluated for immune cells that reside inside the tumor. The graphs show the percentage of cells within the biopsies that are T regulatory cells (CD4+Foxp3+), T helper cells (CD4+FoxP3-), cytotoxic T cells (CD8+), macrophages (CD68+), or PD-L1 expressing macrophages (PD-L1+CD68+). These results show that breast cancers with estrogen receptor mutations have more immune cells. Significance is measured by Student's t-test, ** p<0.01, ***p<0.001, ****p<0.0001. (Figure provided by Principal Investigators.)*

Publications: Williams MM, Spoelstra NS, Arnesen S, et al. 2021. Steroid hormone receptor and infiltrating immune cell status reveals therapeutic vulnerabilities of ESR1-mutant breast cancer. *Cancer Research* Feb 1. 81(3):732-746.

Arnesen S, Blanchard Z, Williams MM, et al. 2021. Estrogen receptor alpha mutations in breast cancer cells cause gene expression changes through constant activity and secondary effects. *Cancer Research* Feb 1. 81(3):539-551.

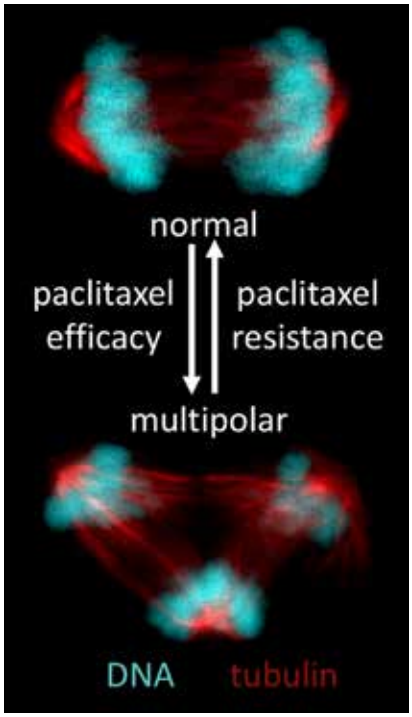


Beth Weaver (left) and Mark Burkard

Predicting Paclitaxel Sensitivity in Breast Cancer Patients

Beth Weaver, Ph.D., and Mark Burkard, M.D., Ph.D., University of Madison–Wisconsin

Paclitaxel is frequently used as first-line chemotherapy in breast cancer, but is only effective in about half of patients. Currently, no clinically available biomarker predicts which individuals will respond, causing many patients to receive ineffective treatment and experience treatment-related side effects. Drs. Weaver and Burkard explored the mechanism by which paclitaxel kills breast cancer cells and the potential of a specific tumor characteristic called chromosomal instability to identify patients that will benefit from paclitaxel treatment. The research teams found that paclitaxel causes multipolar spindles (genetic material is dragged to more than two poles) in cancer cells during cell division, which leads to chromosome missegregation and ultimately cell death, and discovered a novel mechanism some breast cancers use to evade cell death. To investigate paclitaxel's mechanism of action, the teams examined tumor biopsies from breast cancer patients receiving standard-of-care doses of paclitaxel. Before treatment, most dividing cells displayed normal bipolar mitotic spindles. After treatment, there was a substantial increase in multipolar cells but no evidence for mitotic arrest. Multipolarity alone did not predict whether a patient would respond to paclitaxel, suggesting that there are other factors that contribute to paclitaxel sensitivity. They found that multipolar cancer cells can evade cell death by clustering their spindle poles to form near-normal spindles; this spindle focusing reduces chromosome missegregation rates and increases cell viability. The teams explored whether spindle focusing may decrease the sensitivity of cancer cells to paclitaxel treatment in triple-negative breast cancer cell lines. Some cell lines readily focused paclitaxel-induced multipolar spindles, while others did not. Cells that focused their multipolar spindles had a lower rate of cell death compared to cells that did not. They found that increased multipolar divisions led to increased chromosome instability, and thus, sensitivity to paclitaxel. This observation was also seen in mouse models. Importantly, the teams also noted a direct correlation between pretreatment chromosomal instability and paclitaxel response in archived tissue from metastatic breast cancer patients. Breast cancers with higher rates of chromosomal instability before therapy responded preferentially to paclitaxel treatment. Drs. Weaver and Burkard have demonstrated that both multipolarity and chromosome instability contribute to response to paclitaxel. Future studies to evaluate chromosomal instability as a predictive biomarker for patient response to paclitaxel are important, since such a biomarker would substantially improve patient outcomes by sparing nonresponders the toxicity of paclitaxel and reducing delays in receiving effective treatment.



