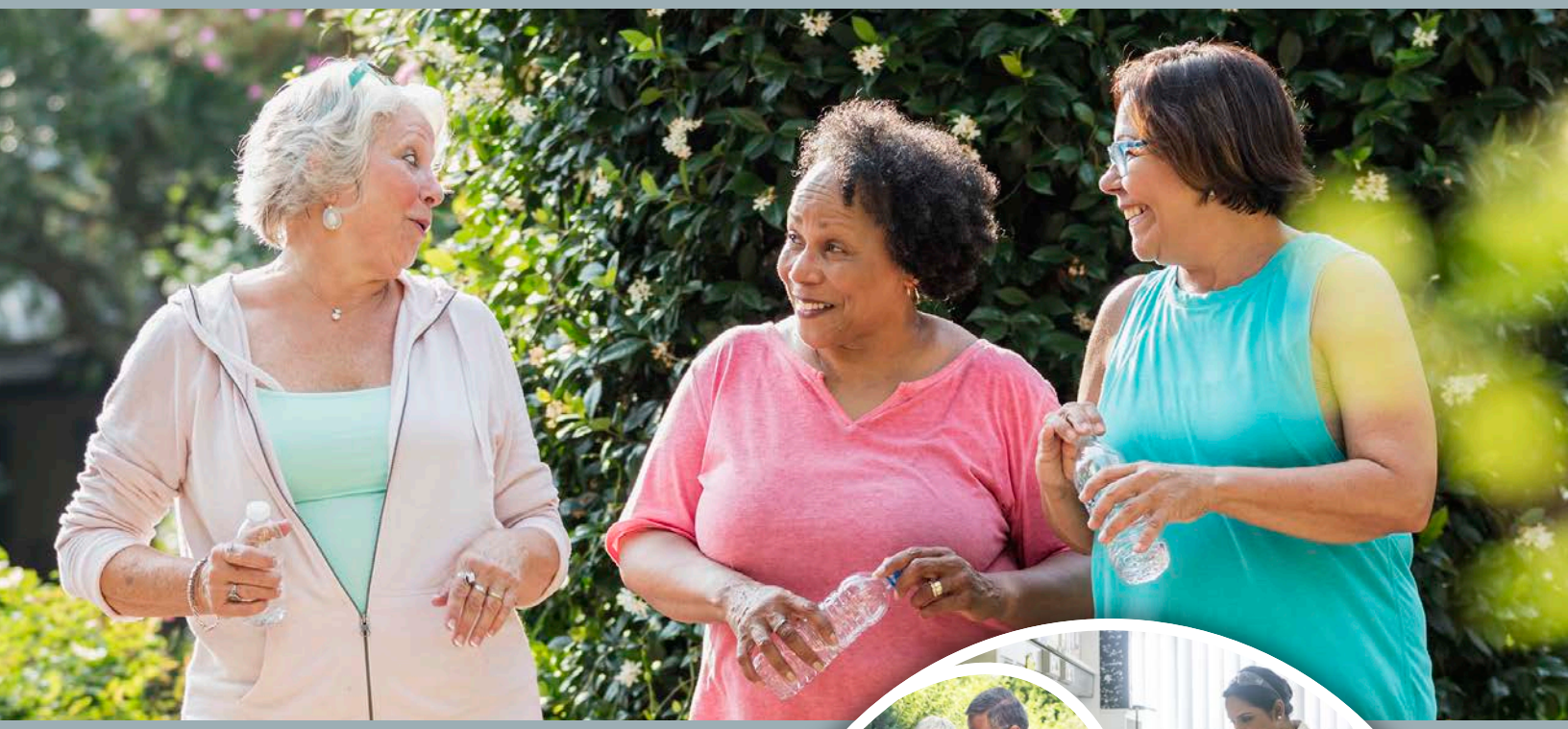
Breast Cancer Research Program



Congressionally Directed Medical Research Programs

CDMRP

Department of Defense

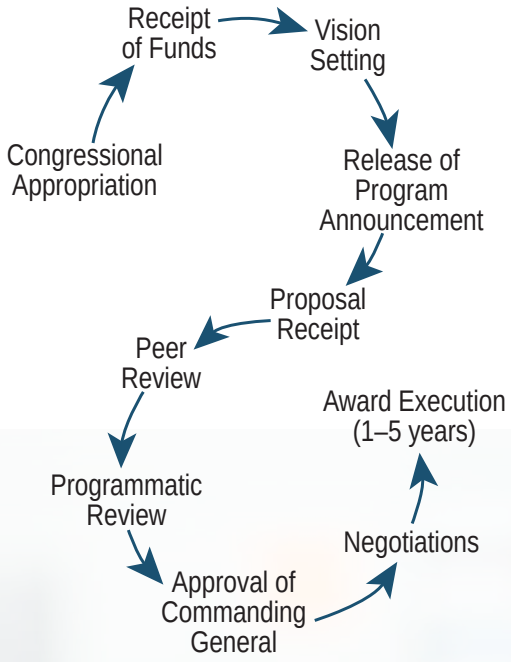
U.S. Army Medical Research and Development Command

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

The Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has been responsible for managing over $17.8 billion since its inception through fiscal year 2021 (FY21). 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.



