DoD Breast Cancer Research Program (BCRP)

Each year, the Department of Defense's office of the Congressionally Directed Medical Research Programs (CDMRP) assesses scientific opportunities to advance research in specific areas. The investigators supported by individual programs are making significant progress against targeted diseases, conditions, and injuries. This list is not intended to be a full representation of accomplishments, but rather a sampling of the broad portfolio of research and advances resulting from congressional appropriations.

Year	BCRP Research Contributions	Additional Information and Hyperlinks
1993	E75 Her2-derived Peptide Vaccine (NeuVax™). The BCRP supported a study led by Dr. Constantin Ioannides that sought to identify cytotoxic lymphocyte-recognized epitopes on HER2-overexpressing human breast tumors, during which Dr. Ioannides, together with Dr. Bryan Fisk, discovered E75, an immunodominant HER2 peptide. The E75 peptide combined with GM-CSF has since been developed into an immunogenic peptide-based vaccine under the commercial name of NeuVax (Galena Biopharma). NeuVax is now in Phase III clinical trials.	• BCRP Research Highlight • FY93 BCRP Investigator-Initiated Award Abstract
1993	Intraductal Techniques. Most breast tumors appear to arise in the cells lining the milk ducts of the breast. With an FY93 BCRP Idea Award, Dr. Susan Love looked for early evidence of cancer in the ducts by modifying an endoscope to enter and examine milk ducts through their openings at the nipple. Her research increased understanding of duct architecture, most importantly in providing evidence that early-stage breast cancer is confined to a single duct system. She laid the groundwork for the development of increasingly sophisticated and miniaturized endoscopes that allow the retrieval of cell samples for analysis, the precise location of intraductal lesions for excision, and the potential to deliver breast cancer therapy intraductally.	• FY93 BCRP Idea Award Abstract
1993	BRCA2 617delT Mutation. Breast cancer and ovarian cancer risk is greater in individuals with mutations in the BRCA1 and BRCA2 tumor suppressor genes. The likelihood of BRCA1 or BRCA2 mutations is higher in certain populations, including individuals of Ashkenazi Jewish descent. BCRP funding of Drs. David Goldgar and Susan Neuhausen contributed to the discovery of the BRCA2 617delT mutation, one of the three founder BRCA1/2 mutations that occur in Ashkenazi Jews. The BRCA2 617delT mutation is now part of a commercialized test for BRCA1/BRCA2 gene mutations in this risk group.	• FY93 Investigator-Initiated Award Abstract

Year	BCRP Research Contributions	Additional Information and Hyperlinks
1993	Herceptin®. Herceptin (trastuzumab) is a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2) receptor. HER2+ breast cancer accounts for approximately 25% of all breast cancers. The BCRP was instrumental in supporting the preliminary in vitro and in vivo studies by Dr. Dennis Slamon that were needed to test the efficacy of Herceptin, which later led to clinical trials and commercialization. Herceptin revolutionized breast cancer treatment and the field of targeted therapeutics. Herceptin is now part of standard-of-care treatment regimens for HER2+ early-stage and metastatic breast cancers.	• FY93 BCRP Investigator-Initiated Award Abstract
1993	Margaret Dyson Family Risk Assessment Program. The BCRP supported Dr. Mary Daly in the establishment of a high-risk breast cancer registry to gather genetic and environmental risk information about women with familial breast cancer. This registry evolved into the Margaret Dyson Family Risk Assessment program for individuals at risk for breast or ovarian cancers. This program, which serves Philadelphia and its surrounding communities, now provides a range of risk assessment, screening, and preventive services to individuals who have a family history of breast or ovarian cancer.	• FY93 BCRP Tumor Sample, Breast Tissue, and Cell Line Repository Award Abstract
