CDMRP

Department of Defense

Breast Cancer Research Semipostal Program

U.S. Army Medical Research and Materiel Command

PROTECT · PROJECT · SUSTAIN

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 over $8.2 billion in appropriations from its inception through fiscal year 2015 (FY15). 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 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.

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) in 1998. Net revenues from sales of the BCRS, which costs 60 cents, are provided to two designated funding agencies, the DoD BCRP and the National Institutes of Health, to support breast cancer research. The Breast Cancer Research Stamp Reauthorization Act of 2015 reauthorized the stamp through 2019.

Research and Management Costs

Breast cancer stamp funding received by the BCRP between FY99 and FY14 has been used to fully or partially fund 59 awards under three award mechanisms: Idea Award, Synergistic Idea Award, and Breakthrough Award 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	**$23,795,004**
Research	$22,648,319
Management Costs	$1,146,685

Figure 1A. BCRS Research and Management Costs, FY99–FY14

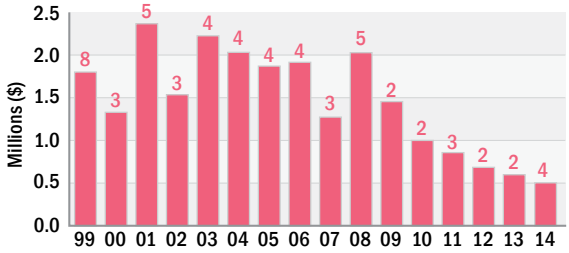


Figure 1B. BCRS Funding and Number of Awards, by Fiscal Year

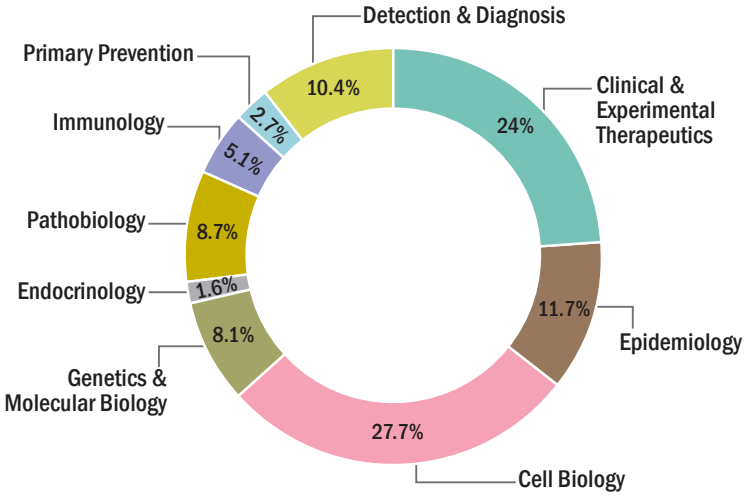
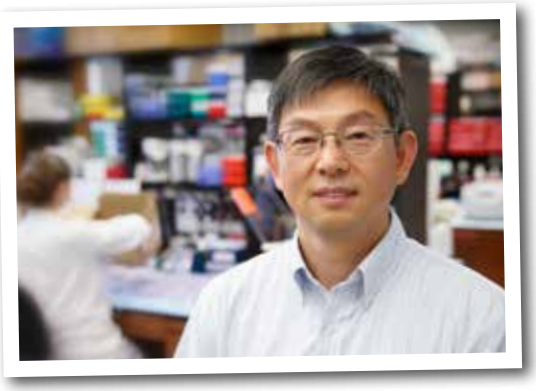


Figure 2. BCRS Award Portfolio Composition, by Percent of Funding Invested

Recent Research Advancements



Genetic Polymorphisms, Mitochondrial DNA Damage, and Breast Cancer Risk

Qiuyin Cai, M.D., Ph.D., Vanderbilt University

Established genetic risk factors, such as BRCA mutations, are effective predictors of breast cancer incidence; however, these factors do not account for the majority of breast cancers. Dr. Qiuyin Cai addresses this gap through his research on mitochondrial DNA (mtDNA) variations and genes that may have an effect on mtDNA damage.

Initially funded through the BCRS in 2001, Dr. Cai used samples and data from the Shanghai Breast Cancer Study to explore the role of the genetic polymorphisms of MnSOD and hOGG1, genes that code for important antioxidant enzymes in the cell's mitochondria, in breast cancer risk. Dr. Cai conducted this research in a population-based case-control study of Chinese women from the Shanghai Breast Cancer Study. Dr. Cai found no link between known hOGG1 polymorphisms and breast cancer risk in Han Chinese women. While a slight elevation of risk was detected for MnSOD polymorphisms only, it was more pronounced in pre-menopausal women.