"Because of my science background, I was instantly drawn to research advocacy and attended my first breast cancer conference, the San Antonio Breast Cancer Symposium (SABCS), in 2017. I met several other patient advocates at SABCS who encouraged me to apply to various advocacy trainings as well as to become a consumer reviewer for the BCRP at the DOD. I distinctly recall discussing a grant for which I had given an outstanding review, but the scientists had not. After I explained how the cohort of patients this research could help was in desperate need of treatment options, they thoughtfully listened and changed their scores to reflect my input. I had researchers approaching me after the meeting to ask what I thought were research priorities for metastatic breast cancer – it was incredibly gratifying and helped me see the value patients bring to research."

Christine Hodgdon, Consumer Reviewer

BREAST CANCER RESEARCH PROGRAM

VISION: A world without breast cancer

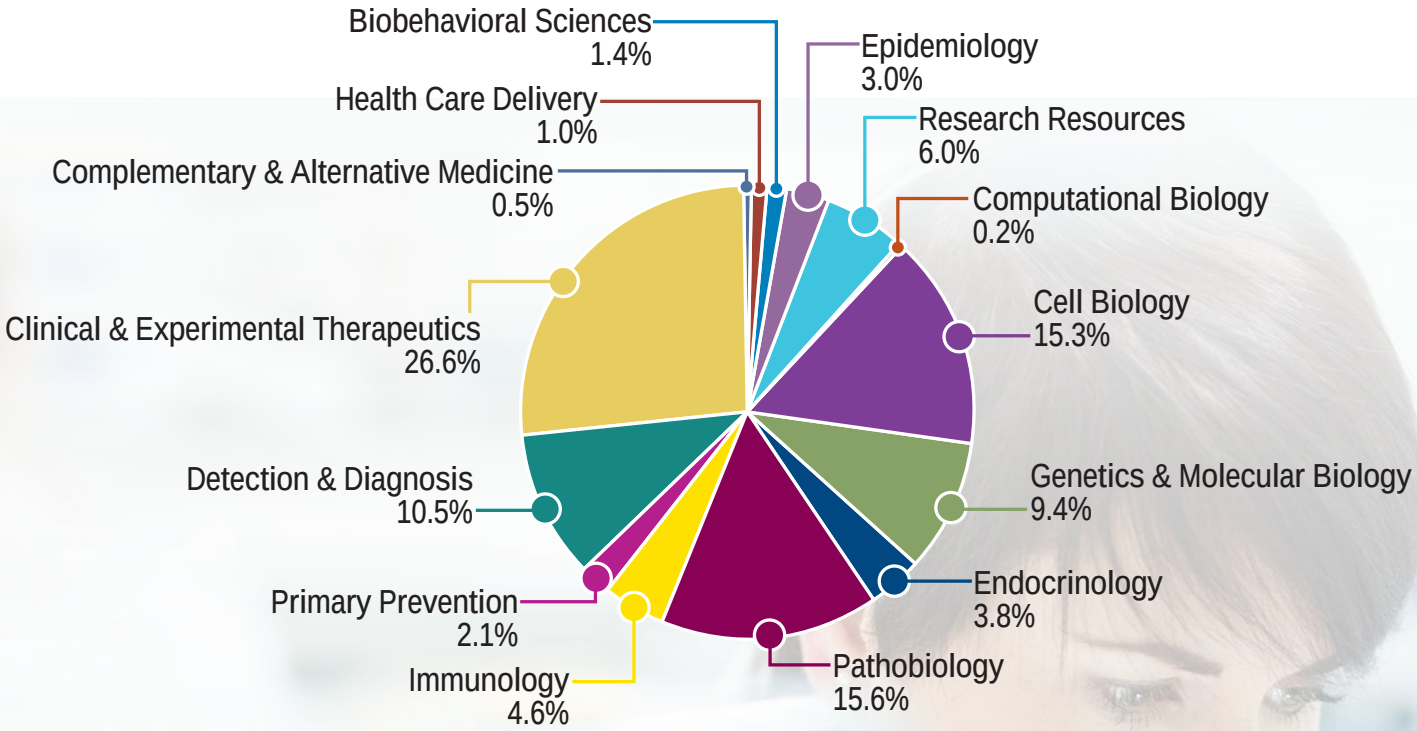
MISSION: To end breast cancer for Service Members, Veterans, and the general public by funding innovative, high-impact research through a partnership of scientists and consumers

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 $3.9 billion in congressional appropriations through FY21. 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–FY20, the BCRP funded 7126 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–FY20 BCRP Portfolio



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).

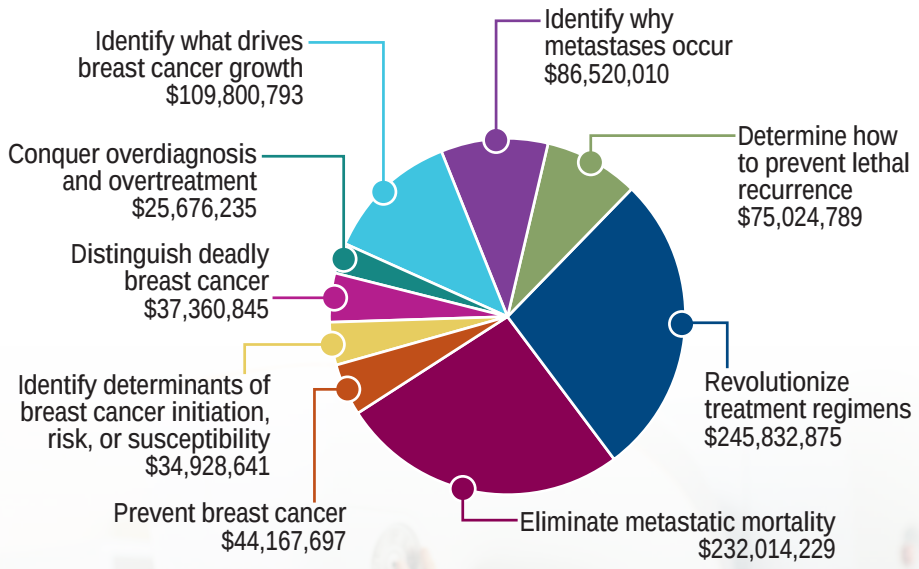
[1] https://cdmrp.army.mil/bcrp/pdfs/Breast%20Cancer%20Landscape2021.pdf.

