CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

HISTORY
The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a Congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has been responsible for managing over $14.7 billion since its inception through fiscal year 2019 (FY19). Funds for the CDMRP are added to the Department of Defense (DoD) budget, in which support for individual programs, such as the Breast Cancer Research Program (BCRP), is allocated via specific guidance from Congress.

APPLICATION REVIEW PROCESS
The CDMRP uses a two-tier review process for evaluating applications, with both tiers involving dynamic interaction between scientists and disease survivors (consumers). The first tier of evaluation is a scientific peer review of the applications, measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Programmatic Panel, which is composed of leading scientists, clinicians, and consumers. The Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit, potential impact, adherence to the intent of the award mechanism, relevance to program goals, and portfolio composition.

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 BCRP 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 $3.6 billion in Congressional appropriations through FY19. The BCRP enables researchers to propose their best innovative ideas that address the urgent need to end breast cancer. Scientists are challenged to pursue high-risk, high-reward research, explore new paradigms that could lead to critical discoveries, and make an unprecedented impact on breast cancer. The BCRP also promotes synergistic collaborations across disciplines and integrates scientists and consumers in unique and meaningful research partnerships.

FY92–FY18 BCRP Portfolio

*Clinical & Experimental Therapeutics: 25.4%
*Cell Biology: 16.0%
*Genetics & Molecular Biology: 10.1%
*Pathobiology: 15.3%
*Immunology: 3.5%
*Endocrinology: 3.9%
*Detection & Diagnosis: 11.0%
*Research Resources: 6.3%
*Biobehavioral Sciences: 1.6%
*Epidemiology: 3.2%
*Health Care Delivery: 1.1%
*Complementary & Alternative Medicines: 0.5%
*Computer Biology: 0.1%

*Primary Prevention: 2.0%
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 40.1 Female active duty Service members have a 20-40% higher incidence rate of breast cancer than the general public.2 The incident rate of breast cancer for active duty women is seven times higher than the average incident rate of fifteen other cancer types across all Service members.3 The outcomes of BCRP-funded research will ultimately benefit military Service members, Veterans, military beneficiaries, and the general public.

1 www.cdc.gov/cancer/dataviz.
“The DoD BCRP has a unique, flexible structure that enables it to fund innovative, high-risk, high-return research that focuses on the continued challenges of breast cancer. The program is able to quickly respond to current scientific advances; it is efficient, and is accountable to the public and is transparent. The program has produced exceptional results through the integrated efforts of the many partners involved in the program. The DoD BCRP continues to challenge the status quo and to encourage new ideas, breakthroughs, and collaboration – all with a sense of urgency. It is an honor to serve, along with other committed advocates, scientists, clinicians, and the U.S. Army, as we work together to end breast cancer.”

Pat Haugen, FY20 Programmatic Panel Chair

“Being a consumer reviewer allows me to continue my passion for being close to research. I have been a reviewer for many years now, and I continue to love being involved in this process. Young scientists are our future and the DoD BCRP is an important step in helping these bright and upcoming scientists get their foot in the door.

My daughters, who have watched me go through breast cancer treatment twice now, know that I am part of the plan to eradicate this disease when they see me reading the long proposals. How better to help the next generation than show them you can stand up to adversity. There is no time to sit idle. I hope they never have to endure this disease, and with the help of the DoD, we have a fighting chance.

The DoD has given this opportunity to me, and I want to thank them along with all the scientists, oncologists, and researchers for respecting patients as partners in such an important decision-making process.”

Patti Kellerhouse, Consumer Reviewer

“Over the past 2 years, I have been blown away by the types of grants that are funded through the BCRP. As a consumer reviewer, it means so much to know that my voice is being heard amongst the brightest scientists, doctors, and advocates. We all immediately have something in common when we enter the room to evaluate the research grants; to eliminate death from breast cancer. And with that crystal clear vision, we discuss which grants will have the most impact. Every year, I leave the BCRP filled with hope that ways to make metastatic breast cancer (MBC) a chronic, manageable illness will be found to help all those fighting MBC to survive and thrive.”

Tami Eagle Bowling, Consumer Reviewer

“The BCRP funds unique projects that are intended to develop new initiatives for problems that are often brought to light by patient advocates. In that way the BCRP is a unique partnership between patients and the research community. It allows the ability to assist in creating the next generation of cancer therapies as well as researchers but also takes into account the breast cancer patients of today.”

