CDMRP

Department of Defense

Breast Cancer Research Semipostal Program





U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs

History of the CDMRP

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 more than $6.5 billion in appropriations from its inception through fiscal year 2011 (FY11). 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 proposal evaluation, with both tiers involving dynamic interaction among scientists and disease survivors. 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 disease survivors (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 balance, 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.

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's issuance of a new first-class stamp, the Breast Cancer Research Semipostal (BCRS). 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.

Research and Management Cost Allocations

Since the BCRS was first issued in 1998, the monies received by the BCRP through FY10 have been used to fully or partially fund 45 Idea Awards and 3 Synergistic Idea Awards (**Figure 1**). Both 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.

Total Proceeds from BCRS	$20,931,948.89
Research	$19,943,323.10
Management Costs	$988,625.78

Figure 1A. BCRS Research and Management Cost Allocation for FY99–FY10

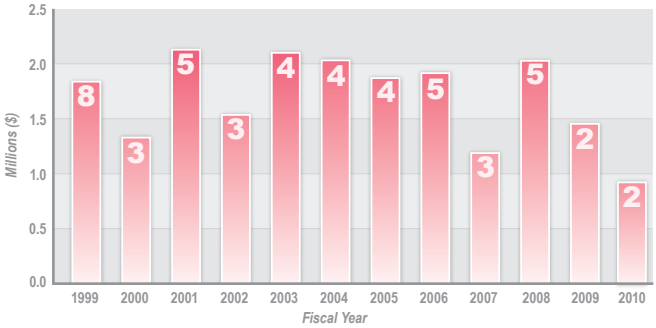


Figure 1B. BCRS Installments and Number of Awards Funded by Fiscal Year

Portfolio Composition

The BCRS Program supports a diverse portfolio of research projects. An evaluation of the awards funded through the BCRS Program shows that studies range from basic to translational research (**Figure 2**).

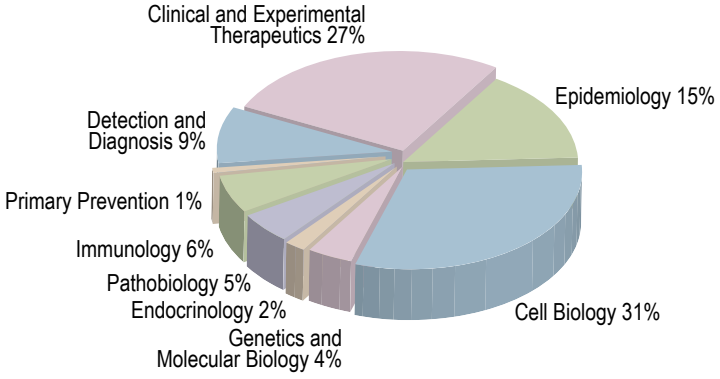


Figure 2. BCRS Award Portfolio Composition

Research Highlights

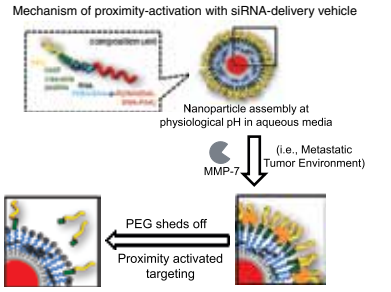
Surface Functionalized Nanoparticles and Nanocrystals for Proximity-Modulated, Early Neoplasia Detection, Imaging, and Treatment of Breast Cancer

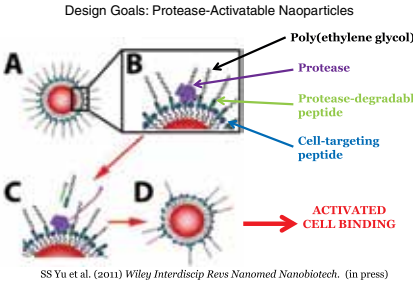
Dr. Todd Giorgio, Vanderbilt University

Despite advances in breast imaging and image interpretation, current standards in breast cancer screening fail to detect up to 30% of existing breast cancers. When a suspicious finding is detected, many women still must undergo tissue biopsy for confirmation. For 75% of these biopsies, the results will come back as negative for breast cancer. To address this lack of detection sensitivity and specificity, Dr. Todd Giorgio of Vanderbilt University, recipient of an FY04 Idea Award, sought to develop a simple, noninvasive screening methodology that could eventually be translated into a better test to detect early breast cancer.

