

CDMRP



Department of Defense

Breast Cancer Research Semipostal Program



U.S. Army Medical Research and Materiel Command



Congressionally Directed Medical Research Programs

Breast Cancer Research Semipostal Program

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 over \$8.2 billion in appropriations from its inception through fiscal year 2014 (FY14). 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, which is composed of leading scientists, clinicians, and consumer advocates. The Integration 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.

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's issuance of a new first-class stamp, the Breast Cancer Research Semipostal (BCRS) in 1998. Net revenues from sales of the BCRS, which costs 55 cents, are provided to two designated funding agencies, the DoD BCRP and the National Institutes of Health, to support breast cancer research. Public Law 110-80 reauthorized the BCRS through December 31, 2015.



Research and Management Costs

Breast cancer stamp funding received by the BCRP between FY99 and FY13 has been used to fully or partially fund 55 awards under three award mechanisms: Idea Award, Synergistic Idea Award, and Breakthrough Award Funding Level 1 (Figures 1A and 1B). These award mechanisms support innovative, high-risk/high-reward research that could lead to major advancements in breast cancer. Applications funded through the BCRS program were reviewed and recommended for funding according to the two-tier review system implemented by the DoD BCRP. An evaluation of the awards funded through the BCRS program shows that the projects encompass a diversity of research areas (Figure 2).

Total Proceeds from BCRS	\$23,106,943
Research	\$22,005,936
Management Costs	\$1,101,007

Figure 1A. BCRS Research and Management Cost Allocation for FY99–FY13

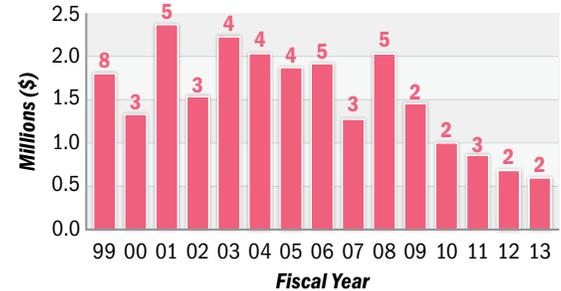


Figure 1B. BCRS Funding and Number of Awards Made by Fiscal Year

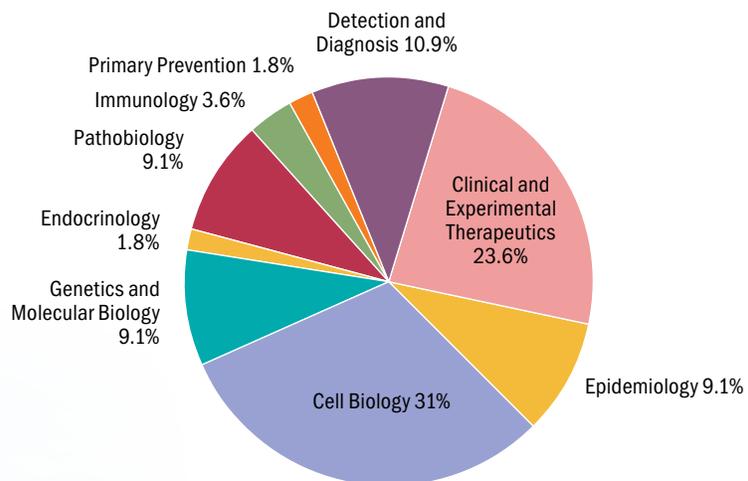


Figure 2. BCRS Award Portfolio Composition



Research Advancements



Genetic Variation and Breast Cancer Risk Among Latinas

Elad Ziv, University of California, San Francisco

The genetic determinants of breast cancer risk remain incompletely understood. Rare mutations in several genes including BRCA1, BRCA2, and others account for ~25% of familial breast cancer cases, but the majority of hereditary risk remains unexplained. Breast cancer incidence varies substantially across racial and ethnic groups in the United States, with the highest incidence found among U.S. women of European descent, a lower incidence for African American women, and lower still for Latinas. While these broad classifications may be useful in some areas, they oversimplify the genetic complexity that exists within each group. Recent genome-wide association studies (GWAS)