Dr. Brian Czerniecki, H. Lee Moffitt Cancer Center & Research Institute
Connecting Blood and Intratumoral Treg Cell Activity in Predicting Future Relapse in Breast Cancer

Peter Lee, M.D., Beckman Research Institute, City of Hope,
FY11 Era of Hope Scholar Expansion Award

Regulatory T (T<sub>reg</sub>) cells modulate the activity of tumor-killing effector immune cells and are implicated in the development of an immunosuppressive tumor microenvironment, allowing tumors to escape immune surveillance. T<sub>reg</sub> cells within tumors are thought to come from precursors circulating in the blood, but the relationship between peripheral T<sub>reg</sub> cells and the immunosuppressive potential of intratumoral T<sub>reg</sub> cells is not well understood. Therefore, Dr. Lee and his team sought to characterize these cells in breast cancer patients and develop a liquid biopsy-type metric that could be used to predict recurrence and monitor disease state based on peripheral T<sub>reg</sub> cell activity. The intratumoral and peripheral T<sub>reg</sub> cells isolated from breast cancer patients were found to share remarkably similar markers of immunologic activity. Peripheral T<sub>reg</sub> cells that were isolated from a cohort of breast cancer patients at diagnosis were found to be activated by immunosuppressive (TGF-β and IL-10) but not immunostimulatory (IL-4 and IFN-γ) cytokines. Importantly, a high patient T<sub>reg</sub> response to immunosuppressive but not immunostimulatory cytokines indicated a worse recurrence-free survival (RFS). Dr. Lee's team created a composite cytokine signaling index (CSI) to evaluate the balance of peripheral T<sub>reg</sub> cell response to TGF-β/IL-10 and IL-4/IFN-γ, and found that approximately 40% of patients with a CSI greater than the median patient CSI experienced recurrence at 36 months, while no patient with a CSI score below the median had detectable relapse. The CSI was predictive of recurrence, independent of tumor stage or subtype, and was found to change with underlying disease relapse and remission. Dr. Lee’s early demonstration of a blood-based indicator for predicting recurrence is an exciting potential tool that is accurate and non-invasive.

Publication:

A Nuclear Lipid Kinase Complex Regulates p53

Vincent Cryns, M.D., and Richard Anderson, Ph.D.,
University of Wisconsin - Madison,
FY16 Breakthrough Award – Funding Level 2
Partnering PI Option

The p53 gene (TP53) is the most commonly mutated gene in cancer, occurring in the majority of all human tumors. Mutant p53 plays a key role in tumor growth and metastasis. Despite the widespread prevalence of TP53 mutations in cancer, there are currently no FDA approved therapies that specifically target mutant p53. In breast cancer, TP53 mutations occur most frequently in clinically aggressive triple-negative breast cancer (TNBC), which often strikes younger, African Americans or Hispanic women. These tumors also commonly express the cell stress protein αB-crystallin, which promotes metastasis. Drs. Cryns and Anderson with postdoctoral fellows Drs. Chen and Choi discovered a direct link between mutant p53 and αB-crystallin in TNBC via the lipid kinase PIPKIα. In this pathway, PIPKIα binds to mutant p53 in the nucleus and transfers its lipid messenger PIP<sub>2</sub> to mutant p53. The PIP<sub>2</sub> serves as a signal for αB-crystallin and related proteins to bind and functionally stabilize mutant p53, which facilitates its tumor-promoting activity. Their team also demonstrated that blocking the expression or activity of PIPKIα destroys mutant p53. Their findings point to PIPKIα inhibition as a promising therapeutic strategy to degrade mutant p53 in the broad spectrum of human tumors driven by TP53 mutations, including TNBC.

