

II. Breast Cancer Research Program





The Breast Cancer Research Program (BCRP) has managed over \$2.2 billion (B) in congressional appropriations and remains the second-largest funding agent of extramural breast cancer research in the world. The BCRP has ensured that its funds are invested in the best science and are managed by an innovative program that will make unprecedented advances in the breast cancer field. By funding high-risk/high-gain research, integrating the voices of consumer advocates in all aspects of the program, and promoting synergistic team science, the BCRP is translating hope into action with the goal of eradicating breast cancer.



Translating Hope into Action

Vision

Eradicate breast cancer by funding innovative, high-impact research through a partnership of scientists and consumers.

“The Breast Cancer Research Program channels powerful synergy from the collaboration of the best and brightest in the scientific world with the primary stakeholder, the consumer, toward bold research efforts aimed at ending breast cancer.”

Carolina Hinestrosa
Nueva Vida
FY08 Integration Panel Chair



Program Background

The Department of Defense (DOD) BCRP was established in fiscal year 1992 (FY92) by a congressional appropriation of \$25 million (M) for research on breast cancer screening and diagnosis for military women and their family members (Appropriations Conference Committee Report No. 102-328). The efforts of grassroots advocacy, led by the National Breast Cancer Coalition, in concert with the program's successes, have resulted in over \$2.2B in congressional appropriations for peer-reviewed breast cancer research through FY08 (Figure II-1). The program has carefully invested these funds each year in innovative research projects that can advance the breast cancer research field toward ending this disease.



Figure II-1. BCRP Funding History

The Disease

Breast cancer is the most commonly diagnosed non-skin cancer in women—accounting for more than one in four cancers diagnosed in women in the United States.¹

- ❖ It is estimated that approximately 182,460 women in the United States will be diagnosed with invasive breast cancer in 2008.
- ❖ In addition to invasive breast cancer, it is estimated that approximately 67,770 women in the United States will be diagnosed with breast cancer in situ in 2008.
- ❖ While breast cancer in males is rare, it is estimated that 1,990 new cases of male breast cancer will be diagnosed in 2008.
- ❖ More than 40,000 women and approximately 450 men are projected to die from breast cancer this year.
- ❖ The incidence rate of invasive breast cancer decreased by 3.5 percent per year from 2001–2004.
- ❖ Death rates from breast cancer have decreased steadily over the past decade.²

Signs and Symptoms

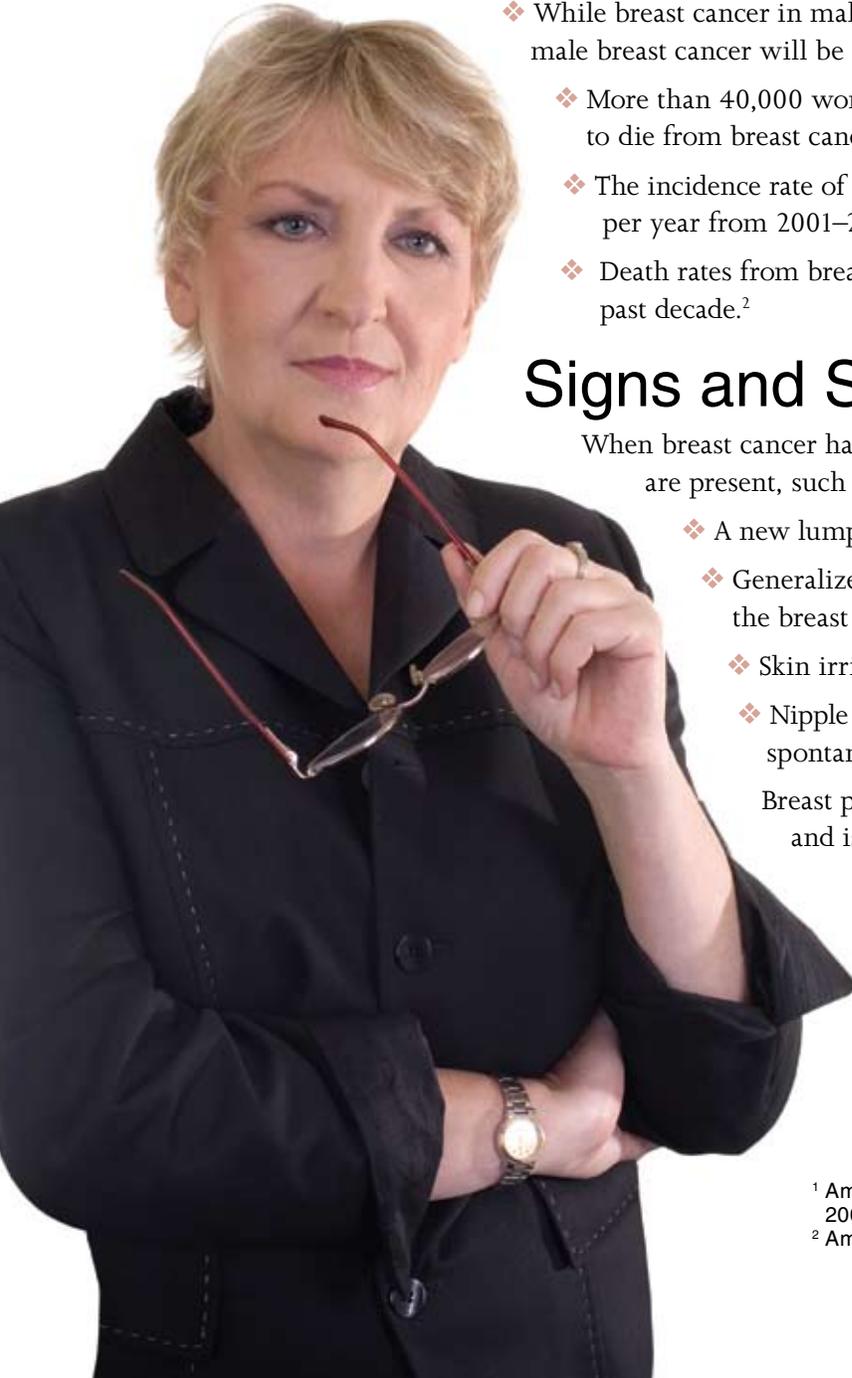
When breast cancer has grown to a point where physical symptoms are present, such indicators may include:

- ❖ A new lump or mass in the breast
- ❖ Generalized swelling, distortion, or tenderness of the breast
- ❖ Skin irritation or dimpling
- ❖ Nipple pain, scaliness, ulceration, retraction, or spontaneous discharge

Breast pain is often attributable to benign conditions and is usually not the first indication of breast cancer.

¹ American Cancer Society, *Breast Cancer Facts & Figures*, 2007–2008.

² American Cancer Society, *Cancer Facts & Figures*, 2008.



Early Detection

Nearly all breast cancers can be treated successfully if detected early in development. The following methods recommended by the American Cancer Society for asymptomatic women with average risk may help them detect breast cancer early.

Breast Self-Exam (BSE)

- ❖ An option for women beginning in their 20s.
- ❖ Women should have a doctor or nurse check their methods to make sure that the BSE is being done correctly.
- ❖ Regular BSE allows women to identify abnormal changes more easily.
- ❖ Women are advised to consult with a doctor right away if any changes are noticed, keeping in mind that most of the time these breast changes are not cancerous.

Clinical Breast Exam

- ❖ Should be part of a regular exam by a health expert for women in their 20s and 30s, preferably every 3 years.
- ❖ After age 40, women should have a breast exam by a health expert every year.

Mammography

- ❖ A valuable radiographic method for the early detection of breast cancer.
- ❖ Women age 40 and older should have a mammogram every year.



Strategic Partnerships

The BCRP is regarded as a world leader in advancing breast cancer research, and meaningful partnerships have been the foundation of the program's successes. Consumer advocates, research managers, and the scientific community have worked together to foster unique opportunities in breast cancer research. Through this program, the integrated efforts of many dedicated and passionate individuals are translating hope into action.

Consumer Advocates

The BCRP set a precedent by including consumer advocates in every aspect of the program and bringing the voice and perspective of breast cancer survivors to the research process. Other programs managed by the Congressionally Directed Medical Research Programs, as well as other funding agencies, have adopted the model established by the BCRP. Consumer advocates partner with the BCRP as active members of the:

- ❖ **Integration Panel (IP)**, where consumer advocates facilitate the development of the program's vision each year and make funding recommendations to the program.
- ❖ **Peer review process**, with more than 550 consumer advocates having provided expert advice on the scientific and technical review of proposals submitted to the BCRP since 1995.
- ❖ **Research process**, by aiding in patient recruitment and public education, and advising researchers.

Consumer advocates' firsthand experiences with breast cancer provide a unique perspective that is complementary to the scientists' expertise. They are the voices and faces that represent the concerns and interests of the consumer community. By participating in the research process, consumer advocates provide a distinctive viewpoint and bring a sense of urgency to the process.

"I have chosen to participate in BCRP peer review to personalize the purpose and goals of breast cancer research for the scientists. I personally know two women who are benefiting from Herceptin[®], the only drug they have positively responded to and which we believe has extended their lives. We must keep trying to find drugs that improve the quality of life, make the treatment less toxic, and ultimately will cure breast cancer, and possibly one day a preventive drug may also be developed as a result of the BCRP."

Shirley Brown
Women of Essence Breast Cancer
Survivors' Support Project



"Participation in the BCRP fulfilled a desire to advocate for the consumer aspect of breast cancer research. As a result of participating, not only have my eyes been opened to the vast amounts of research taking place, but also to the dedication of the scientists who participate in the BCRP as well as conducting research themselves. It has been an honor and privilege to serve as one of the 'people' whom the research has benefited and to carry that knowledge home to advocate more effectively in my community and state."