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–FY20 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 the general public.[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]

[2] https://gis.cdc.gov/Cancer/USCS/#/AtAGlance/.
[3] https://seer.cancer.gov/statfacts/html/aya.html.
[4] Zhu K, Devesa SS, Wu H, et al. 2009. Cancer incidence in the U.S. military population: comparison with rates from the SEER program. *Cancer Epidemiology, Biomarkers and Prevention* 18(6):1740-1745.
[5] Lee T, Williams VF, and Clark LL. 2016. Incident diagnoses of cancers in the active component and cancer-related deaths in the active and reserve components, U.S. Armed Forces, 2005-2014. *Medical Surveillance Monthly Report* 23(7):23-31.

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

"I have been involved with BCRP for more than 25 years. First as a grant recipient, later as a scientific reviewer, an ad hoc programmatic reviewer, as a member of the Programmatic Panel, and more recently as the elected chair for the 2022 Programmatic Panel. From my own experience and closely observing the program over the years, I can confidently say that BCRP has fundamentally changed the way scientists conduct breast cancer research. Scientists feel encouraged to consider high-risk, high-reward science questions that will significantly impact breast cancer patients. The fantastic scientists and patient advocates who serve on the Programmatic Panel have been inspirational to work with. I consider it my privilege to continue to be part of this effort by the Department of Defense."

Senthil Muthuswamy, M.D., FY22 Programmatic Panel Chair

"DOD BCRP awards fund pilot studies, large multi-institutional clinical studies and everything in between. DOD BCRP also stresses engagement with patients to ensure research relevance. Support from a Breakthrough Award Level 1 has enabled our team to develop a novel approach to control breast cancer metastasis. Support from a Breakthrough Award Level 3 has facilitated a clinical study of a novel immunotherapy approach, oncolytic poliovirus PVSRIPO, in women with breast cancer. This DOD-supported bench-to-bedside research has led to biomarker discovery studies. Of utmost importance is the fact that DOD is 100% invested in research and successful completion of the study."

Smita Nair, Duke University

"I learned about the DOD BCRP through individuals connected with the Ithaca Breast Cancer Alliance. They shared their experiences with me and I applied for and began serving on BCRP peer review panels in the early 2000s. Serving on a scientific review panel allows advocates to influence the direction of research and to learn from—and become friends with—esteemed researchers and clinicians. Including advocates as collaborators with scientists and clinicians provides a wonderful synergy, reminding all parties involved that, in addition to being a disease that affects cells, cancer is also a disease that affects people."

Bob Riter, Consumer Reviewer

RESEARCH HIGHLIGHTS

Cluster of Differentiation 73 (CD73) Blockade Promotes Dendritic Cell Infiltration of Primary Tumors and Activation of Antitumor Immune Responses

Erik Wennerberg, Ph.D., Cornell University, Weill Medical College

For approximately 80% of patients diagnosed with triple-negative breast cancer (TNBC), immune checkpoint inhibitors (ICIs) have shown little to no clinical efficacy. The limited or lack of efficacy for ICIs in patients with TNBC is due to the immunosuppressive microenvironment surrounding the primary tumor, characterized by little to no infiltration of antitumor T cells or their activators, dendritic cells (DCs). Recent data demonstrated that CD73 is highly expressed in breast cancer and is responsible for the generation of adenosine, a highly immunosuppressive molecule that inhibits DC activation and thus downstream activation of antitumor T cells. With support from an FY16 Breakthrough Fellowship Award, Dr. Wennerberg investigated whether inhibiting adenosine production through blocking CD73 in combination with radiation therapy could enhance antitumor immunity in breast cancer. Using TNBC cell models, Dr. Wennerberg and his team showed that CD73 levels increased after exposure to radiation treatment. In a mouse model of TNBC, treatment with an anti-CD73 antibody in combination with radiation therapy enhanced tumor response, extended overall survival, and resulted in complete tumor regression in a subset of mice. In addition, the researchers demonstrated that, in conjunction with radiation therapy and an ICI, CD73 blockade was able to offer systemic immunity against metastatic lung lesions in a mouse model of TNBC. Although additional studies are needed, Dr. Wennerberg's work has the potential for clinical translation, where CD73 inhibitors in combination with radiation therapy and ICIs could be used to treat patients with TNBC, particularly metastatic TNBC.

Publication: Wennerberg E, Spada S, Rudqvist N-P, et al. 2020. CD73 blockade promotes dendritic cell infiltration of irradiated tumors and tumor rejection. Cancer Immunol Res 8(4):465-478.