1993	PTEN Tumor Suppressor Gene. BCRP funding of Dr. Michael Wigler contributed to the original discovery of the PTEN (phosphatase and tensin homolog) gene. In normal cells, PTEN functions as a tumor suppressor protein that helps regulate cell division and growth. PTEN is one of the most frequently mutated genes in several cancers, and PTEN mutations have been shown to be predictive of aggressive cancer. PTEN mutations also occur in a group of genetic syndromes that are characterized by malignant and benign tumors. A PTEN test is commercially available to confirm PTEN mutations for clinical and prenatal diagnoses and identification of at-risk family members.	• FY93 BCRP Investigator-Initiated Award Abstract
1993	ATLAS Clinical Trial. BCRP funds supported Dr. Richard Peto in the initiation of the Phase III clinical trial ATLAS (Adjuvant Tamoxifen Longer Against Shorter), the largest breast cancer treatment trial ever undertaken. Adjuvant tamoxifen is the first-line treatment for early-stage ER+ breast cancer. The focus of the ATLAS trial was to examine whether 10 years of adjuvant tamoxifen confers greater benefit overall than 5 years of adjuvant tamoxifen. The clinical trial was initiated in 1996 and completed randomized accrual in 2005. Women with ER+ early stage breast cancer who had completed 5 years of adjuvant tamoxifen were randomized to either continue for another 5 years or to stop the treatment. Preliminary analysis indicated that recurrence rate was lower among those who continued tamoxifen treatment. ATLAS is currently in the follow-up phase until 2015.	• FY93 BCRP Investigator-Initiated Award Abstract

Year	BCRP Research Contributions	Additional Information and Hyperlinks
1997	Digital Mammography and Breast Tomosynthesis. Digital mammography allows for an expanded detection range of X-ray signals than standard film mammography. Through FY97 Clinical Translational Research Awards, the BCRP provided support to Drs. Laurie Fajardo and Daniel Kopans to optimize technology and to conduct a multi-center clinical validation of digital mammography. The study demonstrated that digital mammography is superior to film mammography in detecting breast cancer in women with moderate to marked dense breast tissue, leading to a change in clinical practice. The BCRP also supported the development and clinical evaluation of digital breast tomosynthesis. This three-dimensional (3D) digital mammography tool offers an additional 3D view to capture images for improved sensitivity. A tomosynthesis system is now FDA-approved and commercialized for clinical use.	• FY97 BCRP Clinical Translational Research Award Abstract – Laurie Fajardo • FY97 BCRP Clinical Translational Research Award Abstract – Daniel Kopans
1997	ErbB2 Immunoliposomes for Targeted Drug Delivery. Dr. John Park proposed to develop a novel breast cancer therapy by combining the targeting properties of a monoclonal antibody and the drug delivery advantages of liposomes to deliver the anti-neoplatic drug doxorubicin to tumor cells. Dr. Park collaborated with another BCRP award recipient, Dr. James Marks, to develop a new anti-HER2/neu monoclonal antibody (now called MM-302) and demonstrate its ability to efficiently target breast cancer cells overexpressing HER2. Moreover, they showed that doxorubicin delivered via the antibody-targeted liposomes inhibited tumor growth in mouse models of HER2-positive breast cancer while lowering the toxicity of doxorubicin to normal tissue. MM-302 was licensed by Merrimack Pharmaceuticals and is currently conducting a multi-institutional, Phase II clinical trial involving combination therapy with trastuzumab and standard chemotherapy regimens in advanced HER2+ breast cancer.	• Current clinical trial: Clinical Trials.gov • FY93 BCRP Career Development Award Abstract (DAMD17-94-J-4195) • FY97 BCRP Idea Award Abstract (DAMD-17-98-1-8189) Patents: • 1.) US 7045283 B2: Detecting preferential ligands in cell; obtain cell, incubate with reporter molecules, detect reporter in cell (DAMD17-94-J-4433 and DAMD17-98-1-8189) • 2.) US 8173424 B2: Internalizing ErbB2 antibodies (DAMD17-96-1-6244 and DAMD17-94-J-4433) • 3.) US 6512097 B1: Chimeric molecules that specifically bind a tumor cell bearing a c-erbB-2; immunotherapy (DAMD17-94-J-4433) • 4.) US 7388088 B2: Isolated nucleic acid encoding a human antibody that specifically binds to C-ERBB-2 protein product of HER2/NEU oncogene; for diagnosis of cancer/tumors which over express this gene; for immunotoxins and other antitumor/anticarcinogenic agents; less immunogenic (DAMD17-94-J-4433) • 5.) US 5977322 A: Human antibody that specifically binds to c-erbb-2 protein product of her2/neu oncogene; for diagnosis of cancer/tumors which over express this gene; for immunotoxins and other antitumor/anticarcinogenic agents; less immunogenic (DAMD17-94-J-4433)