have identified approximately 80 genetic loci with small to moderate effects on breast cancer risk. The vast majority of these studies, however, have been limited to women of European, Asian, and African ancestry. Supported by an FY03 BCRP Idea-Epidemiology Award, Dr. Elad Ziv performed a GWAS of the relatively unstudied Latina population, itself a genetically heterogeneous group of varied ancestry, to identify genetic variants associated with breast cancer, and, in doing so, to improve understanding of the genetic factors underlying ethnicity-based health disparities.

Dr. Ziv and colleagues conducted a large population-based, case-control GWAS that included 1,497 Latinas with breast cancer and 3,213 Latinas without breast cancer. Comparing the genomes of both groups revealed a genetic variant, designated rs140068132, that was protective against breast cancer. When the variant was analyzed in the context of ancestry, using genetic markers that estimate the relative Indigenous American, European, and African ancestry, the researchers found that the protective variant is most abundant in Latinas of Indigenous American ancestry. Interestingly, Indigenous American ancestry had been previously associated with a decreased risk of breast cancer among Latinas. Further analysis of the variant showed it to be more protective against estrogen receptor (ER)-negative than ER-positive disease, and more commonly found in Latinas with low breast density, itself an indicator of decreased breast cancer risk. The mechanism by which rs140068132 is protective remains unknown; however, the variant resides near the gene that encodes the ER. Molecular analysis performed by Dr. Ziv's group shows that the protective variant appears to decrease the binding between DNA at this region and proteins that may regulate gene expression.

Thus, this variant may modulate the activity of transcription factors that control the expression of the ER. These findings highlight the importance of conducting genetic studies in different ethnic populations, as these may reveal novel variants and genetic loci contributing to breast cancer.



Publication:

Fejerman L, Ahmadiyeh N, Hu D, et al. 2014. Genome-wide association study of breast cancer in Latinas identifies novel protective variants on 6q25. *Nat Commun.* 5:5260.

Research Advancements



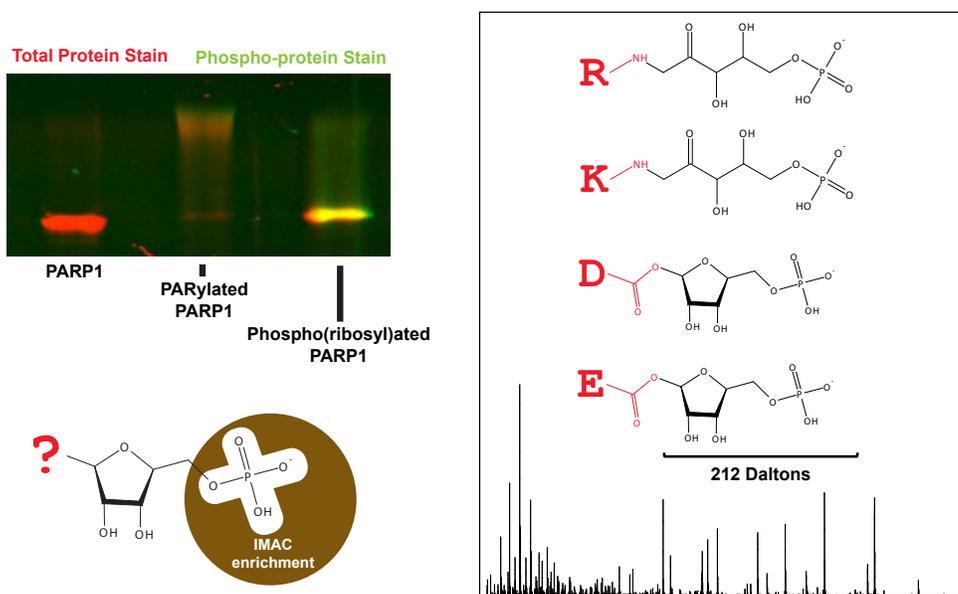
The Role of Poly(ADP-Ribose) in MicroRNA Activity in Breast Cancers