Ori Maller

Valerie Weaver

Stromal Lysyl Hydroxylase 2, a Novel Biomarker for Breast Cancer Patient Prognosis

Ori Maller, Ph.D. and Valerie Weaver, Ph.D., University of California, San Francisco

The extracellular matrix (ECM), composed primarily of collagen fibers that are regularly remodeled through tightly regulated processes, provides physical and structural support for cells and initiates important cues needed for tissue function and survival. An excess buildup of ECM with increased collagen stiffness and crosslinking is often seen in the development of invasive breast carcinomas, and those with the stiffest stroma have been shown to be the most aggressive. With support from an FY13 Postdoctoral Fellowship Award, Dr. Maller, a former member of Dr. Weaver's team and co-lead author in a recent publication, investigated whether changes in ECM mechanical properties cooperate with inflammatory signaling to suppress immune detection and increase metastatic disease. The research team demonstrated that inflammatory stromal cell-mediated collagen crosslinking and stiffening promote breast cancer tumor aggression, and a subgroup of lysyl hydroxylase 2 (LH2)-dependent hydroxylysine aldehyde-derived collagen crosslinks (HLCCs) vital for tissue mechanical strength were identified. Studies by Dr. Weaver and her team using breast cancer patient biopsies showed that the more aggressive breast cancer subtypes have moderate to high stromal LH2 expression, and there was an association between shorter breast cancer-specific survival and high expression of stromal cell LH2, especially in lymph node positive patients. The results implicate stromal LH2 expression as a strong indicator of tumor aggression. Finally, studies using a mouse model of breast cancer metastasis indicated a role for tumor-associated macrophages (TAMs) in promoting stromal lysyl oxidase (LOX)/PLOD2 (the gene encoding the protein LH2) expression, thus increasing ECM collagen stiffness and tumor aggression. Results from this important research pinpoint stromal LH2 as a novel biomarker and potentially early prognostic indicator of metastatic breast cancer disease aggression and poor patient survival. The findings support future preclinical investigations to confirm whether a causal relationship exists between stromal LH2, tumor aggression, and metastasis.

Publication: Maller O, Drain AP, Barrett AS, et al. 2021. Tumour-associated macrophages drive stromal cell-dependent collagen crosslinking and stiffening to promote breast cancer aggression. Nature Materials 20(4):548-559.

Mitochondria-Targeted Copper-Depleting Nanoparticle Inhibits Triple-Negative Breast Cancer Progression in Mice

Liyang Cui, Ph.D., Stanford University

Higher levels of copper have been detected in serum and cancerous tissue samples collected from patients diagnosed with TNBC, and while depletion of copper has been identified as a potential therapeutic option, there are concerns for toxicity associated with systemic copper depletion. For this reason, researchers have focused on copper trafficking in cancer cells to develop a more targeted treatment approach. With support from an FY17 Breakthrough Fellowship Award, Dr. Cui sought to develop a polymer-based copper-depleting nanoparticle (CDN) that selectively delivers a copper chelator to cancer cells for the treatment of TNBC. Using a mouse model of TNBC, Dr. Cui and her team demonstrated that a newly developed CDN selectively depleted intracellular copper and inhibited tumor growth and progression. Mice treated with the CDN exhibited a significant delay in tumor progression and half of the treated mice survived greater than 68 days, compared to a median survival of 25.5 days with saline (control) and 32 to 35 days with other copper chelators. Tumor analyses also confirmed that the CDN treatment resulted in a metabolic shift that may affect energy production and metabolomics for the tumor cells. Importantly, treatment with CDN was well-tolerated in mice, showing minimal acute or cumulative toxicity. While additional research must be done, findings from Dr. Cui's preclinical studies of the newly developed CDN suggest the potential clinical relevance of this treatment strategy and may provide a future targeted therapeutic option for patients with TNBC.

Publication: Cui L, Gouw AM, LaGory EL, et al. 2019. Mitochondrial copper depletion suppresses triple-negative breast cancer in mice. Nature Biotechnology Mar;39(3):357-367. doi: 10.1038/s41587-020-0707-9. PMID: 33077961.

Sophia Lunt and her research team

Metabolomic Targeting of Heterogeneous Breast Cancer for Personalized Therapy Development

Sophia Y. Lunt, Ph.D. and Eran Andrechek, Ph.D., Michigan State University

Given the heterogeneity in morphology, receptor status, and gene expression profiles of breast cancer subtypes, a single therapeutic strategy is not effective for all breast cancer patients. Claudin-low and basal-like breast cancers are two subtypes that are predominantly classified as TNBC and are frequently unresponsive or resistant to standard cancer therapies. Cancer-related metabolomics (i.e., the analysis of metabolites that change during cellular metabolism) has been explored as a way to identify promising diagnostic biomarkers and therapeutic targets. With support from an FY14 Breakthrough Award – Funding Level 1 – Partnering PI Option, Drs. Lunt and Andrechek sought to define the metabolic profiles of claudin-low and basal-like breast cancers as a strategy for identifying metabolic-targeting drugs most likely to be effective against each subtype. In a recent publication, Dr. Lunt and her research team investigated subtypes of primary tumors from a transgenic mouse model that recapitulates the heterogeneity found in human breast cancer. The team studied the metabolic profiles of two subtypes termed epithelial-mesenchymal transition (EMT) and papillary, which corresponded most similarly to the claudin-low subtype and basal-like breast cancer, respectively. Using drugs selected based on the metabolic profiles, they showed that metabolism-targeting drugs can affect cell proliferation in a subtype-specific manner. Targeting glutathione biosynthesis or the tricarboxylic acid cycle more effectively inhibited EMT tumor cell proliferation, whereas targeting nucleotide biosynthesis with 5-fluorouracil was most effective in inhibiting papillary tumor cell proliferation. Moreover, knocking out the preferred metabolic nucleotide biosynthesis pathway slowed tumor growth in both papillary and EMT tumor-bearing mice in a subtype-specific manner. Dr. Lunt's recently published work demonstrates the utility of targeting breast cancer subtype-specific metabolic pathway changes as a way to selectively inhibit cancer cell proliferation. These findings also provide evidence for using metabolic profiles of breast cancer subtypes as a potential prognostic indicator to guide treatment decisions, which may ultimately improve patient outcomes for those with difficult to treat TNBCs.

