CDMRP

Department of Defense

Breast Cancer Research Semipostal Program





U.S. Army Medical Research and Materiel Command

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 received nearly $7 billion in appropriations from its inception through fiscal year 2012 (FY12). 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 application evaluation with both tiers involving dynamic interaction among scientists and disease survivors (consumers). The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Integration Panel (IP), which is composed of leading scientists, clinicians, and consumers. The IP compares applications to each other and makes recommendations for funding based on scientific merit, adherence to the intent of the award mechanism, portfolio composition, and relevance to program goals.

Partnerships

Partnerships between consumers and scientists are an integral component of several CDMRP processes. Consumers and scientists are partners that participate on:

- Peer review panels to provide expert advice on the scientific merit and potential impact of the proposed research
- The IP to make programmatic recommendations for the program's vision, investment strategies, and funding selections to reflect the needs of both the consumer and research communities
- Research projects to integrate their expertise in establishing project goals, and designing and implementing research strategies

Breast Cancer Research Semipostal Program

About the Program

As a result of the efforts of breast cancer advocates, the Stamp Out Breast Cancer Act (Public Law 105-41) led to the U.S. Postal Service issuing a new first-class stamp, the Breast Cancer Research Semipostal (BCRS) in 1998. The Stamp Out Breast Cancer Act has been extended through 2015. The stamp, which costs 55 cents, can be purchased on a voluntary basis by the public. Net revenues from sales of the BCRS are provided to two designated funding agencies, the DoD BCRP and the National Institutes of Health, to support breast cancer research.

Since the BCRS was first issued, the monies received by the BCRP have been invested in 51 awards totaling more than $21.8 million (Figure 1). The Idea Award and Synergistic Idea Award mechanisms support highly innovative, high-risk, high-reward research that could lead to critical discoveries in breast cancer. As with all BCRP awards, applications funded through the BCRS Program are reviewed according to the two-tiered review system.

An evaluation of the awards funded through the BCRS Program shows that the projects encompass a diverse range of research areas (Figure 2).

Total Proceeds from BCRS	$21,809,901
Research	$20,812,435
Management Costs	$997,466

Figure 1A. BCRS Research and Management Cost Allocation for FY99–FY11

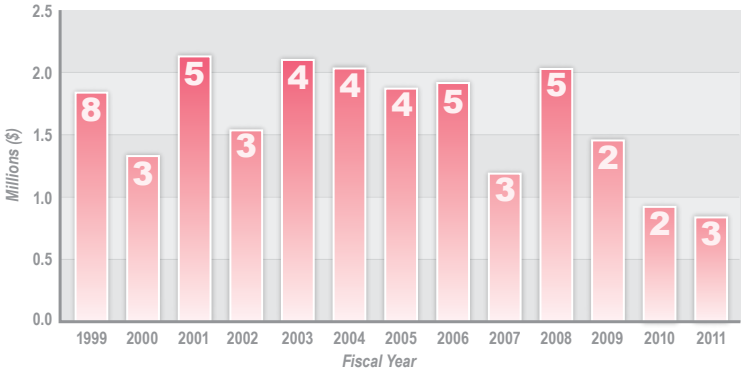


Figure 1B. BCRS Installments and Number of Awards Funded by Fiscal Year

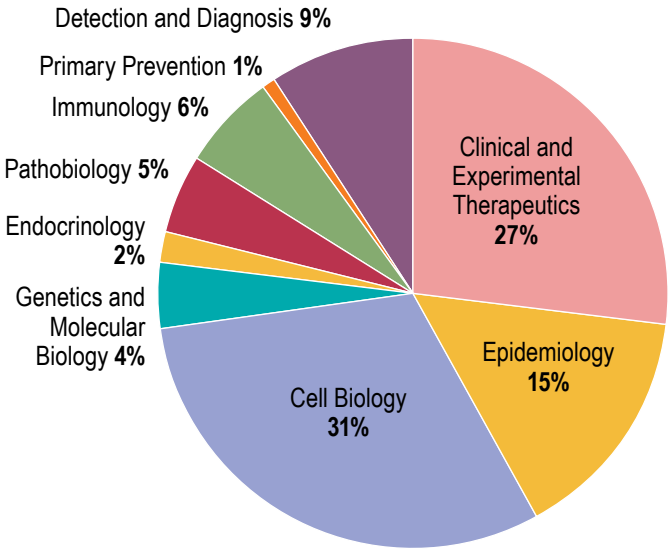


Figure 2. BCRS Award Portfolio Composition

Research Highlights

Effects of Nuclear Parathyroid Hormone-Related Protein Signaling in Breast Cancer