Images of bipolar (top) and multipolar (bottom) anaphase cells (Figure provided by Principal Investigators and adapted from Scribano CM, et al.,2021. Science Translational Medicine*). Paclitaxel induces abnormal multipolar spindles in patient tumors. If these persist, it leads to cell death and paclitaxel efficacy. However, focusing of paclitaxel-induced multipolar spindles into near-normal bipolar spindles leads to paclitaxel resistance.*

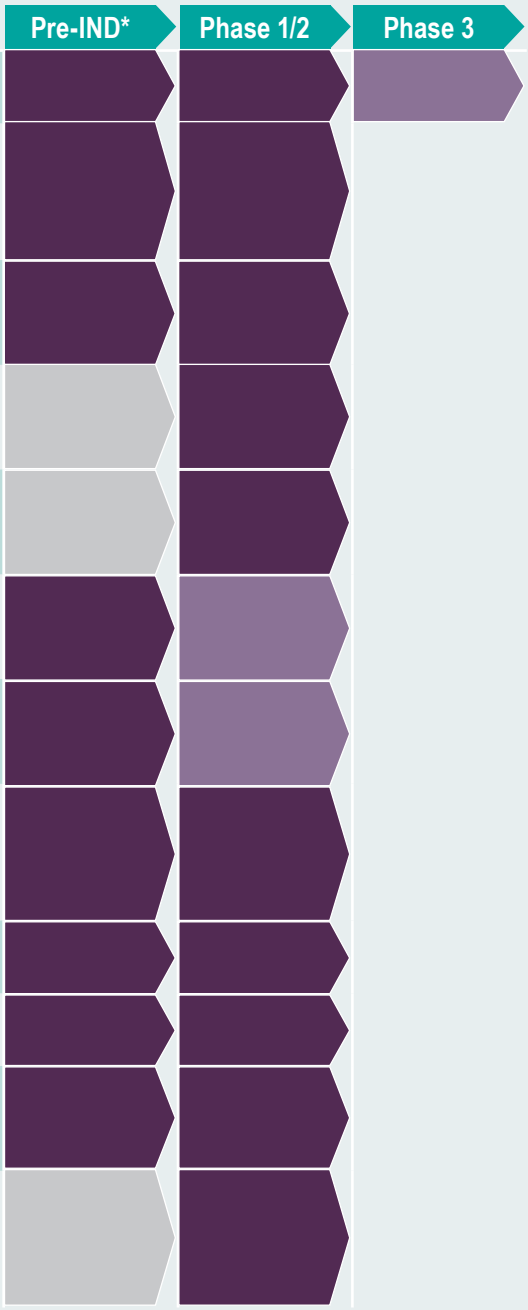
Publication: Scribano CM, Wan J, Esbona K, et al. 2021. Chromosomal instability sensitizes patient breast tumors to multipolar divisions induced by paclitaxel. *Science Translational Medicine* 13(610):eabd4811.

IN THE CLINICAL PIPELINE

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

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

Vaccines and Immunotherapies



***NeuVax™* —** *Constantin Ioannides and Elizabeth Mittendorf*
An immunogenic peptide-based vaccine to prevent or delay breast cancer recurrence.

HER2 Peptide-Based Vaccine — *Mary (Nora) L. Disis*
A HER2 intercellular domain peptide-based vaccine designed to treat breast cancer by stimulating the immune system-mediated destruction of remaining cancer cells after primary cancer therapy.

STEMVAC — *Mary (Nora) L. Disis*
A multi-antigen vaccine comprised of Th1 epitopes derived from five breast cancer stem cell/EMT immunogenic proteins to inhibit tumor growth.

Mammaglobin cDNA Vaccine — *William Gillanders*
A mammaglobin-A DNA vaccine that induces specific IFN-γ-secreting CD8 T cells and results in longer progression-free survival for patients.

Folate Receptor Alpha Vaccines — *Keith Knutson and Edith Perez*
A vaccine targeting the folate receptor alpha in patients with TNBC to prevent or delay recurrence.

HER2 Bi-Armed Activated T Cells (HER2 BATs) — *Lawrence G. Lum*
Therapy that induces the development of "memory" antigen-specific cytotoxic T cells directed at HER2 to treat women with HER2+ metastatic breast cancer.