Deb Haggerty
Florida Breast Cancer Coalition
Research Foundation



“My experience as a first-time consumer reviewer at the BCRP programmatic review was one of total immersion. As consumer reviewers, we prepare conscientiously and we add value by viewing the research from the perspective of the patient community, asking how it will ultimately impact and improve on clinical care.

The DOD process could not be a better illustration of the interaction dynamic between consumers and scientists. How invaluable the sense of fulfillment that comes after a thoughtful, well-defined discussion; as each vote is tallied, my vote, as an advocate and breast cancer survivor, is equally valued with the others.”

Amy Bonoff
National Breast Cancer
Coalition



“As we sit together, researchers and patient advocates alike, reviewing scientific proposals, there is a newfound respect we have for each other’s perspectives and a recognition that, working together, we can reach the goal we all share...an end to breast cancer.”

Alice Yaker
SHARE



“Being a consumer reviewer for the BCRP has been one of the most challenging and gratifying experiences I’ve had on my journey as a breast cancer survivor. I have learned so much about the scope of breast cancer research and have witnessed firsthand the value and impact of survivor involvement. As just one of the 2 million breast cancer survivors in the U.S., I consider it both a privilege and a responsibility to represent the interests of breast cancer patients to the best of my ability in this outstanding program. The promising research that is being conducted makes this a hopeful time to be a survivor.”

Eunice Hostetter
Evergreen Hospital
Medical Center



Peer Review Panel Members

Scientific peer review is a process in which panel members provide unbiased, expert advice on the scientific and technical merit of proposals submitted to the program. Peer review panels are composed of leading investigators from scientific and clinical disciplines as well as consumer advocates. Scientific reviewers are selected for their subject matter expertise and experience with scientific peer review. Consumer reviewers are nominated by an advocacy or support organization and are selected on the basis of their leadership skills, commitment to advocacy, and interest in science. To date, more than 3,600 scientists, clinicians, and consumer advocates have provided their expertise to the BCRP scientific peer review process.

“I was enamored with the visionary goal to fund high-risk, high-impact research where the emphasis was placed on innovation and impact and not on methodological details. Having served on NIH [National Institutes of Health] study sections since 1993, this was a very refreshing approach to prioritizing research that could really make a difference in individuals and families affected by breast cancer. I came away from my first peer review panel with a new appreciation for what I do as a scientific researcher and with a new awareness that my research area may provide insight into inflammatory breast cancer [IBC]. I never would have thought to pursue this direction of research if I had not been sitting next to a consumer reviewer. She explained to me that a diagnosis of IBC was one that patients feared because of its intractable nature for treatment and poor prognosis for survival. Thus, the spirit and passion of the breast cancer advocates rekindled my own passion to redirect my research program. When I got home, I looked into the literature about IBC and came up with a hypothesis that led to the funding of a Concept Award!”

Patricia J. Simpson-Haidaris, Ph.D.
University of Rochester



“The CDMRP maintains a high standard of excellence through self-assessment and peer review. I believe that every penny used for research should be spent wisely in order to maximize benefit to patients and justify the enormous efforts of those who fund the research. Therefore, it is my duty as a member of the research community to act as a reviewer to help maintain the high standards of CDMRP-supported research. I am impressed by the way that the CDMRP strives to evaluate and improve the review process each year and continues to actively integrate breast cancer survivors as reviewers. This makes reviewing an educational and stimulating experience, which I have no doubt will have a real impact on the lives of patients, their families, and our society.”

Richard Neve, Ph.D.
**Lawrence Berkeley National
Laboratory**



“It has been my pleasure to serve on numerous CDMRP scientific review panels for the past 9 years. As a recipient of grants, I can appreciate the innovative approach the CDMRP has used to explore more clinically relevant questions—something that took years for other federal funding agencies to appreciate. The CDMRP has led the way with the use of consumer advocates on the review panels, electronic submissions, etc., and I will be happy to continue to lend my scientific expertise.”

Andrew K. Godwin, Ph.D.
Fox Chase Cancer Center



“My participation as a consumer on a peer review panel was one of the most uplifting experiences of my life. It gave me an insight into the enormous energy and creativity that exists in the research community, it showed me the seriousness of the selection process to maximize the outcome from limited funds, and it gave me a chance to help the scientists remain close to the main concerns affected by the disease.”

Ollie Ferrell
Breast Cancer Network of Strength



Integration Panel Members

The BCRP IP is composed of visionary and innovative scientists, clinicians, and consumer advocates. Members of the IP recommend an annual program vision, investment strategies to meet the needs of the research and consumer communities, and the most meritorious and programmatically relevant proposals for funding.