Publication:
**Targeting the Perivascular Niche to Sensitize Disseminated Tumor Cells to Chemotherapy**

**Cyrus Ghajar, Ph.D., Fred Hutchinson Cancer Research Center, FY14 Era of Hope Scholar Award**

Disseminated tumor cells (DTCs) which have left a primary tumor are often resistant to chemotherapy. The presence of DTCs within the bone marrow of patients at initial diagnosis is predictive of poor metastasis-free survival. Dr. Ghajar set out to understand the mechanisms regulating treatment resistance of DTCs in bone and determine whether chemosensitivity can be induced. In mouse models, DTCs were found to co-localize with endothelial cells of the bone marrow perivascular niche where they were resistant to Adriamycin/cyclophosphamide (AC) and/or paclitaxel chemotherapy regimens. To determine if the endothelial cells activated pathways that protected DTCs from chemotherapy, RNA-seq pathway analysis was conducted; it revealed that integrin binding was one of the most significantly enriched pathways in endothelial cells. Tumor-bearing mice pretreated with an anti-β1 integrin antibody, AIIB2, or a combination of AIIB2 and an anti-αvβ3 integrin antibody, LM609, prior to being given chemotherapy, saw a marked reduction in the number of DTCs present in the bone marrow. Pretreating with AIIB2 or with AIIB2 in combination with LM609 prior to AC treatment led to a 93.9% and a 94.2% reduction, respectively, in DTC burden within femoral bone marrow. In mice given chemotherapy over a 15-week period, 73% of mice pretreated with a control antibody prior to receiving AC succumbed to bone metastases, whereas only 22% of mice pretreated with AIIB2 and 33% of mice pretreated with AIIB2 and LM609 relapsed. Dr. Ghajar’s preclinical discoveries suggest that anti-integrin treatment could potentially sensitize DTCs prior to chemotherapy and ultimately prevent metastatic recurrence.

**Publication:**

---

**Noninvasive Imaging of Tumor Progression, Metastasis, and Fibrosis Using a Nanobody Targeting the Extracellular Matrix**

**Richard Hynes, Ph.D., Massachusetts Institute of Technology, FY13 Innovator Award**

Fibronectin, a protein of the extracellular matrix, plays a role in establishing the pro-tumor microenvironment and is often expressed as a cancer-specific variant containing an extra alternatively spliced domain called, EIIIB (or ED-B). Dr. Hynes and his research team sought to exploit this phenomenon to develop a highly sensitive tool to detect disease emergence and progression. The team created a nanobody, a small alpaca-derived (single-domain, 15KDa) antibody with low immunogenic potential. The nanobody, called NJB2, recognizes only the EIIIB-containing variant of fibronectin. NJB2 with bound radioactive $^{64}$Cu ($^{64}$Cu-NJB2) specifically localized to both primary and metastatic breast cancers in vivo. Using PET-CT imaging, the team determined that uptake of $^{64}$Cu-NJB2 was specific for tumors as it was not detected in normal tissue. $^{64}$Cu-NJB2-mediated imaging detected metastases as small as 2.5mm in diameter and with a sensitivity 3- to 6.5-fold higher than conventional imaging modalities. To determine if NJB2 could noninvasively detect disease progression, the group investigated individual tumors in a longitudinal mouse model of breast cancer development and found that $^{64}$Cu-NJB2 uptake increases as tumor stage progresses, even in low EIIIB-variant models. The Hynes laboratory’s development of NJB2 as a noninvasive imaging agent has exciting potential to detect early-stage breast cancers, monitor disease progression and responses to treatment, and signal the development of metastases with greater sensitivity than current modalities. The nanobody could also be used to deliver to tumors and metastases diverse therapeutic payloads such as drugs, toxins, high-energy isotopes, immune-modulators or nanoparticles.

**Publication:**
Platelet Decoys Inhibit Thrombosis and Prevent Metastatic Tumor Formation in Preclinical Models
Anne-Laure Papa, Ph.D., The George Washington University, FY14 Breakthrough Award – Funding Level 1