Year	BCRP Research Contributions	Additional Information and Hyperlinks
1997	Combination Treatment - Aromatase and Src Inhibitors. The proliferative effects of estrogen in breast cancer are due in part to its ability to induce cells to enter the cell cycle. Through work supported by the BCRP, Dr. Joyce Slingerland found that estrogen stimulation of cell cycle progression was dependent on inhibiting p27, a negative regulator of the cell cycle protein, cyclin E-cdk2. She found that both estrogen-stimulated progression and resistance to anti-estrogen drugs, such as Tamoxifen, involved a decrease in p27 and subsequent increase in cyclin E-cdk2 activity, leading to cell cycle entry and proliferation in breast cancer cells. Further work showed that inhibition of p27-required phosphorylation of another protein, Src, led to p27 degradation in cells, and that inhibiting Src prevented p27 degradation. These studies suggest that a two-pronged approach that includes both anti-estrogens and drugs that preserve p27 may be effective in arresting cell cycle progression in breast cancer. Dr. Slingerland is currently leading Phase I and Phase II clinical trials to test the tolerability and efficacy of anastrozole, an aromatase inhibitor that stops estrogen production, together with the Src inhibitor, AZD0530, in post-menopausal women with ER+ breast cancer.	• FY97 BCRP Idea Award Abstract • FY97 BCRP Career Development Award Abstract
1999	HER2 Bi-Armed Activated T Cells. With an FY99 Concept Award, the BCRP supported the preclinical studies of Dr. Lawrence Lum focusing on HER2 bi-armed activated T cells, which induces the development of "memory" antigen-specific cytotoxic T lymphocytes directed at Her2. This led to a Phase I clinical trial in women with Her2+ metastatic breast cancer, which indicated that the treatment infusions are safe and induced long-term anti-tumor responses. The Her2 bi-armed activated T cells are currently in Phase II clinical trials for treating breast cancer.	• FY99 Concept Award Abstract
1999	Skp2 Oncogene. Skp2 and p27 are genes involved in the regulation of the cell cycle. The BCRP supported Dr. Michele Pagano in the establishment of Skp2 as an oncogene that is overexpressed in human breast tumors. High Skp2 expression correlating with destabilization of p27 was found to be associated with poor prognosis in breast cancer patients. These findings contributed to the practice of Skp2/p27 immunohistochemical analysis as a prognostic test performed in clinical pathology laboratories.	• FY99 BCRP Concept Award Abstract

Year	BCRP Research Contributions	Additional Information and Hyperlinks
1999	Sentinel Lymph Node Biopsy. The previous standard for detecting breast cancer invasion into the lymph nodes was to remove the majority of axillary lymph nodes and search for cancer cells. In a significant proportion of women, this causes lymphedema of the arm, a condition that compromises functionality and quality of life. In sentinel lymph node biopsy, lymph node removal is limited to only the first few nodes that receive lymph drainage from the breast. This diagnostic/prognostic technique enables clinicians to determine tumor staging and if more extensive lymph node surgery is necessary. The BCRP provided funding to Drs. Douglas Reingen and Kathryn Verbanac for multi-center clinical trials that validated lymph node mapping and sentinel lymph node biopsy as an accurate method to predict the presence of disease in the axillary lymph nodes.	• FY96 BCRP Research with Translational Potential Award Abstract – Douglas Reintgen • FY99 Clinical Translational Research Award Abstract – Kathryn Verbanac
2000	Prone Radiotherapy. With BCRP support through an FY00 Idea Award, Dr. Silvia Formenti conducted clinical trials to assess the efficacy of an accelerated, hypofractionated whole-breast radiation therapy designed to minimize the length of radiotherapy required after partial mastectomy in patients with DCIS. In this method, patients are treated in the prone position rather than in the supine position on a specially designed table, greatly reducing unnecessary radiation exposure of the heart and lungs. Importantly, prone radiotherapy offered heart and lung protection regardless of breast size. Prone radiotherapy is poised to become a standard choice in breast radiotherapy.	• FY00 BCRP Idea Award Abstract