Publications:

Ogrodzinski MP, Teoh ST, and Lunt SY. 2020. Metabolomic profiling of mouse mammary tumor-derived cell lines reveals targeted therapy options for cancer subtypes. Cellular Oncology 43(6):1117-1127. https://link.springer.com/article/10.1007%2Fs13402-020-00545-1.

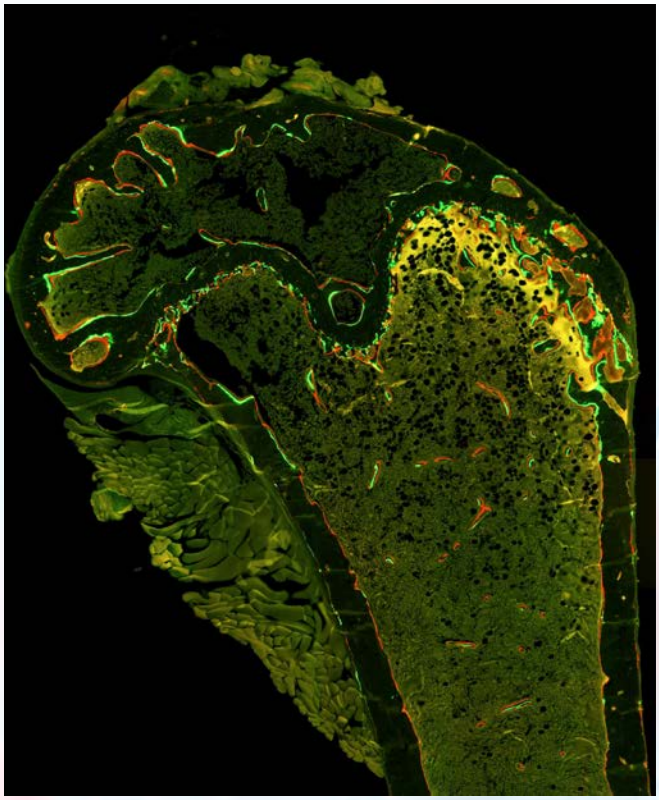
Ogrodzinski MP, Teoh ST, and Lunt SY. 2021. Targeting subtype-specific metabolic preferences in nucleotide biosynthesis inhibits tumor growth in a breast cancer model. Cancer Research 81:303-314. https://pubmed.ncbi.nlm.nih.gov/33115804/.

Targeting Senescence May Prevent Chemotherapy-Induced Bone Loss in Breast Cancer Patients

Sheila Stewart, Ph.D., Washington University in St. Louis, School of Medicine

Chemotherapy-induced bone loss is a significant problem that negatively impacts the quality of life in breast cancer survivors. While this bone loss has long been attributed to the drop in estrogen that occurs during chemotherapy, similar to that which occurs during menopause, substantial data suggest an estrogen-independent mechanism as well. With support from an FY15 Breakthrough Award - Funding Level 2, Dr. Sheila Stewart investigated how senescence contributes to bone loss following chemotherapy. Dr. Stewart and her team demonstrated that chemotherapy-induced bone loss was more severe than bone loss initiated by estrogen deprivation in studies with mouse models. The team reasoned that senescence might be a contributing factor to chemotherapy-induced bone loss since chemotherapy drugs used to treat breast cancer induce cellular senescence and age-related increases in senescent cells have been shown to drive age-related bone loss. To assess the presence of senescence in the bone following chemotherapy or radiation, the team assayed for changes in senescence-associated secretory phenotype (SASP) factors that senescent cells express. They observed increased expression of SASP factors in bone-resident cells from the tibias of mice that had been treated with chemotherapy or radiation and also demonstrated that estrogen loss alone was not sufficient to induce senescence in the bone. Additional studies with mouse models showed that senescence was driving the chemotherapy-induced bone loss and inhibitors of the p-38MAPK-MK2 pathway reduced SASP factors and mitigated chemotherapy-induced loss. Through this important work, Dr. Stewart and her team have identified a role for senescence in chemotherapy-induced bone loss and illustrated that targeting the p38MAPK-MK2 pathway may help minimize this negative effect. With support from an FY20 Breakthrough Award – Funding Level 3 – Partnering PI Option, Dr. Stewart and Partnering PI Dr. Cynthia Ma plan to test a MK2 inhibitor in combination with chemotherapy in a phase I/II clinical trial. The trial will evaluate safety, as well as the effectiveness of the test compound in combination with chemotherapy to limit disease progression, along with disease- and therapy-induced bone loss in metastatic breast cancer patients.

Publication: Yao Z, Murali B, Ren Q, et al. 2021. Therapy-induced senescence drives bone loss. Cancer Research, 80(5):1171-1182.



A mouse femur showing calcein (green) and alizarin 7 (red) staining, which were used to indicate regions of bone growth in the mouse models.