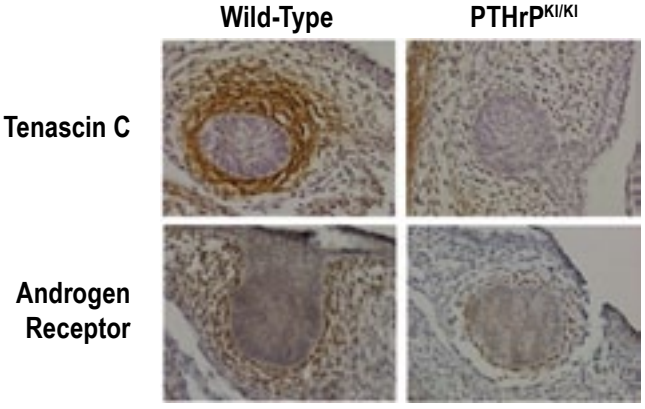
Dr. John Wysolmerski, Yale University

Parathyroid hormone-releasing protein (PTHrP) is secreted from breast epithelial cells to regulate mammary gland development and to promote calcium accumulation in the mammary gland for milk production during lactation. While many functions of PTHrP require it to be secreted from cells, a segment of the protein may be retained within a cell and can enter the nucleus. Previous breast cancer studies have suggested that nuclear PTHrP may contribute to more aggressive tumors. Dr. John Wysolmerski received an FY09 Idea Award to investigate the role of nuclear PTHrP in normal mammary gland development and in the maintenance and expansion of mammary stem cells. Dr. Wysolmerski will also determine whether expression of nuclear PTHrP predicts poor outcomes in breast cancer patients.

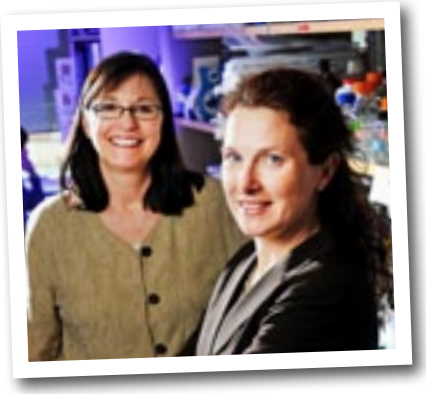
To examine the effects of nuclear PTHrP, Dr. Wysolmerski employed a genetically modified mouse model that has a shortened form of the protein that is unable to enter cell nuclei. Unexpectedly, Dr. Wysolmerski observed that loss of nuclear PTHrP resulted in defective mammary ductal outgrowth in female mouse embryos while mammary buds, which are normally ablated in the presence of androgens, persisted in male mouse embryos. In addition, proteins that normally appear in the surrounding dense mammary mesenchymal tissue were absent or significantly reduced. These results led to a novel hypothesis of PTHrP action during embryonic mammary gland development: PTHrP is secreted from mammary epithelial cells and binds to receptors on nearby mesenchymal cells where it is internalized and shuttled into the cell nucleus to mediate mammary gland development. Experiments are in progress to further validate these findings. Additionally, Dr. Wysolmerski's preliminary analysis of PTHrP in more than 600 human breast tumor samples suggests that PTHrP expression may predict poor clinical outcome. PTHrP expression correlated with markers of aggressive breast cancer (node-positive, estrogen receptor-negative, and progesterone receptor-negative). Analysis of mortality data from this breast cancer cohort also indicated that PTHrP may be associated with increased risk of death. Elucidating the role of PTHrP in mammary gland development, mammary stem cell maintenance, and cancer progression may result in a novel target for breast cancer treatment.

"The DoD Breast Cancer Research Program has been an important source of funding in my lab for the past 10 to 12 years. My laboratory is committed to understanding breast cancer in the context of the normal development and physiology of the breast. With the help of the BCRP, we have defined important roles for PTHrP in normal development and lactation. The task now is to use this knowledge to understand how it influences breast cancer in patients and to determine whether this pathway can serve as a therapeutic target for treatment."