2000	OncoVue®. Risk-association studies led by Dr. Eldon Jupe and funded by the BCRP formed the foundation for a breast cancer risk assessment test that is now commercially available. Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide (A,T,C,or G) in the genome sequence is altered. SNPs can help determine the likelihood that someone will develop a particular disease. OncoVue is the first genetic-based breast cancer risk test that incorporates a woman's SNPs with personal history to estimate her risk for breast cancer. This commercially available test can identify women at high-risk of breast cancer and enable clinicians to individualize breast cancer screening and monitoring.	• FY00 BCRP Idea Award Abstract

Year	BCRP Research Contributions	Additional Information and Hyperlinks
2001	PALB2. BCRP funding of Dr. Bing Xia contributed to discovery of PALB2, a BRCA2 binding protein. PALB2 and BRCA2 work together to mend broken strands of DNA, which helps to maintain the rate of cell growth and division. While BRCA1 and BRCA2 gene mutations are high-risk factors for breast cancer, these mutations do not account for all familial breast cancers. Identification of mutations in the PALB2 gene indicates an approximate two-fold increase in breast cancer susceptibility due to its inability to interact with BRCA2. A commercialized PALB2 genetic test is available for those with familial breast cancer who tested negative for BRCA1 and BRCA mutations.	• FY01 BCRP Postdoctoral Traineeship Award Abstract
2001	Three-dimensional Culture Systems. The BCRP supported Dr. Mina Bissell in the development of 3D culture systems that have made important contributions in understanding the tissue microenvironment and how interactions between epithelial cells and the extracellular matrix control cancer development. As surrogates for in vivo studies, 3D culture models have enabled the elucidation of oncogenic and other cell signaling pathways that are controlled by cell-matrix interactions. 3D culture models are currently utilized across academic laboratories and by drug companies as screening assays to test for therapeutic response.	• FY01 BCRP Innovator Award Abstract
2002	IDO Inhibitor. Indoleamine 2,3 Dioxygenase (IDO) is an enzyme that is commonly activated in breast cancer and is implicated in preventing the anti-tumor immune response by blocking T cell activation. The BCRP supported Dr. George Prendergast in preclinical studies that identified and characterized lead inhibitors of IDO that have pharmacological properties suitable for testing in clinical trials. As a result of this work, Dr. Prendergast demonstrated that the D isomer of an IDO inhibitor called 1MT (D-1MT) has potent anti-tumor properties, and his group discovered IDO2, an IDO-related gene, as one of its molecular targets. D-1MT is now in clinical trials for breast cancer and other solid tumors.	• BCRP Research Highlight • FY02 BCRP Idea Award Abstract
2002	TRC105 Antibody. Through an FY02 Clinical Translational Research Award, the BCRP supported Dr. Ben Seon in the development of TRC105, a monoclonal antibody which targets endoglin and inhibits angiogenesis. Preclinical results indicated that systemic administration of TRC105 and other anti-endoglin antibodies could suppress the growth of established tumors as well as new tumor growth. These results led to a current Phase I clinical trial of TRC105 in combination with capecitabine in breast cancer patients, as well as several other early-phase clinical trials in other cancer types.	• FY02 BCRP Clinical Translational Research Award Abstract

Year	BCRP Research Contributions	Additional Information and Hyperlinks
2002	BreastCancerTrials.org. Breast cancer patients can benefit from objective information about clinical trials. The process of identifying an appropriate clinical trial by performing independent research is challenging. BCRP funding of Dr. Laura Esserman contributed to the development of an online resource (BreastCancerTrials.org) that educates patients about breast cancer clinical trials and matches them with appropriate trials.	• BCRP Research Highlight • FY02 BCRP Breast Cancer Center of Excellence Award Abstract