Dr. Cai's group was one of the first to publish findings on the association of germline mtDNA variations in the mtDNA Displacement loop (D-loop) region, with breast cancer risk and survival. Dr. Cai ruled out the mtDNA D-loop (CA)n repeat polymorphism in the mtDNA D-loop as a factor in breast cancer risk. His findings suggest a link between heteroplasmy (having multiple alleles of (CA)n repeat polymorphism), an indicator of mitochondrial genome instability, with breast cancer survival. He also detected mtDNA D-loop somatic mutations in breast tissues and found that these mutations may contribute to breast cancer development. Dr. Cai's group also developed a sensitive method to measure large mtDNA deletion mutation. He also examined the relationship of breast cancer risk and survival with polymorphisms in other genes that encode antioxidant enzymes and DNA damage in other mtDNA regions. His research showed that these mtDNA alterations may not be involved in breast carcinogenesis.

In summary, Dr. Cai's BCRS-supported research elucidated a breast cancer susceptibility gene (MnSOD) as well as mtDNA polymorphisms and mutations that correlate with breast cancer risk and survival in a large population-based study. These findings may inform future studies that seek to identify breast cancer susceptibility genes in other diverse populations of women.

Publications:

Cai Q, Shu XO, Wen W, Cheng JR, Dai Q, Gao YT, Zheng W. Genetic polymorphism in the manganese superoxide dismutase gene, antioxidant intake, and breast cancer risk: Results from the Shanghai Breast Cancer Study. *Breast Cancer Res*. 6: R647-R655, 2004. PMID: 15535847. PMCID: PMC1064076

Cai Q, Shu XO, Wen W, Courtney R, Dai Q, Gao YT, Zheng W. Functional Ser326Cys polymorphism in hOGG1genes is not associated with breast cancer risk. *Cancer Epidemiol Biomark Prev*. 15: 403-404, 2006. PMID: 16492938

Ye C, Gao YT, Wen W, Breyer JP, Shu XO, Smith JR, Zheng W, Cai Q. Association of mitochondrial DNA D-loop (CA)n dinucleotide repeat polymorphism with breast cancer risk and survival among Chinese women. *Cancer Epidemiol Biomark Prev.* 17: 2117-2111, 2008. PMID: 18708405. PMCID: PMC2643086

Ye C, Shu XO, Wen W, Pierce L, Courtney R, Gao YT, Zheng W, Cai Q. Quantitative analysis of mitochondrial DNA 4977-bp deletion in sporadic breast cancer and benign breast disease. *Breast Cancer Res Treat*. 108: 427-434, 2008. PMID: 17541740. PMCID: PMC3836503

Ye C, Shu X, Pierce L, Wen W, Courtney R, Gao YT, Zheng W, Cai Q. Mutations in the mitochondrial DNA D-loop region and breast cancer risk. *Breast Cancer Res Treat*. 119: 431-436, 2009. PMID:19381801. PMCID: PMC2796283

A New Mechanism for Estrogen-Starvation Resistance in Breast Cancer

Amy Lee, Ph.D., University of Southern California

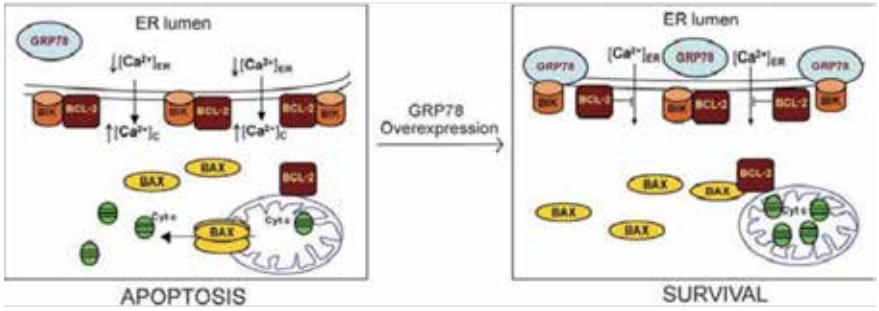
Aromatase inhibitors (AIs) are established as anti-estrogen therapeutics in estrogen receptor-positive (ER+) breast cancers. AIs block estrogen production, which leads to suppression of hormone-dependent cancer cell growth and activation of apoptosis (programmed cell death). Long-term anti-estrogen treatment is limited by the development of drug resistance at the cellular level. Resistance ultimately renders anti-estrogen treatment ineffective and may lead to disease recurrence.