Dr. John Wysolmerski



Loss of Dense Mammary Mesenchyme Markers in PTHrPKI/KI Mammary Buds. *Note the normal mesenchymal pattern of tenascin C (top row) and androgen receptor (bottom row) in wild-type E15 mammary buds (left column). Note dramatic reduction of staining in PTHrPKI/KI buds (right column).*



The Immune Modulatory Program of Postpartum Involution Promotes Pregnancy-Associated Breast Cancer

Dr. Pepper Schedin and Dr. Virginia Borges, University of Colorado, Denver, Anschutz Medical Center

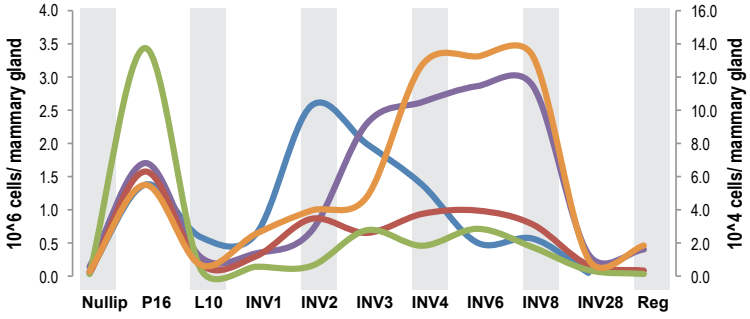
Breast cancer is the most common cancer diagnosis among pregnant and postpartum women, and epidemiological evidence suggests that women with postpartum breast cancer have a higher risk of metastases and death. Studies using mouse models of breast cancer indicate that postpartum breast involution—the return of the lactating mammary gland to its pre-pregnancy state—promotes tumor growth and metastasis. One theory for this increased risk is that involution results in suppression of the immune cells that target and kill tumor cells within the breast tissue. Dr. Pepper Schedin received an FY10 Idea Award to further investigate the role of immunosuppression in the involuting mammary gland in breast cancer. Working first with normal mouse mammary tissue, Dr. Schedin's group characterized the immune cell profile of the mammary gland throughout the entire reproductive cycle and confirmed that the postpartum involuting gland has an immune suppressive environment. Next, the researchers developed an immune competent murine model for the study of postpartum breast cancer and found that injection of mammary tumor cells into mammary glands during involution developed significantly larger tumors than tumor cells injected into glands of nulliparous mice (mice that never produced offspring). Characterization of the immune cell profile of tumors from these involuting and nulliparous mammary glands confirmed that involution is correlated with immune suppression, which may be the cause of increased tumor growth.

To complement these mice studies, Dr. Schedin is collaborating with Dr. Virginia Borges on a project studying the immune profile of breast tumor tissues from cases in women under 45 years of age. Preliminary analyses have demonstrated an increase in immune cell infiltrate into pregnancy-associated breast tumors, defined as having the last child birth within 2 years of breast cancer diagnosis. Further analyses will determine whether these immune cells support an immunosuppressive phenotype in pregnancy-associated breast tumors. Drs. Schedin and Borges hope that increased understanding of the role of the immune system in breast involution will lead to potential targets to prevent and treat postpartum breast cancer.

"The DoD BCRP has been critical in the development of the scientific principles that our laboratory research program is based upon: identifying windows of risk associated with mammary gland biology that can be targeted for the prevention and treatment of breast cancer. Starting with Concept Awards investigating normal gland development, postpartum involution, and the menopausal window, we have moved these areas of investigation forward with subsequent Idea Award funding. Currently, we are translating our results in the area of postpartum breast cancer to the clinic. Because of BCRP funding, postpartum breast cancer is now recognized as a significant component of breast cancer research focused on targeted interventions."

Dr. Pepper Schedin

Evidence for Dynamic Immune Modulation in the Mammary Gland with Reproductive Cycle



Immune cells infiltrate the mammary gland during pregnancy and then again during postpartum involution. Each colored line represents a unique immune cell type. During involution, the types of immune cells and their timing resemble immune cell infiltrates that enter wounds with early (activation), mid (clean-up), and late (resolution) stages. These data show that normal mammary gland involution shares immunologic characteristics with pathological wound healing. These observations may help explain why breast cancers diagnosed postpartum have an increased risk for metastasis, as similar immune cell programs are known to promote metastasis.