Anthony Leung, Johns Hopkins University

Inhibitors of poly(ADP-ribose) polymerase 1 (PARP-1) have shown promise in clinical trials for breast cancer patients. PARP-1 is the first identified polymerase of a protein superfamily, which consists of 17 PARP family members. PARP proteins are crucial components of a cell's DNA repair machinery, and recent studies suggest that they may also decrease the activity of microRNAs, which are master regulators of gene expression. Because current inhibitors target the PARP-1 catalytic domain, which is similar to the catalytic domain of all PARP protein family members, it is not clear which PARP proteins account for the therapeutic effects seen with these inhibitors. Dr. Anthony Leung, recipient of an FY10 BCRP Idea Award, sought to elucidate how PARP family members regulate microRNA and how this contributes to breast cancer progression. A clearer understanding of PARP function and microRNA regulation could lead to the development of more specific PARP inhibitors.

However, one major problem in furthering the mechanistic studies of PARP's role in microRNA regulation is the lack of proteomics techniques which can identify PARP-modified sites. PARP is a class of protein modification enzymes that adds polymers of ADP-ribose units onto proteins in cells. Due to the heterogeneous length of these polymers, it is difficult to use mass spectrometry (the most common and powerful proteomics tool available) to identify sites on proteins that have been modified by PARP. Through the support of this Idea Award, Dr. Leung and his team have devised an enzymatic strategy to tackle the heterogeneity problem, and they recently succeeded in developing a mass spectrometry method to identify PARP-modified sites from cells. The ability to identify these sites on microRNA regulatory proteins will allow mechanistic studies on how PARP regulates microRNA activities in breast cancers.

As several PARP inhibitors are currently in Phase III clinical trials for breast cancer, it is important to identify which PARP-modified proteins are inhibited by these drugs. Therefore, the successful clinical application of this method on patient samples will likely offer new insights into the therapeutic benefits and side effects of this promising class of drugs for breast cancer patients.



Publication:

Daniels CM, Ong SE, Leung AK. 2014. Phosphoproteomic approach to characterize protein mono- and poly(ADP-ribose)ylation sites from cells. *J. Proteome Res.* 13(8):3510-3522.



Modulation of Regulatory T Cells as a Novel Adjuvant for Breast Cancer Immunotherapy

Gayathri Devi, Duke University

Immune therapies have shown some success for the treatment of breast cancer, but the efficacy of these therapies has been limited by the activity of immunosuppressive T cells (Treg). Treg cells suppress antitumor immunity by decreasing the immune response to tumor-associated self-antigens such as human epidermal growth factor receptor 2 (HER2), which is widely used as a target for breast cancer immunotherapy. Dr. Gayathri Devi of Duke University had previously shown that Treg levels are higher in cancer patients as compared with healthy volunteers, and that they are especially high in patients with advanced breast cancer, suggesting that suppressed immunity caused by high Treg levels contributes to breast cancer progression.

Two proteins are known to be associated with maintaining the immunosuppressive function of Treg cells: transforming growth factor beta 1 (TGFbeta-1) and forkhead box protein 3 (FOXP3). With support from an FY06 BCRP Idea Award, Dr. Devi built upon her previous work and hypothesized that inhibition of Treg activity by blocking TGFbeta-1 or FOXP3 function would enhance the antitumor effect of immunotherapies, such as those that target the receptor HER2. Dr. Devi and her team developed several novel ways to inhibit TGFbeta-1 and FOXP3, and they generated novel anti-HER2 vaccines. They also established that FOXP3 expression is not restricted to T-cell lineage and demonstrated for the first time that FOXP3 is expressed in the most aggressive subset of breast cancer cells, called inflammatory breast cancer (IBC) cells. Analysis of recurrence-free survival data from a collection of 23 datasets posted on the NCBI Gene Expression Omnibus (GEO) database revealed high expression of FOXP3 was significantly associated with higher risk of recurrence in triple negative breast cancer. Proof-of-principle experiments showed that inhibition of TGFbeta-1, in combination with anti-HER2 therapy, led to a dramatic decrease in tumor growth in mice as compared with tumor growth following either treatment alone. Inhibition of FOXP3 expression caused depletion of the immunosuppressive FOXP3+ Treg cells and enhanced antigen-specific T-cell reactivity of human peripheral blood mononucleocytes. This work provides strong evidence for use of TGFbeta-1 and FOXP3 inhibitors in combination with immune-based therapies for the treatment of breast cancer.