Dr. Amy Lee was awarded BCRS funding through an FY06 BCRP Idea Award to explore mechanisms of drug resistance in ER+ breast cancer. She identified the glucose-regulated protein GRP78 as a "pro-survival" inhibitor of apoptotic pathways in ER+ cancer cells. Dr. Lee postulated that GRP78, a regulator of protein folding in the endoplasmic reticulum, plays a major role in the inhibition of a known pro-apoptosis protein called BIK. BIK, a mediator of the mitochondrial apoptotic pathway, is triggered by signals — such as the inactivation of another protein, BCL-2 — indicating estrogen starvation in cancer cells.

Drawing on evidence that GRP78 formed a complex with BIK, Dr. Lee demonstrated that GRP78 competes with BCL-2 for physical interaction with BIK. Overexpression of GRP78 leads to sequestration of BIK, release of BCL-2, and cancer cell survival. The knockdown of GRP78 in estrogen-starved breast cancer cells leads to an increase in apoptosis. Dr. Lee concluded that these findings support her theory that GRP78 acts as a pro-survival factor in cancer cells through its interactions with BIK and inhibition of the apoptotic pathway.

Dr. Lee is continuing efforts to translate these findings to the clinic. After screening reagents that inhibit GRP78 function, she and her collaborators discovered a monoclonal antibody against GRP78 that is able to induce apoptosis in cancer cells, including breast cancer cells. This antibody shows high efficacy in suppressing tumor development in a variety of xenograft and endogenous mouse models of cancer. This antibody has now been humanized and is under development through USC's partnership with Pfizer.

Model for GRP78 overexpression in inhibiting apoptosis through reduction of BCL-2 binding to BIK.



The endoplasmic reticulum, as a major intracellular Ca2+ store, regulates apoptosis by sensitizing mitochondria to the death of stimuli through Ca2+ release to the cytosol. This process is blocked by BCL-2 as part of its anti-apoptotic function. BIK is primarily localized to the endoplasmic reticulum. Induction of BIK, such as under estrogen-starvation conditions, leads to binding and inactivation of BCL-2 through complex formation. This triggers Ca2+ release from the endoplasmic reticulum and initiates the apoptotic process including BAX translocation to mitochondria and release of cytochrome c to the cytosol. When GRP78 is overexpressed under stress conditions such as long-term estrogen starvation, GRP78 binds to and sequesters BIK through complex formation. With reduced binding to BIK, BCL-2 is able to suppress endoplasmic reticulum Ca2+ release, thereby suppressing apoptosis. This promotes cell survival and resistance to therapy. (Zhou et al., J Biol Chem, 2011)

Publication:
Zhou H, Zhang Y, Fu Y, et al. 2011. Novel mechanism of anti-apoptotic function of 78-kDa glucose-regulated protein (GRP78): Endocrine resistance in breast cancer, through release of B-cell lymphome 2 (BCL-2) from BCL-2 interacting killer (BIK). *J Biol Chem.* 286(29):25687-25696.

Targeted Delivery and Remote-Controlled Release of Chemotherapeutic Agents

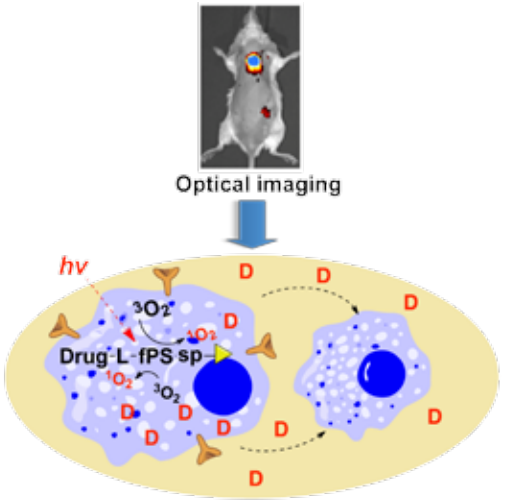
Youngjae You, Ph.D., University of Oklahoma Health Sciences Center

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 significant and undesirable side effects. Dr. Youngjae You, recipient of an FY08 Idea Award supported with BCRS funds, successfully developed an innovative strategy for local, targeted delivery that limits side effects caused by breast cancer chemotherapy. This strategy employed photo-unclick chemistry, a method by which low-energy light activates pro-drugs delivered to specific foci, thus having the ability to selectively target cancer cells and avoid normal tissue.