Platelets normally function to regulate vascular integrity and prevent blood loss. These critical components of the blood are frequently elevated in patients with cancer, where they are implicated in promoting metastasis and recurrence by binding to circulating tumor cells. As such, platelets are an attractive therapeutic target in breast cancer. Current platelet-targeting therapies lack potent reversal agents and can pose the risk of uncontrolled bleeding as it may take several days to replenish functional circulating platelets after treatment. Dr. Papa and her team approached this problem by creating rapidly reversible, dominant negative platelet decoys from normal human platelets. Platelet decoys are stripped of cell membranes and intracellular components, but retain a normal shape and importantly cell surface proteins. Normal platelets bind to extracellular matrix components to initiate clotting; however, platelet decoys reduce this binding in vitro. Importantly, this inhibition is reversed by infusion of new normal platelets in a clinically achievable dose, indicating platelet transfusion may alleviate bleeding risks associated with platelet decoy therapy. Like normal platelets, platelet decoys bind to breast cancer cells in culture. Further, in an in vitro blood vessel model, platelet decoys inhibit the ability of normal platelets to induce breast cancer cell aggregation and extravasation (emergence), which are necessary for progression to metastatic disease. In a mouse model of breast cancer metastasis, platelet decoy therapy provided a dose-dependent reduction in metastatic burden, reaching nearly 90% inhibition after 5 weeks when injected at a ratio of 40% of normal platelets. Dr. Papa’s work represents a potential anti-metastatic, platelet-targeting therapy that can be rapidly reversed to prevent the risk of uncontrolled bleeding. This exciting breakthrough has generated recent additional funding from the BCRP through an FY18 Expansion Award to build toward optimizing platelet decoys for future use in the clinic.

Publication:

JAK/STAT Inhibition in Macrophages Promotes Therapeutic Resistance in Breast Cancer
Kathryn L. Schwertfeger, Ph.D., University of Minnesota Twin Cities, FY15 Breakthrough Award – Funding Level 1

Tumor-associated macrophages (TAMs) contribute to tumor progression and therapeutic resistance in breast cancer. The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway is known to promote tumor formation, and STAT factors, such as STAT3, influence cancer-promoting versus cancer-inhibiting phenotypes of TAMs. However, the mechanisms by which STAT3 and the JAK/STAT pathway modulate protumor activities of TAMs are unclear. Using human in vitro assays and mouse models, Dr. Schwertfeger and her research team noted breast cancer subtype-specific activation of STAT3 in macrophages. TNBC cells, and not estrogen receptor (ER)-positive or human epidermal growth factor receptor 2 (HER2)-positive cells, produced soluble factors that rapidly activated STAT3 in macrophages. Moreover, TNBC patient samples exhibited the highest proportion (76%) of STAT3+ macrophages compared to ER+ (52.5%) or HER2+ (13.6%) samples. In mouse models, pharmacological inhibition of the STAT pathway with the JAK inhibitor ruxolitinib (Rux) failed to improve overall survival of tumor-bearing mice. However, macrophage depletion in tumor-bearing mice significantly improved survival through enhanced ability of tumors to respond to Rux. Soluble factors secreted by Rux-treated TAMs enhanced their expression of a subset of protumorigenic genes, including cyclooxygenase-2 (COX-2). In tumor-bearing mice, the combination of Rux and the COX-2 inhibitor celecoxib significantly prolonged survival and decreased tumor growth rates compared to either agent administered alone. This research demonstrates that the phenotype of TAMs is largely influenced by the tumor microenvironment and provides a rationale for combination therapies that suppress macrophage-driven tumor cell therapeutic resistance.

Reference:
Neutralization of BCL-2/XL Enhances the Efficacy of T-DM1
Joan Brugge, Ph.D., and Jason Zoeller, Ph.D., Harvard Medical School, FY15 Breakthrough Award – Funding Level 2

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate (ADC) that has demonstrated clinical benefits for advanced and metastatic HER2+ breast cancer patients. However, many patients develop resistance to T-DM1 and their cancer ultimately progresses to lethal disease. Since the B-cell lymphoma 2 (BCL-2) and B-cell lymphoma extra-large (BCL-XL) family of anti-apoptotic proteins are expressed and/or upregulated in breast cancers and able to compromise the efficacy of treatment, a team led by Drs. Brugge and Zoeller examined whether BCL-2/XL inhibition by ABT-263/navitoclax could enhance the effectiveness of T-DM1. Using five HER2-expressing patient-derived xenograft (PDX) mouse models, derived from primary and metastatic breast tumors with and without prior treatment exposure, the combination of T-DM1 and ABT-263 was compared to treatment with either agent alone. Two of the treatment-exposed metastatic models, PDX12 and PDX8, had the most robust responses to combination therapy. Treatment with combination therapy, compared to either agent alone, significantly enhanced PDX12 and PDX8 tumor killing. To overcome thrombocytopenia, a side effect associated with ABT-263 treatment, the team devised a pulsed dosing regimen where ABT-263 was administered in intervals rather than continuously. T-DM1 treatment given with pulsed ABT-263 did not reduce the clinical effectiveness of combination treatment in PDX12 and PDX8 tumors, and, remarkably, mitigated the platelet side effects associated with ABT-263. These results demonstrate for the first time that the effectiveness of T-DM1 can be enhanced by inhibition of BCL-2/XL, and provide evidence for a translational paradigm involving ADCs together with anti-apoptotic inhibitors in order to ameliorate the systemic toxicities associated with these therapies.