Dr. Giorgio developed surface functionalized gold monolayer-protected nanoparticle clusters (AuMPCs) that incorporate both peptide-bridged polyethylene glycol (PEG) and folic acid-containing molecules. Breast tumors secrete an enzyme known as matrix metalloproteinase 7 (MMP-7), a member of the matrix metalloprotease family that is involved in the establishment and growth of both primary breast tumors and metastatic lesions. MMP-7 levels can be detected in measurable quantities during early cancer development, implicating the enzyme's potential as a biomarker for breast cancer detection. Capitalizing on this specific proteolytic activity, functionalized AuMPCs are designed to have their peptide bridges cleaved by MMP-7, resulting in the release of the PEG protective outer component and revealing the folate-targeting ligand underneath. This process, referred to as proximity activated targeting (PAT), will only occur in the presence of MMP-7 secreting breast cancer cells, thus allowing for the detectible release of PEG and providing evidence that an early tumor is forming. In the future, this concept of molecule release could potentially be applied toward the development of an ELISA-based screening test. Because an increase in folic acid receptor expression also occurs in breast cancer cells, the introduction of folic acid into the functionalized nanoparticles creates an additional targeting agent that allows even greater specificity for detecting breast cancers.

As a result of his Idea Award, Dr. Giorgio successfully developed this model, originally designed as a proof-of-concept, which allows for both the synthesis of the proposed functionalized molecules and the assessment of their performance in the PAT system. Expanding upon this work, Dr. Giorgio has now teamed with Dr. Craig Duvall, also from Vanderbilt University, to modify the PAT model and address the critical problem of chemotherapeutic drug resistance in breast cancer metastasis. With their 2009 BCRP Idea Expansion Award, these investigators are taking the framework developed by Dr. Giorgio and will expand PAT to target and knock down the efflux transporters found in metastatic breast cancer cells. These transporters essentially pump chemotherapy drugs right back out from the cells where they are needed the most. Not only do Drs. Giorgio and Duvall seek to knock down these pumps, but they will also use PAT for the delivery of high-dose, but low side-effect, chemotherapy, which could turn metastatic breast cancer into a more manageable disease.





SS Yu et al. (2011) *Wiley Interdiscip Revs Nanomed Nanobiotech.* (in press)

Hazardous Air Pollutants and Breast Cancer: An Unexplored Area of Risk

Dr. Peggy Reynolds, Cancer Prevention Institute of California

The incidence rates of breast cancer have been known to vary dramatically based on geographic region, with higher rates found in industrialized and urban regions. This disparity led to the idea that these rates could be associated with higher exposures to such environmental hazards as air pollutants. California has some of the highest rates of breast cancer worldwide, with higher concentrations of cases in the San Francisco and Los Angeles urban centers. These areas have high levels of hazardous air pollutants (HAPs). Considering a potential link, Dr. Peggy Reynolds proposed as the objective of an FY09 Idea Award to evaluate the risk of developing breast cancer in association with the estimated exposure to HAPs through an analysis of the California Teachers Study (CTS). The CTS is the largest prospective cohort study to date that was specifically designed to study breast cancer. Approximately 125,000 women have taken part in this study and represent a geographically dispersed population of California. The focus of Dr. Reynolds' study is to analyze the identified cases of invasive breast cancer within this cohort, as obtained through the California Cancer Registry, along with data obtained from the Environmental Protection Agency regarding the estimated outdoor concentrations of HAPs. The use of a geographic information system will allow for an assignment of the levels of specific HAP compounds or classes of compounds with the individual addresses of CTS participants. Analysis will include evaluating the importance of individual compounds and their effects on breast cancer risk, along with the collective risk of exposures to multiple HAPs. Currently, Dr. Reynolds has completed the necessary residential address geocoding and has focused on selecting the priority compounds and identifying the optimal strategy for using the EPA modeled data in this study. The overall impact of this study would come from the identification of specific air pollutants that increase the risk of developing breast cancer following exposure.

Targeted Delivery and Remote-Controlled Release of Chemotherapeutic Agents

Dr. Youngjae You, University of Oklahoma Health Sciences Center

The systemic delivery of chemotherapy results in the death of both cancerous cells and fast growing but otherwise healthy cells. Patients receiving this type of nonselective therapy unfortunately experience very significant and undesirable side effects. One approach to avoid the collective death of actively dividing cells is to deliver a form of targeted therapy that affects only the area of interest in the body. Dr. Youngjae You, recipient of an FY08 Idea Award, is addressing this problem by developing a novel drug delivery strategy involving the use of localized chemotherapy specifically engineered to target breast cancer cells. Since breast cancer cells have been found to express a higher level of folate receptor over that of normal cells, Dr. You is developing a strategy that will capitalize on this difference by conjugating folic acid with a core-modified porphyrin and a linker tethered to the drug of choice. The addition of folic acid will allow for the specific targeting of breast cancer cells, while the linker will be cleavable during the irradiation of breast tissue. The release of drugs would then be controlled, thus minimizing the side effects seen with systemic delivery. Dr. You proposed the synthesis of the envisioned conjugated molecules using the drugs paclitaxel and topotecan and will conduct studies to measure not only the kinetics of the controlled release of these drugs, but also the mechanisms of folate receptor-mediated uptake, along with the pharmacology, toxicology, and efficacy of these molecules. The impact of this method of drug therapy would lie not only in the selective targeting of breast cancer tumors, but also in the reduction of the side effects experienced by women undergoing conventional chemotherapy for breast cancer.

BCRS Research 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

[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.

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