In Memory of Karin D. Noss **Virginia Breast Cancer Foundation**

The DOD BCRP and the breast cancer advocacy community suffered a tremendous loss when Ms. Karin Noss, the original Chair of the FY08 BCRP IP, died of metastatic breast cancer on February 16, 2008. Ms. Noss once noted, "Consumer involvement in all facets of the BCRP has proven crucial to ensuring not only that the best and most innovative science gets funded, but that the science will really make a difference to those of us living with the disease." In honor of her position as the FY08 BCRP IP Chair, the BCRP dedicated its efforts throughout 2008 to the enduring memory of Karin Noss.

FY08 BCRP IP Members

M. Carolina Hinestrosa, M.A., M.P.H. (Chair)
Nueva Vida

Graham Casey, Ph.D. (Chair Emeritus)
University of Southern California

Frank J. Calzone, Ph.D. (Executive Committee Member-at-Large)
Amgen, Inc.

Frances M. Visco, Esq. (Executive Committee Member-at-Large)
National Breast Cancer Coalition

Susan G. Hilsenbeck, Ph.D.
Baylor College of Medicine

Clifford A. Hudis, M.D.
Memorial Sloan-Kettering Cancer Center

H. Kim Lysterly, M.D.
Duke Comprehensive Cancer Center

Ngina Lythcott, Dr.P.H.
Black Women's Health Imperative and Boston University School of Public Health

Malcolm C. Pike, Ph.D.
University of Southern California

Donald B. Plewes, Ph.D.
University of Toronto Sunnybrook & Women's College Health Sciences Centre

William H. Redd, Ph.D.
Mount Sinai School of Medicine

Scientific Community

The scientific community is a crucial partner in the BCRP, composed of highly regarded researchers who are exploring the cutting edge of science to cure breast cancer. The program has funded approximately 4,200 scientists and clinicians since its inception. This chapter highlights some of the exceptional BCRP-supported investigators and their progress to fulfill the program's vision.

“An Idea Award from the BCRP has helped me to use the full potential of my creativity and launch my original, unrestricted ideas that are not appreciated by conventional wisdom.”

Lalita Shevde-Samant, Ph.D.
University of South Alabama



“One of the key characteristics of the BCRP is the strong emphasis on encouraging collaborative, interdisciplinary research efforts to combat breast cancer. Support from the BCRP Multidisciplinary Postdoctoral Award allowed me to acquire the necessary training in multiple research areas, including biomaterials and cancer biology, to develop innovative polymer therapeutics for treatment of breast cancer. This support at an early stage of my career positively shifted my attention to focus on developing new drug delivery systems that can selectively target the cancer tissue with cellular and subcellular accuracy, which represents the foundation of my independent research career as an assistant professor at the University of Michigan. In my opinion, the level of research support provided by the BCRP is critical to attracting talented investigators from across disciplines to address different pieces of the puzzle and eventually eradicate breast cancer.”

Mohamed E.H. El-Sayed, Ph.D.
University of Michigan



“The BCRP has been extremely valuable to my research program. With its support, my research team has been able to enjoy the pursuit of nonconventional concepts and ideas, which are usually not fundable through other agencies.”

Yi Li, Ph.D.
Baylor College of Medicine



“The BCRP is an extremely important mechanism for funding breast cancer research. In particular, the Era of Hope Scholar Award allows an opportunity for new investigators to immediately and vigorously build their research programs at a critical point in their early careers.”

Alana Welm, Ph.D.
University of Utah



“The uniqueness and importance of the Multidisciplinary Postdoctoral Award lie in the platform it provides to bring in experts in different research areas. While other funding agencies questioned my transition to a new research path, the Department of Defense took a chance to nurture my inquisitiveness. Scientifically, this fellowship has provided me with immense initiative to dig into and solve the problems associated with breast cancer. Academically, the fellowship has helped me to start an independent career in much needed targeted drug delivery research for the treatment of breast cancer.”

Rohit Kolhatkar
University of Maryland



Recent Advances Supported by the BCRP

Prominent BCRP-supported research publications from the past year:

- ❖ Finak G, Bertos N, Pepin F, et al. 2008. Stromal gene expression predicts clinical outcome in breast cancer. *Nature Medicine* 14(5):518–527.
- ❖ Kinder M, Chislock E, Bussard KM, et al. 2008. Metastatic breast cancer induces an osteoblast inflammatory response. *Experimental Cell Research* 314(1):173–189.
- ❖ Silva JM, Marran K, Parker JS, et al. 2008. Profiling essential genes in human mammary cells by multiplex RNAi screening. *Science* 319(5863):617–620.
- ❖ Domchek SM, Recio A, Mick R, et al. 2007. Telomerase-specific T-cell immunity in breast cancer: Effect of vaccination on tumor immunosurveillance. *Cancer Research* 67(21):10546–10555.
- ❖ Panigrahy D, Kaipainen A, Huang S, et al. 2008. The PPARalpha agonist fenofibrate suppresses tumor growth through direct and indirect angiogenesis inhibition. *Proceedings of the National Academy of Sciences* 105(3):985–990.
- ❖ Stull MA, Pai V, Vomachka AJ, et al. 2007. Mammary gland homeostasis employs serotonergic regulation of epithelial tight junctions. *Proceedings of the National Academy of Sciences* 104(42):16708–16713.
- ❖ Harris LN, You F, Schnitt SJ, et al. 2007. Predictors of resistance to preoperative trastuzumab and vinorelbine for HER2-positive early breast cancer. *Clinical Cancer Research* 13(4):1198–1207.
- ❖ Braunstein S, Karpisheva K, Pola C, et al. 2007. A hypoxia-controlled cap-dependent to cap-independent translation switch in breast cancer. *Molecular Cell* 28(3):501–512.
- ❖ Kim H, Chen J, and Yu X. 2007. Ubiquitin-binding protein RAP80 mediates BRCA1-dependent DNA damage response. *Science* 316(5828):1202–1205.
- ❖ Bowie ML, Troch MM, Delrow J, et al. 2007. Interferon regulatory factor-1 regulates reconstituted extracellular matrix (rECM)-mediated apoptosis in human mammary epithelial cells. *Oncogene* 26(14):2017–2026.
- ❖ Xu X, Gammon MD, Zhang H, et al. 2007. Polymorphisms of one-carbon metabolizing genes and risk of breast cancer in a population-based study. *Carcinogenesis* 28(7):1504–1509.
- ❖ Rizki A, Weaver VM, Lee SY, et al. 2008. A human breast cell model of preinvasive to invasive transition. *Cancer Research* 68(5):1378–1387.
- ❖ Klein DE, Stayrook SE, Shi F, et al. 2008. Structural basis for EGFR ligand sequestration by Argos. *Nature* 453(7199):1271–1275.

Award Mechanisms

Evolving to Meet Program Goals

FY04–FY08

- ❖ Synergistic partnerships (Synergistic Idea)
- ❖ Multidisciplinary research (Multidisciplinary Postdoctoral)
- ❖ Future innovators (Era of Hope Scholar, Era of Hope Postdoctoral)

FY00–FY03

- ❖ Team science (Center of Excellence, Biotech Clinical Partnership)
- ❖ Leading innovation (Innovator)
- ❖ Specialized training (HBCU/MI [Historically Black Colleges and Universities/ Minority Institutions] Partnership, Clinical Research Nurse)

FY95–FY99

- ❖ Early career development (Career Development, Linked Career Development)
- ❖ New ideas (Idea, Concept)
- ❖ Translational (Clinical Translational Research)

FY92–FY94

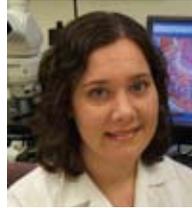
- ❖ Research resources (Registries, Repositories, Information Systems)
- ❖ Innovative research (Innovative Developmental and Exploratory)
- ❖ Training (Predoctoral, Postdoctoral, New Investigator)

BCRP Award Mechanisms: Filling Research Gaps Through Innovative Award Mechanisms

Since its inception, the BCRP has created and introduced unique award mechanisms that fulfill unmet needs in breast cancer. After supporting such areas as research resources and early career awards in its initial years, the BCRP shifted its approach by promoting innovative and translational breast cancer research. The program continues to encourage innovative, out-of-the-box thinking by supporting innovative leaders at every career level. Recognizing the need to promote team science, the BCRP also designed new award mechanisms that foster multidisciplinary and synergistic partnerships.

Program Awards

Training and Mentoring the Next Generation



Valerie Siclari
University of Virginia

Valerie Siclari, an FY05 Predoctoral Traineeship Award recipient, is studying the role of adrenomedullin (AM), a factor

known to increase bone metastasis in several types of cancer. Ms. Siclari has produced in vitro models to analyze the expression of AM in breast cancer cell lines. Using these AM-expressing cell lines for injection into mice, Ms. Siclari is researching the ability of AM to induce bone lesion formation. Her study encompasses the role of AM in chemotherapy resistance and cell proliferation in addition to bone metastasis.



Lindsay Orr
University of Minnesota, Twin Cities
FY06 Predoctoral Traineeship

Award recipient Lindsay Orr intends to pursue a research career focused on nontoxic, noninvasive

methods of diet and lifestyle modification to reduce breast cancer mortality. Ms. Orr's current training award moves her one step closer to her goal by evaluating the effect of a low-fat diet that includes omega-3 fatty acids on reducing breast cancer risk in postmenopausal women.



Spencer Cutler
Duke University

Spencer Cutler, an FY06 Predoctoral Traineeship Award recipient, was motivated to pursue a career in breast cancer research

after watching a close family member struggle with the disease. The objective of Mr. Cutler's research project is to fully automate and optimize the performance of a three-dimensional (3D) emission mammotomography system for enhanced clinical testing to improve the detection and in vivo characterization of small, early-stage breast cancers.