2003	Expression Arrest™ shRNA Libraries. RNA interference (RNAi) is a cellular system that controls which genes are active or silent. The selective effect of RNAi on specific gene expression makes it a valuable research tool. Small hairpin RNAs (shRNAs) are one of the gene silencing mechanisms of RNAi. The BCRP supported Drs. Gregory Hannon and Stephen Elledge in the development of whole genome shRNA libraries that target over 30,000 genes. This commercially available research tool provides researchers with 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.	• FY01 BCRP Innovator Awards Abstract – Gregory Hannon • FY03 BCRP Innovator Awards Abstract – Stephen Elledge
2003	HER2 Peptide-Based Vaccine. Dr. Nora Disis utilized an FY03 BCRP Clinical Translational Research Award to develop a vaccine that, when concurrently administered with trastuzumab, strongly elicits an immune response to the growth factor receptor HER2, generating long-term tumor-specific immunity. The HER2 intercellular domain (ICD) peptide-based vaccine is designed to treat breast cancer by stimulating the immune destruction of remaining cancer cells after primary cancer therapy. The HER2 ICD peptide vaccine was evaluated in a Phase II clinical trial in stage III and stage IV HER2+ breast cancer patients concurrently receiving trastuzumab. Results of the trial indicated considerable improvements in relapse-free survival, as well as minimal toxicity and prolonged, robust, antigen-specific immune responses. The vaccine has been licensed commercially for further investigation.	• BCRP Research Highlight • FY03 BCRP Clinical Translational Research Award Abstract
2003	5-Flouro-2'deoxycytidine (FdCyd). DNA methylation inappropriately turns several genes off in cancer cells. Preclinical studies led by Dr. Edward Newman and supported by the BCRP demonstrated the effects of FdCyd with tetrahydrouridine on reversal of DNA methylation in several genes expressed by breast cancer cells. This combination treatment not only reversed DNA methylation, but also induced mRNA expression. A Phase I clinical trial funded by the BCRP was completed. A Phase II clinical trial examining the combination of FdCyd and tetrahydrouridine in breast and other cancer types has been initiated by the National Cancer Institute.	• FY03 Clinical Translational Research Award Abstract

Year	BCRP Research Contributions	Additional Information and Hyperlinks
2003	Breast Cancer Index[SM]. Women with ER+ breast cancer have an increased risk of relapse many years after their initial diagnosis and treatment. To identify women with an increased risk of disease recurrence, Dr. Dennis Sgroi validated biomarkers that correlated with relapse-free survival and tumor grade, leading to a risk assessment test termed the Breast Cancer Index (BCI). BCI, which is commercially available through bioTheranostics, provides a quantitative assessment of the likelihood of early and late recurrence, as well as the benefit from extended endocrine therapy.	• FY03 BCRP Idea Award Abstract
2005	BrainMetsBC.org. Breast cancer advocates on this team-based Breast Cancer Center of Excellence award led by Dr. Patricia Steeg resulted in the development of an online resource (BrainMetsBC.org) that provides the latest information about brain metastases. The website, which is available in English and Spanish, includes updates on current research, treatments, and clinical trials, as well as personal experiences written by patients.	• FY05 BCRP Breast Cancer Center of Excellence Award Abstract
2006	Molecular Breast Imaging. Molecular breast imaging (MBI) is a nuclear medicine technique that uses high resolution dual-head gamma cameras to detect the functional uptake of a radiotracer in the breast. Following a Mayo Clinic study that demonstrated MBI to be more sensitive than conventional mammograms for detecting breast cancer in women with dense breast tissue, the BCRP funded Dr. Carrie Hruska with an FY06 Multidisciplinary Postdoctoral Award to evaluate the concordance of MBI with magnetic resonance imaging of the breast, to investigate the effects of fluctuating hormonal levels on the appearance of MBI, and to develop important quantitative analysis software for MBI. Later clinical trials demonstrated that MBI may be used to monitor patients' response to chemotherapy. Currently, two FDA-approved MBI units are commercially available.	• FY06 BCRP Multidisciplinary Postdoctoral Award Abstract