Christopher Li

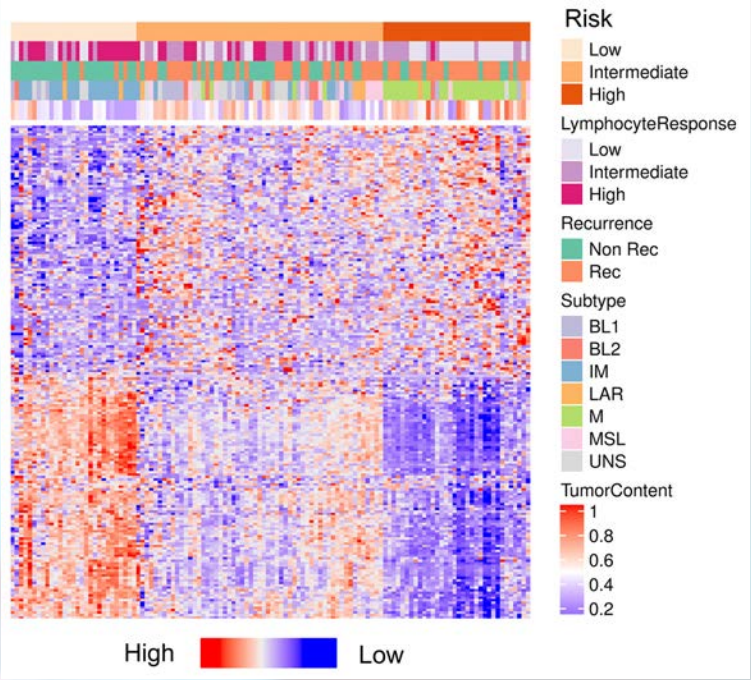
Arul Chinnaiyan

Identifying a Gene Panel to Predict Risk of Recurrence in Patients with Basal-Like Breast Cancer

Christopher Li, M.D., Ph.D., Fred Hutchinson Cancer Research Center, and Arul Chinnaiyan, M.D., Ph.D., University of Michigan

Basal-like breast cancer (BLBC), which accounts for up to 70% of TNBC, is particularly aggressive and lacks targeted therapies leading to a poorer prognosis (compared to other forms of breast cancer). A test to predict a patient's risk of BLBC recurrence does not exist in the clinical setting and, given the poor prognosis, there is an urgent need for such a test. With support from an FY11 Collaborative Innovators Award, Drs. Li and Chinnaiyan aimed to identify tumor characteristics that are associated with BLBC recurrence and therefore may be useful for distinguishing patients with BLBC who will develop a recurrence from those who will not. Through their work, the team found that tumors from patients who had developed a recurrence had increased growth factor signaling and stem cell-like features, while tumors from recurrence-free patients showed high immune cell infiltration and movement of macrophages. To develop a set of genes associated with prognosis, the team used a multi-step procedure focused on gene expression levels and association with recurrence. The researchers selected the 21 top-ranked genes for their panel (BRAVO-DX), which was then validated in five independent cohorts of patients. The BRAVO-DX panel was shown to outperform existing prognostic markers and was strongly predictive of recurrence-free survival in patients with BLBC. In addition, a smaller 12-gene set (BRAVO-IMMUNE) that was focused on tumor-immune characteristics was also highly prognostic for overall survival. Importantly, this panel could further stratify patients with BLBC and highlight those who would benefit from immunological therapeutic strategies. While further validation is needed, these findings indicate that the BRAVO-DX gene signature is a strong predictor of recurrence-free survival in patients with BLBC. Identification of prognostic biomarkers and the BRAVO-DX panel provide potential for earlier identification of beneficial treatments, which could drastically improve breast cancer patient survival.

Publication: Li CI, Zhang Y, Cieslik M, Wu Y-M, Xiao L, Cobain E, Tang M-TC, Cao X, Porter P, Guenthoer J, Robinson DR, and Chinnaiyan AM. 2021. Cancer cell intrinsic and immunologic phenotypes determine clinical outcomes in basal-like breast cancer. Clinical Cancer Research. 27(11):3079-3093. doi: 10.1158/1078-0432.CCR-20-3890.



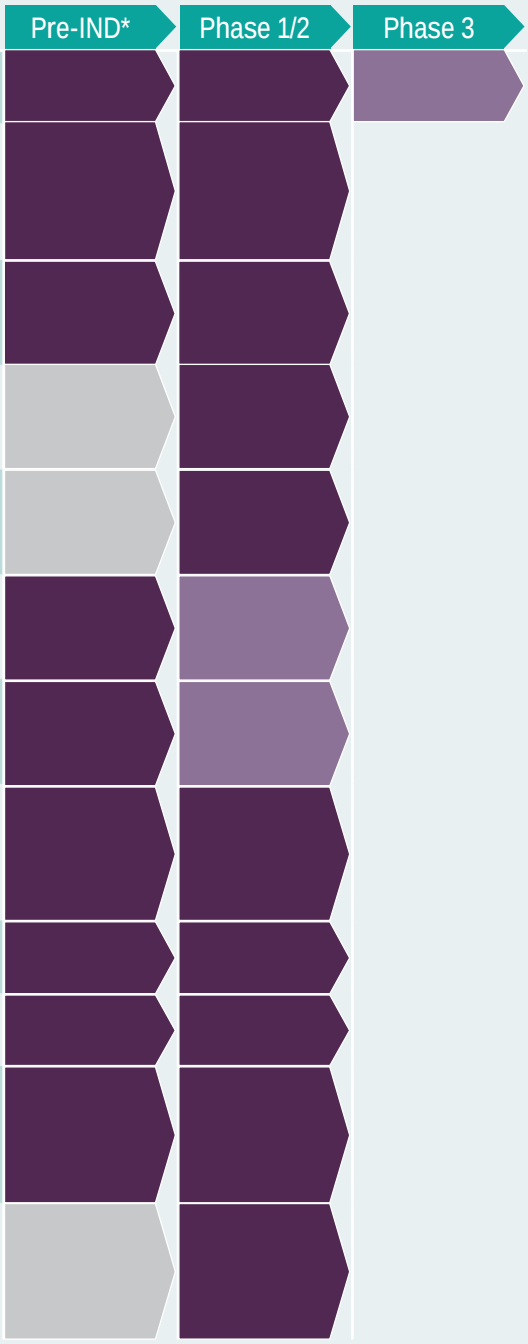
This heatmap groups BLBC tumors based on their expression of genes associated with a risk of recurrence and reveals three well-defined groupings (low risk, intermediate risk, and high risk). The annotation strips at the top help illustrate the patterns in the heatmap below. These patterns revealed that characteristics like lymphocyte (immune cell) response, tumor subtypes, and tumor purity are associated with a certain risk of recurrence.