Julia Etchin
Yale University

Julia Etchin, recipient of an FY06 Predoctoral Traineeship Award, is focusing on research to determine the mechanistic role of BRCA2 in homologous recombination. Germ-line mutations in BRCA2, which is involved in double-strand break repair through the homologous recombination pathway, are associated with early-onset breast cancer. Through her research project, Ms. Etchin intends to delineate how BRCA2 mutations result in genome instability and subsequent breast tumor formation.



Steven Carey
University of Arizona, Tucson

Steven Carey, Principal Investigator of an FY05 Predoctoral Traineeship Award, has been studying agents that can target secondary DNA structures to control transcriptional activation. An overexpression of the transcriptional activator c-Myc has been associated with poor prognosis through genetic instability and subsequent tumor progression. By characterizing the roles of secondary structures and their associations with transcription factors, Mr. Carey can then screen small molecules for interruption of these associations by either stabilizing or disrupting the structures. The goal of this project is to identify potential drug candidates that could lower c-Myc levels and improve breast cancer outcomes.



Gene Bidwell, Ph.D.
University of Mississippi Medical Center

Dr. Gene Bidwell, an FY07 Era of Hope Postdoctoral Award recipient, will investigate the novel approach of using

thermally responsive polypeptides (i.e., CPP-ELP-H1) to treat breast cancer by inhibiting c-Myc activity. Dr. Bidwell will evaluate the biodistribution of CPP-ELP-H1 in normal and neoplastic tissues in the athymic tumor-bearing mouse model. Additionally, the project will include the assessment of the therapeutic efficacy

of polypeptides with respect to c-Myc activity in normal and cancerous breast tissues in the athymic tumor-bearing mouse model.



Jaydutt Vadgama, Ph.D.
Charles R. Drew University of Medicine and Science

As an FY04 HBCU/MI Partnership Training Award recipient, Dr. Jaydutt Vadgama is partnering with Dr. Dennis Slamon to establish a breast cancer research program at Charles R. Drew University of Medicine and Science that is focused on minority and underserved populations. Through the mentorship and collaboration supported by this award, Drew faculty and postdoctoral fellows are being developed into independent and competitive breast cancer researchers; unique resources from each institution are available to share between both institutions; and innovative research focused on the cell and molecular biology, detection, diagnosis, etiology, and treatment of HER-2/neu expressing breast tumors in minority and underserved women is being pursued.



Creating Partnerships and Crossing Disciplines



Arul Chinnaiyan, M.D., Ph.D.

University of Michigan

Dr. Arul Chinnaiyan, an FY07 Era of Hope Scholar Award recipient, has assembled a multidisciplinary team of researchers and

physicians to undertake a comprehensive and systematic evaluation of breast tumor genomes. They will use specially developed and adapted hardware, software, and algorithms to create a novel, customized, high-throughput technology to examine gene rearrangements in breast tumor samples. The ultimate objective of this work is to identify recurrent gene fusions and translocations associated specifically with breast cancer, thus providing novel targets for developing improved therapeutic modalities.



Vy Lai, Ph.D.

University of Washington

Dr. Vy Lai, an FY06

Multidisciplinary Postdoctoral Award recipient, is developing an effective use of human

epidermal growth factor receptor 2 (HER2)-specific CD4+ Th1 cells for adoptive T-cell therapy to treat advanced-stage breast cancer. In preclinical studies in neu-transgenic mice, Dr. Lai has identified two neu peptides that stimulate an immune response against the neu protein. Working under the guidance of a primary mentor who is an expert in breast cancer immunology and immunotherapy, as well as two other mentors who are both engineers, Dr. Lai is developing methods to assess whether the adoptive T-cell therapy is effective and viable for a Phase I study in women with metastatic breast cancer.



Roberto Diaz, M.D.
Vanderbilt University
FY06 Multidisciplinary
Postdoctoral Award recipient
Dr. Roberto Diaz will combine

expertise in cancer biology, polymer chemistry, and molecular imaging to develop a rapid, noninvasive method that will monitor tumor response to therapy. He proposes to identify recombinant peptides from phage-displayed peptide libraries that selectively bind to receptors activated in response to tyrosine kinase inhibitor (TKI)-based therapies. The peptides will be labeled with internal emitters to allow for noninvasive monitoring of therapy response. In the first year of his award, Dr. Diaz identified six peptides that bind to TKI-treated breast tumors. Future work will focus on validation of the peptides and identification of the receptors to which they bind.



Gertraud Maskarinec, M.D.
University of Hawaii
FY06 Synergistic Idea Award
recipient Dr. Gertraud Maskarinec
(pictured at top) and Dr. Rachel



Novotny (pictured at bottom)
are developing an innovative
methodology to replace
mammography for early
detection of breast cancer and to
observe very early characteristics
of breast development to prevent

breast cancer during adulthood. The investigators will study 100 pairs of mothers and their adolescent daughters, ages 10–16. Development of a technique to detect breast density, a known breast cancer risk indicator, at an early age should allow for a wide range of further studies to examine factors that can modify breast development and decrease breast cancer risk. Furthermore, by studying mother-daughter pairs, credible hypotheses can be developed about heritable versus behavioral factors influencing breast density and breast cancer.