TRC105 — *Ben Seon*
A monoclonal antibody that targets endoglin, inhibits angiogenesis, and was found in preclinical models to suppress the growth of both established and new tumors.

Mesothelin-Targeted T Cell Therapy for Metastatic Breast Cancer — *Michel Sadelain, Prasad Adusumilli and Shanu Modi*
A mesotelin-targeted chimeric antigen receptor (CAR) T cell therapy for patients with treatment-refactory, metastatic TNBC.

AVX901 HER2 Vaccine — *H. Kim Lyerly*
A vaccine composed of adenoviral and alphaviral vectors expressing the human HER2 gene.

P10s-PADRE — *Thomas Kieber-Emmons*
A carbohydrate mimetic peptide vaccine that targets tumor-associated carbohydrate antigens.

Combination Vaccine for HER2+ Metastatic Breast Cancer — *Leisha Emens*
Combining trastuzumab, cyclophosphamide, and an allogeneic GM-CSF-secreting breast tumor vaccine for HER2+ metastatic breast cancer.

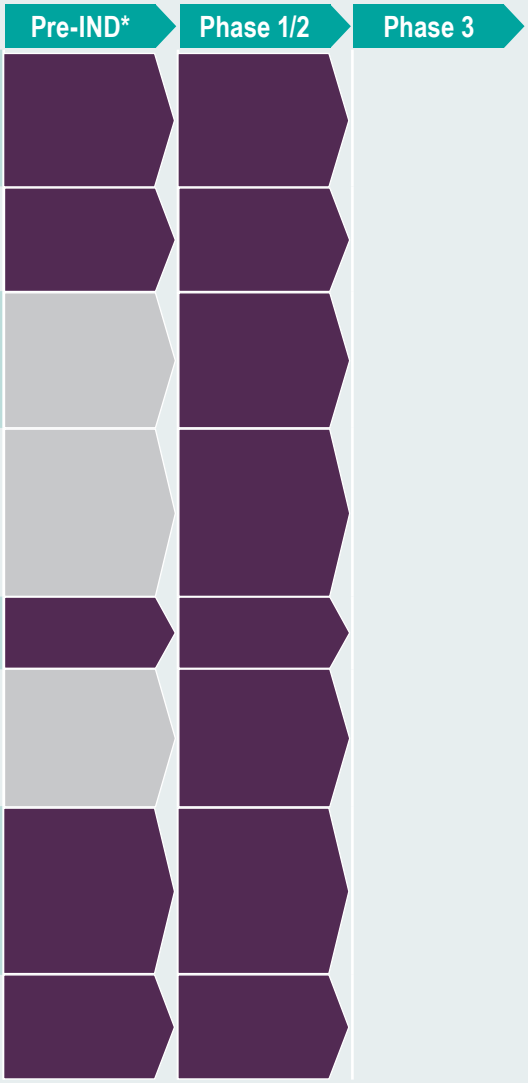
Alpha-Lactalbumin Vaccine for Triple-Negative Breast Cancer — *Vincent Tuohy and George Budd*
A vaccine for TNBC patients that have recovered from current standard-of-care therapy with potential use in a prophylactic setting.

* Investigational New Drug (IND) application

IN THE CLINICAL PIPELINE (cont.)

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

Vaccines and Immunotherapies (cont.)



Engineered T Cells to Treat Locally Advanced or Metastatic Triple-Negative Breast Cancer — *Rongfu Wang and Jenny Chang*
Therapy using T cell receptors engineered to recognize the NY-ESO-1 cancer antigen (NY-ESO-1 TCR-transduced T cells) for treatment of TNBC.

HER2-Specific Helper T Cell Epitope Vaccine — *Keith Knutson and Amy Degnim*
A HER2/neu subdominant epitope-based vaccine that will enhance HER2-specific CD4 T cell immunity.

Enhancing the Anti-HER2 CD4 Th1 Response to Prevent Recurrence — *Brian Czerniecki*
Combining a multivalent Th1 epitope anti-oncodriver DNA vaccine and HER2-pulsed IL-12 secreting dendritic cell (DC1) vaccine to improve complete pathologic response rates in HER2+ breast cancer.

Trastuzumab/Pertuzumab with HER2 HLA-DR Vaccine Therapy — *Keith Knutson and Saranya Chumsri*
A multi-epitope vaccine used to boost HER2-specific T cells during trastuzumab and pertuzumab maintenance therapy in patients with residual disease post neoadjuvant chemotherapy to block disease recurrence and metastasis.