2006	GM-CSF-secreting Vaccine. Utilizing an FY06 BCRP Clinical Translational Research Award, Dr. Leisha Emens developed a therapeutic granulocyte/macrophage colony-stimulating factor (GM-CSF)-secreting breast cancer vaccine to be used in combination with standard cancer therapies. Her preclinical data provided the basis for a clinical trial that tested vaccine–cyclophosphamide–trastuzumab combination therapy in women with stage IV metastatic HER2+ breast cancer. Clinical benefit, defined as complete or partial response to treatment (tumor shrinkage) or stabilization of disease (halted growth or spread), was present at 35% after one year. Analysis showed that overall survival was 42 months, which was a significant improvement over the historical outcomes for patients who received trastuzumab alone. Dr. Emens is continuing clinical trials on this vaccine in a larger Phase II clinical trial in breast cancer, as well as expanding to similar immune-based strategies in other gynecological malignancies.	• BCRP Research Highlight • FY06 BCRP Clinical Translational Research Award Abstract

Year	BCRP Research Contributions	Additional Information and Hyperlinks
2008	BROCA Cancer Risk Panel. An estimated 70% of families with multiple cases of breast cancers have no known gene mutations that increase their risk to the disease. Dr. Tomas Walsh, in collaboration with Dr. Mary-Claire King, identified and validated rare mutations termed copy-number variants. This led to development of a comprehensive test named "BROCA," which enables assessment of all known breast cancer genes and all mutation types in a single assay. The BROCA test is currently available through the University of Washington by physician request.	• FY08 BCRP Idea Award Abstract • FY12 BCRP Idea Expansion Award: Collaborative Option Abstract • FY12 BCRP Idea Expansion Award: Collaborative Option Abstract
2009	Targeting Autophagy to Eradicate DCIS. Although most ductal carcinoma in situ (DCIS) lesions remain dormant and do not invade or spread to the lymph nodes, some lesions progress to eventually become invasive and metastatic. There are no methods to predict which DCIS lesions will become invasive, and no therapeutic options exist to prevent the invasive phenotype. Drs. Lance Liotta and Kirsten Edmiston tested the hypothesis that some DCIS lesions are preprogrammed with invasive properties and that the mammary duct microenvironment provides a unique niche for DCIS cell survival. Their findings indicated that autophagy may play a key role in regulating the emergence of DCIS invasive progenitor cells and that chloroquine is a potential new therapeutic for treating DCIS. They are now conducting a neoadjuvant clinical trial using chloroquine as a potential DCIS treatment to prevent progression to invasive breast cancer.	• BCRP Research Highlight • FY06 Synergistic Idea Award Abstract – Lance Liotta • FY09 Idea Expansion Award Abstract – Lance Liotta • FY09 Idea Expansion Award Abstract – Kirsten Edmiston
2010	Palbociclib (Ibrance®). Preclinical research supported by the BCRP led to the identification of cyclin-dependent kinases (CDKs) as a target for ER+ breast cancer and the discovery that ER+ breast cancer cells are sensitive to a CDK inhibitor, PD-0332991. These and other findings provided the basis for Phase I and II clinical trials, supported by Pfizer, in which PD-0332991 (palbociclib) in combination with the aromatase inhibitor letrozole demonstrated an increase in median progression-free survival. These results prompted "Breakthrough Therapy" status by the FDA and Pfizer's initiation of a Phase III clinical trial. In February 2015, preliminary results of the Phase III trial showed improvements to progression-free survival, resulting in accelerated FDA approval of palbociclib (commercial name Ibrance®) combined with letrozole for the treatment of advanced ER+ HER2- breast cancer in postmenopausal women. If the ongoing Phase III clinical trial confirms clinical benefit, Ibrance® could become a new standard of care therapeutic for ER+ breast cancer.	• BCRP Research Highlight • FY10 Innovator Award Abstract