Lewis Romer, M.D.
Johns Hopkins University School
of Medicine
FY06 Synergistic Idea Award
recipient Dr. Lewis Romer and
Dr. Jan Hoh are motivated by

the unremitting toll that metastatic disease takes on women with breast cancer. Together these scientists are working to discover how cancer cells modulate properties of the extracellular matrix (ECM) and how cancer cells in turn are strongly influenced by the mechanical properties of their matrix microenvironment. Findings to date include interesting and exciting new understandings of the mechanical properties of the ECM and identification of major proteins and glycosaminoglycans in the ECM under study.



Lance Liotta, M.D., Ph.D.
George Mason University
Innova

FY06 Synergistic Idea Award
recipient Dr. Lance Liotta
(pictured at top) and Dr. Kirsten
Edmiston (pictured at bottom)
are using novel technology to
address fundamental questions
that could not be approached
previously, challenging the
current dogma about the



invasive potential of human ductal carcinoma in situ (DCIS). It has been assumed that DCIS is a preinvasive stage that exists along a spectrum of lesions that have progressed part of the way toward becoming a fully invasive carcinoma. Additional genetic hits are thought to be required for DCIS cells to acquire the full capability of invasion and metastasis. For this research, the investigators are developing and employing a wholly new technology to microdissect the 3D structures of living human DCIS lesions. The technology will provide the means to conduct studies on the nature of DCIS that were never before possible.

Thinking Outside the Box



Yuling Luo, Ph.D.

Advanced Cell Diagnostics, Inc.

Dr. Yuling Luo was awarded an FY05 Concept Award to develop a new technology called Quantitative Multiplexed

Analysis of Gene Expression in single cells (QMAGEX) to enable molecular characterization of circulating tumor cells (CTCs). The QMAGEX assay demonstrated high resolution of gene amplification, such as HER2, and multiplex detection of two genes simultaneously. The development of the QMAGEX assay is an important first step toward detection of CTCs based on their genetic profiles.



Balaji Panchapakesan, Ph.D.

University of Delaware

Dr. Balaji Panchapakesan was awarded an FY05 Concept Award to develop nanostructures that are tagged with HER2- and

IGF1R-specific antibodies and that will change color from red to blue when aggregated. The nanostructures were designed to facilitate imaging and enable near-infrared pulses to selectively target breast cancer cells. The nanostructures developed in this study showed that molecular targeting with the antibodies resulted in high efficacy of breast cancer cell death.



Wende Kozlow, M.D.

University of Virginia

Dr. Wende Kozlow, recipient of an FY04 Multidisciplinary Postdoctoral Award, is using mouse models to explore the

potential use of bisphosphonates, inhibitors of bone resorption, to block the increase in bone turnover resulting from a reduction in estrogen in postmenopausal women treated with aromatase inhibitors (AIs). Dr. Kozlow hypothesized that high bone turnover in AI-treated patients increases

the development and progression of breast cancer bone metastases. Additionally, osteoporosis caused by estrogen deficiency may predispose high-risk women to the development of bone metastases. Thus, inhibiting high bone turnover may reduce the development and progression of breast cancer bone metastases.



Rita Nahta, Ph.D.

Emory University

In this FY05 Idea Award, Dr. Rita Nahta explores the fundamental mechanisms linking obesity with an increased risk of

breast cancer. In breast cancer patients' sera, the hormones IGF-I and leptin are found at high levels. Their corresponding receptors are also found to be overexpressed in the majority of breast cancer tumor samples. Studying the cellular pathways triggered by IGF-I and leptin in breast cancer cells may reveal how obesity causes an increase in breast cancer risk. Dr. Nahta has delineated pathways of intracellular communication for the hormones and is currently pursuing understanding of the molecular and biological consequences.



Rudolph Rull, Ph.D.

Northern California Cancer Center

Dr. Rudolph Rull, an FY07 Idea Award recipient, is undertaking the first evaluation of cadmium (Cd) exposure and risk of breast

cancer in the California Teachers Study (CTS), a large prospective cohort study of women. Cd, a trace element found naturally in the environment in a variety of sources, can be built up in the body over time, and limited but compelling evidence shows that high urinary Cd levels are associated with a higher risk of breast cancer. Dr. Rull plans to estimate dietary, environmental, and total exposure to Cd for all participants in the CTS cohort and evaluate whether exposure to Cd increases the risk of breast cancer. Exposure to Cd is potentially a modifiable risk factor, and lifestyle changes and environmental interventions to avoid exposure may help women control their risk.