Regional Oncolytic Poliovirus Immunotherapy for Breast Cancer — *Smita Nair*
Using the oncolytic poliovirus PVSRIPO to eradicate tumors in TNBC.

Overcoming Immunotherapy Resistance Using RT-Mediated Immunomodulation — *Stephen Shiao and Simon Knott*
Using focal radiation combined with pembrolizumab to generate anti-tumor immune response in patients diagnosed with early-stage TNBC.

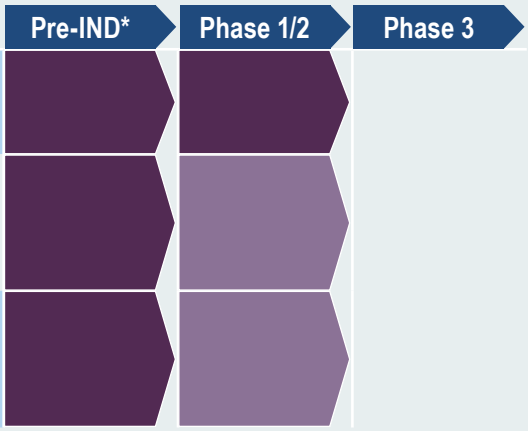
Novel Immunotherapy for Brain-Metastatic Breast Cancer — *Pawel Kalinski and Brian Czerniecki*
HER2/HER3-loaded dendritic cell (alpha-DC1) vaccine combined with PD-1 blockade for treatment of patients with parenchymal brain-metastatic breast cancer. DC vaccine for treatment of patients with leptomeningeal disease from TNBC or HER2+ breast cancer.

B7-H3 Specific CAR T-Cell Immunotherapy — *Soldano Ferrone and Marcela Maus*
A B7-H3 specific CAR T-cell with an inducible safety switch for the treatment of patients with metastatic TNBC.

IN THE CLINICAL PIPELINE

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

Diagnostics and Imaging

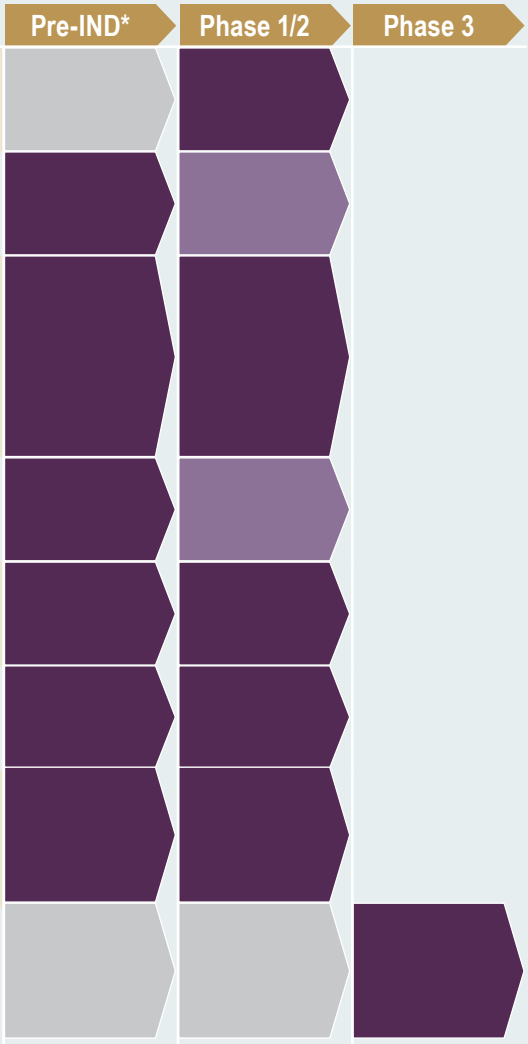


Targeted HER2 Radiotracer — *Gary Ulaner*
Using 89Zr-trastuzumab to determine the proportion of patients with HER2-negative primary breast cancer who develop imagable HER2-positive metastases.

Polycationic Peptides for Fluorescence-Guided Surgery — *Roger Tsien*
Intravenous injection of the protease-activatable fluorescent peptide AVB-620 prior to surgery to enable surgeons to identify critical cancer margins for tumor resection and examine lymph nodes for invasive disease.

Monitoring Tumor Response to Neoadjuvant Chemotherapy with TrackDOI — *Darren Roblyer*
Using a new optical metabolic scanning technology, TrackDOI, to monitor breast cancer patient tumor response to neoadjuvant chemotherapy in real time.