BCRS Program Funded Awards

Fiscal Year	Principal Investigator	Amount	Institution	Proposal Title
FY99	Daly	$283,649	Garvan Institute	Identification of Novel Prognostic Indicators for Breast Cancer Through Analysis of the EMS1/Cortactin Signaling Pathway
	Deuel	$5,000[1]	Scripps Institute	Novel Angiogenic Domains: Use in Identifying Unique Transforming and Tumor-Promoting Pathways in Human Breast Cancer
	Heyer	$111,444	University of California, Davis	In Vitro Recombination Activities of the Breast Cancer Predisposition Protein BRCA2
	Musgrove	$222,652	Garvan Institute	Role of Cyclin D1 and p27 in Steroidal Control of Cell Cycle Progression in the Mammary Gland in Vivo
	Shah	$279,000	University of Arkansas	Role of a Novel Matrix-Degrading Metalloproteinase in Breast Cancer Invasion
	Wang	$317,510	Texas A&M University	Scanning Microwave-Induced Acoustic Tomography
	White	$334,094	University of Texas Southwest Medical Center	Isolation of Factors That Disrupt Critical Protein/Protein Interactions Within the Telomerase Holoenzyme for Use in Breast Cancer Therapeutics
	Wreschner	$225,000	Tel Aviv University	Analysis of the Secreted Novel Breast Cancer-Associated MUC1/Zs Cytokine
FY00	Adamson	$578,183	Burnham Institute	Cripto: A Target for Breast Cancer Treatment
	Akporiaye	$454,500	University of Arizona	Tumor-Mediated Suppression of Dendritic Cell Vaccines
	Penn	$296,142	University of Toronto	Exploiting the Novel Repressed Transactivator Assay to Identify Protein Interactors and Peptide Inhibitors of the Myc Oncoprotein
FY01	Cai	$560,144	Vanderbilt University	Genetic Polymorphisms, Mitochondrial DNA Damage, and Breast Cancer Risk
	Carraway	$427,225	University of California, Davis	Identification of a Functional Human Homolog of Drosophila Kek1, an Inhibitor of Breast Tumor Cell Growth
	Chaudhary	$312,000	University of Texas Southwest Medical Center	The Role of Ectodysplasin A (EDA) and Its Receptors in the Pathogenesis of Breast Cancer
	Geahlen	$425,425	Purdue University	Characterization of Syk in Breast Carcinoma Cells
	Rosner	$454,181	St. Luke's-Roosevelt Hospital Center	Autocrine and Paracrine Control of Breast Cancer Growth by Sex Hormone-Binding Globulin
FY02	Dou	$491,999	University of South Florida	Synthetic Beta-Lactam Antibiotics as a Selective Breast Cancer Cell Apoptosis Inducer: Significance in Breast Cancer Prevention and Treatment
	Godwin	$504,000	Fox Chase Cancer Center	The Nuclear Death Domain Protein p84N5, a Candidate Breast Cancer Susceptibility Gene
	Perkins	$490,500	Yale University	Rapid Genomic Approach to Cancer Gene Discovery in Breast Cancer
FY03	Chung	$490,447	Yale University	Quantitative in Situ Assessment of the Somatostatin Receptor in Breast Cancer to Assess Response to Targeted Therapy with 111-in-Pentetreotide
	Kaaks	$367,639	International Agency for Cancer Research	Fatty Acid Synthesis Gene Variants and Breast Cancer Risk: A Study Within the European Prospective Investigation into Cancer and Nutrition (EPIC)
	Yaswen	$508,790	Lawrence Berkeley National Laboratory	Functional Analysis of BORIS, a Novel DNA-Binding Protein
	Ziv	$767,171	University of California, San Francisco	Admixture and Breast Cancer Risk Among Latinas
FY04	Bissell	$386,569	Lawrence Berkeley National Laboratory	Use of HA-Metal Nanoparticles to Identify and Characterize Tumorigenic Progenitor Cell Subsets in Breast Tumors
	Clarke	$588,738	Northern California Cancer Center	The Hygiene Hypothesis and Breast Cancer: A Novel Application of an Etiologic Theory for Allergies, Asthma, and Other Immune Disorders
	Giorgio	$453,000	Vanderbilt University	Surface Functionalized Nanoparticles and Nanocrystals for Proximity-Modulated, Early Neoplasia Detection, Imaging, and Treatment of Breast Cancer
	Lemmon	$475,500	University of Pennsylvania	Harnessing Novel Secreted Inhibitors of EGF Receptor Signaling for Breast Cancer Treatment