Since breast cancer cells have been found to express a higher level of folate receptor than normal cells, Dr. You developed a strategy that links folic acid with a photosensitizer and a linker tethered to the drug of choice. Combretastatin A-4 and irinotecan were used in this study. His group demonstrated that the folic acid delivered the prodrug much more to the folate receptor-expressing cancer cells than to normal cells. Upon irradiation with a nontoxic and deep-penetrating light source, the photosensitizer generated singlet oxygen, which cleaved the linker-prodrug nearly 100% of the time. The released drug demonstrated a significant antitumor effect in in vitro cell experiments and in a mouse tumor model.

With support from an FY13 BCRP Idea Expansion Award, Dr. You is currently applying this technology to triple-negative breast cancer in the laboratory. His current project aims to develop pharmacokinetic and pharmacodynamic models for the antitumor effects of doxorubicin and paclitaxel, delivered via this system using a phthalocyanine photosensitizer.

If successful, Dr. You's technology may represent a solid foundation for a therapeutic delivery system with the flexibility to utilize various prodrugs and chemotherapies. This novel method of drug therapy will not only enable the selective targeting of breast tumor cells, but also the reduction of the side effects of chemotherapy in treating localized tumors.



Combined Effects of PDT and Site-Specific Chemotherapy

In the new multifunctional prodrug strategy, antitumor therapy is maximized by a unique combination of optical imaging, PDT (photodynamic therapy) and site-specific chemotherapy. Fluorescent prodrugs are visualized by optical imaging and then the target tumor is ablated by a synergistic effect of PDT and locally released anticancer drugs. Since a small quantity of anticancer drug is released only in tumor, systemic side effects can be avoided.

Publications:

Bio M, Rajaputra P, Nkepang G, et al. 2014. Far-red light activatable, multifunctional prodrug for fluorescence optical imaging and combinational treatment. *J Med Chem.* 57:3401-3409.

Nkepang G, Bio M, Rajaputra P, et al. 2014. Folate receptor-mediated enhanced and specific delivery of far-red light-activatable prodrugs of Combretastatin A-4 to FR-positive tumor. *Bioconjug Chem.* 25:2175-2188.

Hossion AML, Bio M, and You Y. 2013. Visible light controlled activation of prodrugs via photo-unclick chemistry. *ACS Med Chem Let.* 4:124-127. Selected highlighted article by Editor.

Moses M, Pallavi R, Nkepang G, et al. 2013. Site-specific and far-red light-activatable prodrug of combretastatin A-4 using photo-unclick chemistry. *J Med Chem.* 56:3936-3942. PMID: 23631389 – Highlighted in SciBX: Science-Business eXchange.

Bio M, Nkepang G, and You Y. 2012. Click and photo-unclick chemistry of aminoacrylate for visible light-triggered drug release. *Chem Comm.* 48:6517-6519. PMID: 22622787.

Nkepang G, Pogula PK, Bio M, et al. 2012. Synthesis and singlet oxygen reactivity of 1,2-diaryloxyethenes and selected sulfur and nitrogen analogs. *Photochem Photobiol.* 88:753-759. PMID: 22268454.

Link:

http://cdmrp.army.mil/search.aspx?LOG_NO=BC134053
Public and Technical Abstracts: A Synergistic Combination Therapy of Photodynamic Therapy and Chemotherapy for Breast Cancer

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
FY14	Shu	$364,343	University of Kentucky	Ultrastable Nontoxic RNA Nanoparticles for Targeting Triple-Negative Breast Cancer Stem Cells
	Ellisen	$93,050[13]	Massachusetts General Hospital	Defining High-Risk Precursor Signaling to Advance Breast Cancer Risk Assessment and Prevention
	Brown	$7,457[14]	University of Rochester	Prediction of Metastasis Using Second Harmonic Generation
	DeNardo	$7,061[15]	Washington University	Reprogramming the Metastatic Microenvironment to Combat Disease Recurrence

[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.

[13] Total award amount was $605,208; remaining funds were from the FY14 BCRP.

[14] Total award amount was $216,085; remaining funds were from the FY14 BCRP.

[15] Total award amount was $527,797; remaining funds were from the FY14 BCRP.

For more information, visit:
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301-619-7071

January 2016