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 granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting breast tumor vaccine for HER2+ metastatic breast cancer.

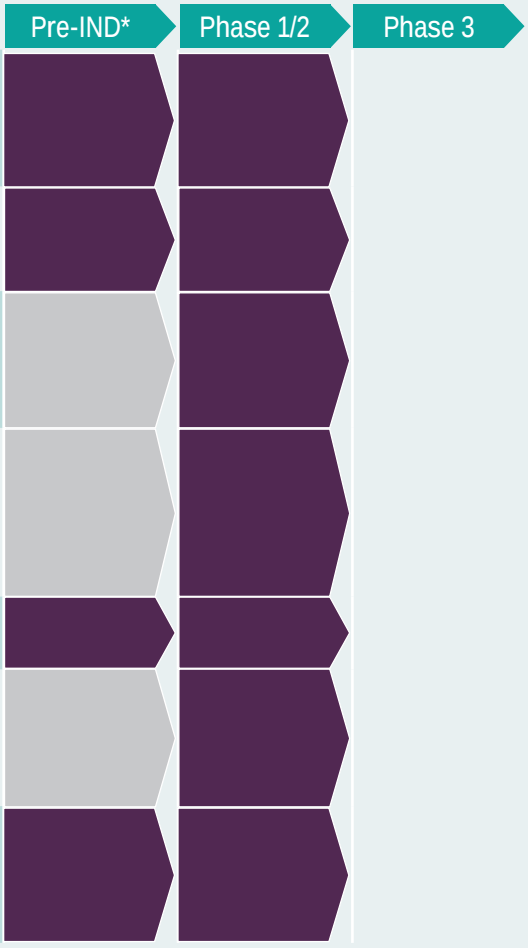
Alpha-Lactalbumin Vaccine for Triple-Negative Breast Cancer — Vincent Tuohy and George Budd
A vaccine for TNBC patients that have recovered from current standard-of-care therapy with potential use in a prophylactic setting.

* Investigational New Drug (IND)

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.

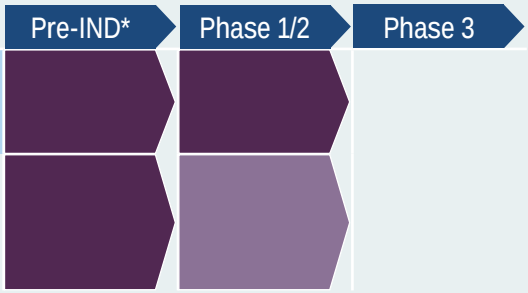
Trastuzumab/Pertuzumab with HER2 HLA-DR Vaccine Therapy — Keith Knutson and Saranya Chumsri
A multi-epitope vaccine used to boost HER2-specific T cells during trastuzumab and pertuzumab maintenance therapy in patients with residual disease post neoadjuvant chemotherapy to block disease recurrence and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

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

Overcoming Immunotherapy Resistance in Breast Cancer Using RT-Mediated Immunomodulation — Stephen Shiao and Simon Knott
Using focal radiation combined with checkpoint inhibitors 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 chemokine modulation and PD-1 blockade in patients with parenchymal brain-metastatic breast cancer