Therapeutics



Fatty Acid Synthase Inhibitor — *Ruth Lupu and Tufia Haddad*
Treatment of taxane-resistant metastatic HER2+ breast cancer with the fatty acid synthase inhibitor, TVB-2640 (3-V Biosciences), in combination with paclitaxel and trastuzumab.

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.

Pembrolizumab and Tremelimumab for Treatment of Oligometastasis — *Andy Minn*
Radiation to metastatic lesions in combination with the immune checkpoint inhibitor pembrolizumab (PD-1 inhibitor) for patients with metastatic cancers for which anti-PD-1 therapy has failed. Radiation in combination with dual immune checkpoint blockade using tremelimumab (anti-CTLA-4) and MED14736 (anti-PDL1) to treat metastatic breast cancer and other cancers.

Combining Aromatase and Src Inhibitors — *Joyce Slingerland and Isabel Chu*
Combination therapy using anastrazole, an aromatase inhibitor that stops estrogen production, with Src inhibitor AZD0530 in post-menopausal women with ER+ breast cancer.

5-Fluoro-2'deoxycytidine (FdCyd) — *Edward Newman*
Reversal of DNA methylation in several genes expressed by breast cancer cells with FdCyd and tetrahydrouridine.

Anti-Androgen Therapy (Enzalutamide) — *Anthony Elias and Jennifer Richer*
Combining enzalutamide with fulvestrant to limit signaling through androgen receptors (AR) expressed on ER+ breast cancers that are resistant to anti-estrogen therapy.

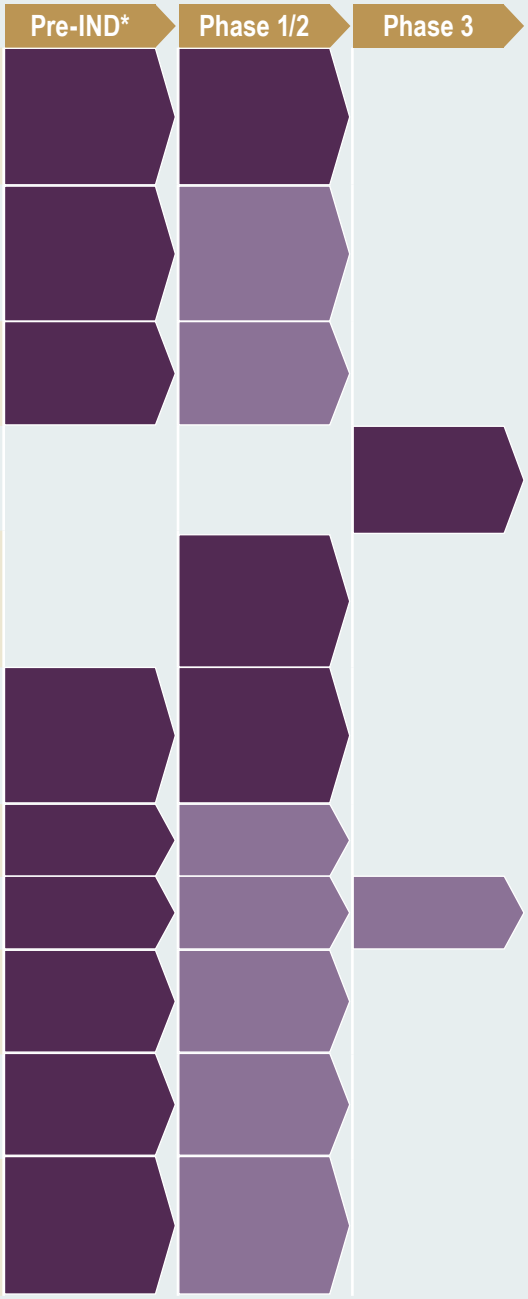
Meclofenamate for Brain Metastasis — *Joan Massague*
A FDA-approved non-aspirin, non-steroidal, anti-inflammatory drug to prevent new brain metastases in patients with recurrent or progressive brain metastasis from a solid primary tumor.

Aspirin as Adjuvant Therapy for Node-Positive Breast Cancer — *Eric Winer, Wendy Chen, and Michelle Holmes*
Long-term aspirin use to reduce breast cancer recurrence and improve survival in patients with node-positive breast cancer.

IN THE CLINICAL PIPELINE (cont.)