Fiscal Year	Principal Investigator	Amount	Institution	Proposal Title
FY05	Zinn[2]	$436,500	University of Alabama at Birmingham	Novel Screening and Precise Localization of Early Stage Breast Cancer in Animal Model
	Huang	$483,600	Cornell University, Weill Medical College	Migrastatin Analogues as Potent Inhibitors of Breast Cancer Metastasis
	Liu	$448,500	Ohio State University	Hunting for Novel X-Linked Breast Cancer Suppressor Genes in Mouse and Human
	Rao	$468,000	Stanford University	Ribozyme-Mediated Imaging of Oncogene Expression in Breast Tumor Cells
FY06	Devi	$155,085[3]	Duke University Medical Center	Modulation of Regulatory T Cells as a Novel Adjuvant for Breast Cancer Immunotherapy
	Lee	$489,000	University of Southern California	A New Mechanism for Estrogen-Starvation Resistance in Breast Cancer
	Li	$438,455	Baylor College of Medicine	The ER/PR Status of the Originating Cell of ER-Negative Breast Cancer
	Mousa	$377,620	Albany College of Pharmacy	Enhancing the Efficacy of Chemotherapeutic Breast Cancer Treatment with Non-Anticoagulant Heparins
	Rastinejad	$454,500	University of Virginia	Structural Characterization of the Interdomain Features of the Estrogen Receptor
FY07	Kuperwasser	$817,500	Tufts University	Mechanisms of Breast Cancer Associated with Obesity
	Kelly	$244,450[4]	University of Virginia	Genetically Encoded Targeted, Amplifiable, Imaging Agents for Early Detection of Breast Cancer
	Gerbi	$155,550[5]	Brown University	Hormonal Involvement in Breast Cancer Gene Amplification
FY08	Park	$111,663	North Dakota State University	In Utero Exposure to Dietary Methyl Nutrients and Breast Cancer Risk in Offspring
	Radosz	$528,939	University of Wyoming	Breast Cancer-Targeted Nuclear Drug Delivery Overcoming Drug Resistance for Breast Cancer Therapy
	Hill	$577,500	Oregon Health and Science University	Vaccine Vector for Sustained High-Level Antitumor CTL Response
	You	$503,666	University of Oklahoma Health Science Center	Targeted Delivery and Remote-Controlled Release of Chemotherapeutic Agents
	Seagroves	$166,667[6]	University of Tennessee Health Science Center	The Role of HIF-1 Alpha in Breast Cancer: A Positive Factor in Cancer Stem Cell Expansion via Notch?
FY09	Reynolds	$730,000[7]	Cancer Prevention Institute of California	Hazardous Air Pollutants and Breast Cancer: An Unexplored Area of Risk
	Wysolmerski	$620,626	Yale University	Effects of Nuclear Parathyroid Hormone-Related Protein Signaling in Breast Cancer
FY10	Schedin	$368,125[8]	University of Colorado, Denver	The Immune Modulatory Program of Post-Partum Involution Promotes Pregnancy-Associated Breast Cancer
	Leung	$556,875[9]	Johns Hopkins University	The Role of Poly(ADP-Ribose) in microRNA Activity in Breast Cancers
FY11	Minn	$399,955	University of Pennsylvania	Regulation of Metastasis and DNA Damage Resistance Pathways by Transposable Elements
	Wang	$409,693	Baylor College of Medicine	Copy Number Signature of Recurrent Gene Fusions Reveals Potential Drug Targets in Invasive Breast Cancer
	Gonzalo Hervas	$58,975[10]	St. Louis University	Stabilization of 53BP1 in Triple-Negative and BRCA-Deficient Breast Tumors: A Novel Therapeutic Strategy

[1] Total award amount was $404,176; remaining funds were from the FY99 BCRP.

[2] The original Principal Investigator, Dr. Tandra Chaudhuri, is deceased.

[3] Total award amount was $461,933; remaining funds were from the FY06 BCRP.

[4] Total award amount was $687,397; remaining funds were from the FY06 BCRP.

[5] Total award amount was $787,325; remaining funds were from the FY06 and FY07 BCRP.

[6] Total award amount was $554,987; remaining funds were from the FY08 BCRP.

[7] Total award amount was $860,883; remaining funds were from the FY09 BCRP.

[8] Total award amount was $556,028; remaining funds were from the FY10 BCRP.

[9] Total award amount was $585,652; remaining funds were from the FY10 BCRP.

[10] Total award amount was $744,761; remaining funds were from the FY11 BCRP.

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