Dr. Devi was asked to elaborate on her research supported by the BCRP and Breast Cancer Research Semipostal:

What is the most important thing that breast cancer researchers and survivors should know about your research?

Resistance to immunotherapy is a critical problem in breast cancer. Many cancer immunotherapies are being developed for breast cancer and some have shown promising efficacy, but their benefits remain modest. Furthermore, human immune cells are very difficult to target. The goal is to develop a nontoxic product that can get into specific subsets of immune cells and stay for a long period of time to elicit its response before it gets degraded. This CDMRP-funded research allowed us to develop a novel strategy that is easy to deliver to human cells: This oligomer-based chemistry allows us to target specifically a small subset of these regulatory T cells that causes resistance to various immunotherapeutic strategies. Reduction of these immunosuppressive T cells allows us to get an enhanced immune response and thereby increases the potency of cancer vaccines.

How has your BCRP funding helped advance your research?

This BCRP-funded research also gave us new insights into the biology of interaction between tumor cells and their immune-microenvironment. In a therapy-resistant breast cancer model, we identified the mechanism of FOXP3 signaling, and that effective elimination of therapy-resistant breast cancer cells may require immunologic intervention coupled with strategies that target dysregulation in the cancer cell's ability to undergo programmed cell death, which we call apoptosis. We identified a class of anti-apoptosis/cell death proteins that are overexpressed in breast tumor cells, and these anti-apoptotic proteins cause resistance to immunotherapy. This research also allowed collaboration between my laboratory and others, and led to a recently funded BCRP Idea Partnership Award with Dr. Michael Morse at Duke and TetraLogic Pharmaceuticals to address how defects in the apoptosis pathway in cancer cells cause resistance to tumor-antigen-specific killing by T cells and/or by antibody-dependent cellular cytotoxicity. The goal is to test a clinically relevant small molecule inhibitor that targets the tumor cells to decrease the anti-cell death proteins and overcome resistance to cancer vaccines.

Publication:

Nair S, Aldrich AJ, McDonnell E, et al. 2013. Immunologic targeting of FOXP3 in inflammatory breast cancer cells. *PLoS One*. 8(1):e53150.

BCRS Program Funded Awards

FY	PI	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
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

FY	PI	Amount	Institution	Proposal Title
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	\$399,942	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	\$58,975 ¹⁰	St. Louis University	Stabilization of 53BP1 in Triple-Negative and BRCA-Deficient Breast Tumors: A Novel Therapeutic Strategy
FY12	Yang	\$465,000	University of California, San Diego	Regulation of Breast Cancer Stem Cell by Tissue Rigidity
	Giancotti	\$174,837 ¹¹	Memorial Sloan-Kettering Cancer Center	Autophagy and TGF-Beta Antagonist Signaling in Breast Cancer Dormancy at Premetastatic Sites
FY13	Rubin	\$457,075	University of California, Santa Cruz	Inhibition of Retinoblastoma Protein Inhibition
	Luke	\$96,992 ¹²	University of Texas at Austin	Noninvasive Label-Free Detection of Micrometastases in the Lymphatics with Ultrasound-Guided Photoacoustic Imaging

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 \$744,661; remaining funds were from the FY11 BCRP.

¹¹ Total award amount was \$331,449; remaining funds were from the FY12 BCRP.

¹² Total award amount was \$497,288; remaining funds were from the FY13 BCRP.



For more information, visit:

<http://cdmrp.army.mil>

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