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

Therapeutics (cont.)



Molecular Triage Approach for a More Effective and Less Toxic Therapy for HER2+ Breast Cancer — *Mothaffar Rimawi and Rachel Schiff*
A molecular classifier, based on detection of resistance-associated genomic alterations, used to identify patients who may benefit from anti-HER2 therapy without added chemotherapy.

A Novel Druggable Pathway That Prevents Bone Loss in Breast Cancer Patients — *Alana Welm*
Using the RON kinase inhibitor, BMS-777607/ASLAN002 in metastatic cancer patients to decrease osteolysis and promote bone repair.

Talazoparib — *Dennis Slamon*
The novel PARP inhibitor talazoparib used in combination with other therapies to treat non-BRCA mutant TNBC.

Denosumab (XGEVA®) — *Josef Penninger, Judy Garber, and Christian Singer*
Prophylactic administration to reduce the risk of breast cancer in women with BRCA1 mutations.

Biomarker-Driven Targeted Therapy for Late-Recurring ER-Positive Breast Cancer — *Christina Curtis and George Sledge*
Targeting driver gene amplifications present in integrative clusters (IC1, IC2, and IC6) in high-risk ER+/HER2- breast cancer.

Neoadjuvant Endocrine Therapy (NET) + Radiotherapy — *Silvia Formenti and Sandra Demaria*
Treatment of HR+ breast cancer with a combination of focal radiotherapy and letrozole NET to enable a response to immunotherapies.

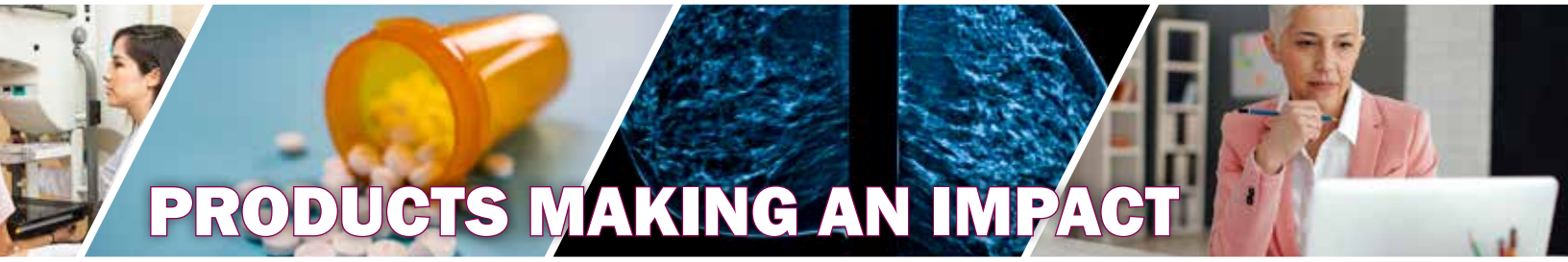
Ruxolitnib — *Yi Li*
Ruxolitinib for premalignant breast disease with potential use for prevention of breast cancer.

Selective Androgen Receptor Targeting Agonist — *Theresa Hickey*
Enobosarm, a selective AR targeting agonist, for treatment of AR+ breast cancer.

AOH1996 — *Robert Hickey and John Perry*
A novel inhibitor of the cancer-associated proliferating cell nuclear antigen (caPCNA) protein, AOH1996, for breast cancer treatment.

Sabizabulin (VERU-111) — *Wei Li and Tiffany Seagroves*
An orally bioavailable tubulin targeting agent, Sabizabulin (VERU-111), for the treatment of ER+/HER2- metastatic breast cancer.

Fulvestrant and Binimetinib for NF-1-Deficient Breast Cancer — *Eric Chang, Bora Lim, and Matthew Ellis*
Combining fulvestrant with the mitogen-activated protein kinase (MEK) inhibitor, Binimetinib, for the treatment of ER+ metastatic breast cancers expressing mutated neurofibromatosis 1.



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 (CDK) inhibitor is FDA-approved to treat hormone receptor (HR)-positive, HER2-negative 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 to treat HR-positive, HER2-negative 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-positive, HER-2 negative 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

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

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

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

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

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
(301) 619-7071

01/2023
DOD visual images are for illustrative purposes only.
Some images were cropped to emphasize subject matter.

The Congressionally Directed Medical Research Programs is a part of the U.S. Army Medical Research and Development Command, U.S. Army Futures Command.