Publication:
Impeding Circulating Tumor Cell Reseeding Decelerates Metastatic Progression and Potentiates Chemotherapy

Alessandro Fatatis, M.D., Ph.D., Drexel University, FY15 Breakthrough Award – Funding Level 2

Circulating tumor cells (CTCs) are shed from breast cancers and reseed distant sites as DTCs to establish lethal metastatic disease. Developing an understanding of CTC longevity and the timeline and mechanisms associated with reseeding are critical for producing targeted breakthrough therapies to halt metastasis. Dr. Fatatis validated FX-68, a novel small-molecule antagonist of the chemokine receptor CX3CR1, a protein which is expressed by both primary and metastatic breast tumors. In mouse models of metastatic breast cancer, FX-68 reduces the number of DTCs found in the bone and increases median survival from 8 to 13 weeks relative to control treatment. Following the entry of DTCs back into circulation, FX-68 treatment causes increases in vascular retention of CTCs, inhibits their dissemination to other target organs, and induces markers of programmed cell death. FX-68 reduces the number of CTCs that reseed within both bone and lung tissues by more than two-fold after 24 hours, indicating an inhibition of metastatic spreading. By retaining CTCs longer in circulation, FX-68 also increases the uptake of the chemotherapeutic doxorubicin by these cells by fifty percent. Further, when used alone FX-68 reduces total tumor burden at a level similar to the standard of care docetaxel, as compared to untreated control animals. When co-administered, FX-68 and docetaxel work synergistically to reduce metastatic tumor burden by 80% relative to each therapy alone. Dr. Fatatis’ work demonstrates that holding CTCs in circulation, through antagonism of CX3CR1, decreases their reseeding potential, sensitizes them to programmed cell death, and synergizes with a standard of care chemotherapeutic to significantly decelerate the metastatic spread of breast cancer.

Publications:

In the Clinical Pipeline

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

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

**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.

Using focal radiation combined with checkpoint inhibitors to generate anti-tumor immune response in patients diagnosed with early-stage TNBC.

**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 imageable HER2-positive metastases.

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

**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 expressed on ER+ breast cancers that are resistant to anti-estrogen therapy.

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

**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.)

**Therapeutics (cont.)**

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

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

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

**Neoadjuvant Endocrine Therapy (NET) + Radiotherapy — Silvia Formenti and Sandra Demaria**
Treatment of HR+ breast cancer with a combination of focal radiotherapy and letrozole NET to enable a response to immunotherapies.
Trastuzumab (Herceptin®)
Dennis Slamon
This monoclonal antibody that targets the HER2 receptor revolutionized breast cancer treatment and the field of targeted therapeutics for HER2+ early-stage and metastatic breast cancers.

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

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

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

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

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

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

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

Digital Mammography and Breast Tomosynthesis
Laurie Fajardo and Daniel Kopans
This 3-D digital mammography tool improved sensitivity for detection of breast cancer in women with dense breast tissue and is FDA-approved and commercially available.

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 NCI Breast Cancer Surveillance Consortium, a national registry that provides a resource for researchers to study mammography screening on a national level.

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

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

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

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

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

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

**BROCA Cancer Risk Panel**  
*Tomas Walsh and Mary-Claire King*  
A comprehensive test that enables assessment of all known breast cancer genes and mutation types in a single assay.

### Prognostics

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

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

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

### Research Resources

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

**Three-Dimensional Culture Systems**  
*Mina Bissell*  
3-D culture models are currently utilized across academic laboratories and by drug companies as screening assays to test for therapeutic response.

**Novel Models for Breast Tumor Growth and Metastasis**  
*Alana Welm*  
Publicly available, patient-centric tumor graft mouse models that replicate the diversity of human breast cancer and enhance the study of tumor growth, metastasis, drug efficacy, and prognosis.
For more information, please visit
https://cdmrp.army.mil
or contact us at:
usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil
(301) 619-7071