Diagnostics and Imaging



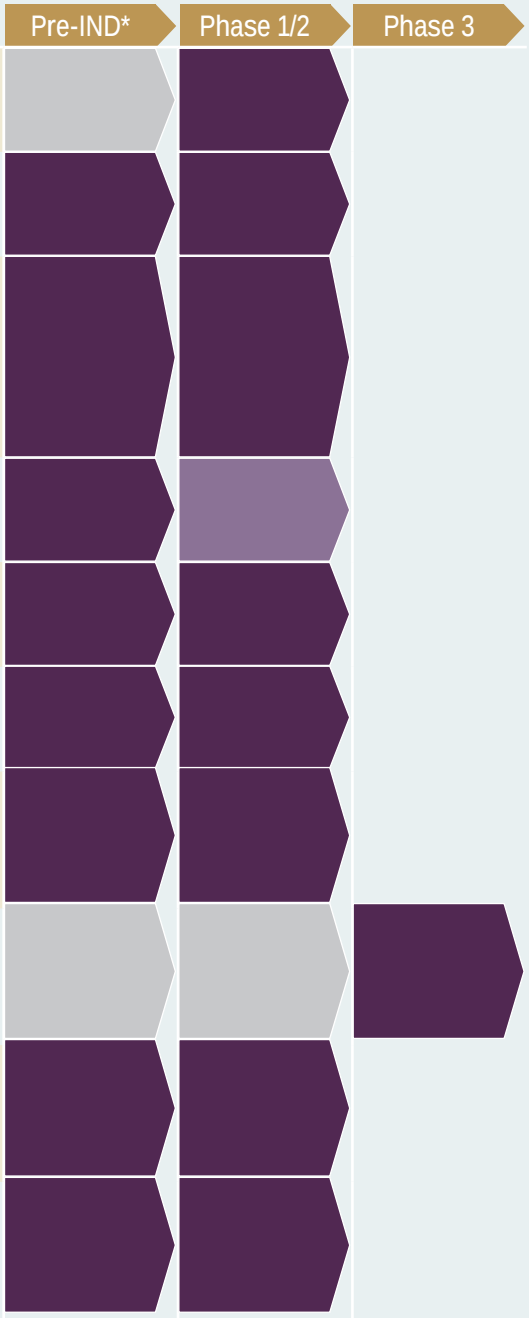
Targeted HER2 Radiotracer — Gary Ulaner
Using 89Zr-trastuzumab to determine the proportion of patients with HER2-negative primary breast cancer who develop imagable HER2-positive metastases.

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.

IN THE CLINICAL PIPELINE (cont.)

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

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 Food and Drug Administration (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 and Michelle Holmes
Long-term aspirin use 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
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.

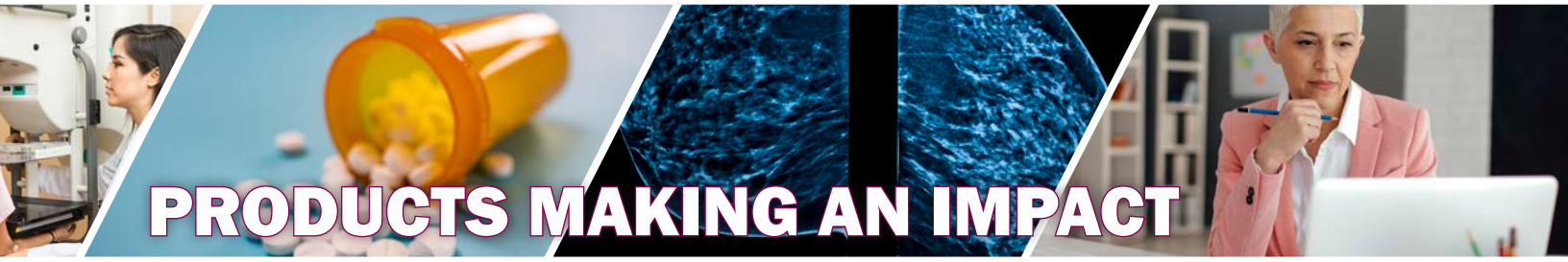
A Novel Druggable Pathway That Prevents Bone Loss in Breast Cancer Patients — Alana Welm
Using the RON kinase inhibitor, BMS-777607/ASLAN002 in metastatic cancer patients to decrease osteolysis and promote bone repair.

IN THE CLINICAL PIPELINE (cont.)

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

Therapeutics (cont.)

	Pre-IND*	Phase 1/2	Phase 3
Talazoparib — Dennis Slamon The novel PARP inhibitor talazoparib using 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+ER+HER2- metastatic breast cancer.	■	■	■



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

Palbociclib (Ibrance®)
Dennis Slamon
This small-molecule cyclin-dependent kinase (CDK) inhibitor is FDA-approved to treat metastatic HR-positive, HER2-negative breast cancer in combination with an aromatase inhibitor or fulvestrant.

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

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

DIAGNOSTICS

Sentinel Lymph Node Biopsy
Douglas Reintgen and Kathryn Verbanac
This diagnostic/prognostic technique enables clinicians to determine both tumor staging and the extent to which more extensive lymph node surgery is necessary.

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

Digital Mammography and Breast Tomosynthesis
Laurie Fajardo and Daniel Kopans
This 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.

PATIENT RESOURCES AND REGISTRIES

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

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

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

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

RISK ASSESSMENT

BRCA2 617delT Mutation
David Goldgar and Susan Neuhausen
One of the founder BRCA1/2 mutations that occurs in Ashkenazi Jews, a population with increased likelihood of BRCA1/2 mutations, is now part of a commercialized test for this risk group.

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

PTEN
Michael Wigler
A test is commercially available to confirm PTEN 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.

PROGNOSTICS

Breast Cancer Index
Dennis Sgroi
A commercialized test that evaluates the likelihood of recurrence and benefit from extended endocrine therapy.

MetaSite Breast™
John Condeelis and Allison Harney
Clinical Laboratory Improvement Amendments–certified and publicly available test measuring Tumor Microenvironment of Metastasis (TMEM) levels to predict the metastatic potential of the primary tumor.

MenaCalc™
John Condeelis and Jeanine Pignatelli
This test has been clinically validated for use in cancer treatment decision making and as an independent prognostic factor and predictor of metastasis.

RESEARCH RESOURCES

Expression Arrest™ shRNA Libraries
Gregory Hannon and Stephen Elledge
This commercially available research tool provides ready-to-use, rapid RNA interference (RNAi) screens for the entire human and mouse genomes to study gene regulation and identify new therapeutic targets in many diseases and conditions, including cancer.

Three-Dimensional Culture Systems
Mina Bissell
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.army.mil
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(301) 619-7071

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