Senthil Muthuswamy, Ph.D.
Cold Spring Harbor Laboratory
Dr. Senthil Muthuswamy, an
FY07 Era of Hope Scholar, is
working to unravel why some
early breast lesions progress

to invasive cancer while others remain benign. Premalignant breast lesions and malignant cancers exhibit significant changes in cell shape (polarity) and tissue architecture. Dr. Muthuswamy aims to identify and characterize the changes in polarity genes and polarity pathways and determine how these changes contribute to the progression to malignancy. Identification of clinically relevant alterations is likely to lead to new prognostic or therapeutic advances.



Christopher Haiman, Sc.D.
University of Southern California
FY07 Era of Hope Scholar
Dr. Christopher Haiman will lead
a large-scale collaborative effort
to identify novel mechanisms

for preventing and treating breast cancer in African Americans as well as in other populations. Dr. Haiman's team will perform a whole-genome association scan to identify genetic predictors of breast cancer in African American women as well as genetic variants that may contribute to aggressive breast cancer and that are disproportionately more common in African Americans. The findings in this study will significantly advance knowledge of the etiology of breast cancer among African Americans and lay the groundwork for the development of future preventive, early-detection, prognostic, and therapeutic measures.



Donald E. Ingber, M.D., Ph.D.
Children's Hospital, Boston
Dr. Donald E. Ingber, recipient
of an FY07 Innovator Award,
hypothesizes that cancer
is a disease of deregulated

developmental control and that the inductive properties of embryonic tissues can reverse cancer growth by altering the tumor microenvironment. He will lead a collaborative effort to determine

the mechanisms by which embryonic mammary mesenchyme induces breast carcinomas to differentiate into normal tissue. This knowledge will be applied to the development of a novel therapeutic system based on synthetic biomimetic materials that replicate the inductive property of embryonic tissues.



Michael G. Rosenfeld, M.D.
University of California, San Diego
Dr. Michael G. Rosenfeld,
recipient of an FY07 Innovator
Award, will explore the novel
observation that liganded

estrogen receptors (ERs) initiate rapid, broad alterations in nuclear architecture that create fundamental changes in gene regulation and establish sites for potential chromosomal rearrangements. He hypothesizes that estrogen-induced, specific noncoding RNAs in ER gene targets bind complexes required for rapid changes in nuclear architecture, presenting the potential for small interfering RNA-based therapeutics targeting breast cancer. His group will also examine whether common translocation and amplification events in cancer reflect long-distance interactions at specific hubs and whether these events can be interrupted by motor protein inhibitors and noncoding RNA transcripts.



Touching Lives and Accelerating Translation



Chanita Hughes-Halbert, Ph.D.
University of Pennsylvania

Dr. Chanita Hughes-Halbert has developed a Culturally Tailored Genetic Counseling (CTGC) protocol for African American women at increased risk for having a BRCA1 or BRCA2 mutation. An FY99 Linked Career Development Award has allowed Dr. Hughes-Halbert to address cultural beliefs and values regarding genetic testing for inherited cancer risk as well as cancer prevention and control in a medically underserved population. A comparison of culturally tailored genetic counseling versus the standard counseling protocol in African American women at risk for developing breast cancer was conducted. The study identified predictors of test result acceptance and assessed the outcomes of genetic counseling. Women who received CTGC had a greater level of satisfaction over those who received standard counseling. The CTGC protocol can also be applied to develop culturally tailored protocols for other populations and diseases.



Dr. Jae Gwan Kim, Ph.D.
University of California, Irvine
Dr. Jae Gwan Kim, an FY07 Era of Hope Postdoctoral Award recipient, is studying tumor oxygenation with respect

to tumor detection, efficacy of therapeutic interventions, and prediction of chemotherapeutic response. Using respiratory challenges to differentiate between normal and neoplastic tissues, a respiratory profile of tumors in animals will be created. This will allow Dr. Kim to further analyze how chemotherapeutic responses are modified due to respiratory challenges and if these challenges do affect treatments.



Cheng Liu, M.D., Ph.D.

The Scripps Research Institute

Legumain is a proteinase that is overexpressed in breast cancer tissues and that has been shown to promote

cellular migration and invasion of tumor cells to surrounding sites. FY04 Idea Award recipient Dr. Cheng Liu and colleagues have developed a cell-impermeable, tumor-activated prodrug, called legubicin (a derivative of doxorubicin). Preclinical in vivo studies showed that legubicin was targeted to and cleaved by legumain on the tumor cell surface, resulting in the release of doxorubicin in the tumor microenvironment and the localized killing of tumor cells while normal cells were largely spared from toxicity. Legubicin significantly reduced tumor metastases in mouse models of breast cancer. In collaboration with Dr. Rong Xiang, Dr. Liu developed a legumain-based DNA vaccine and tested it in mouse models of metastatic breast cancer. The effectiveness of legubicin in arresting and preventing metastases without myelosuppression and cardiac toxicity, as well as evidence supporting its improved efficacy and safety over doxorubicin, support the clinical development of legubicin as a therapeutic agent for breast cancer.



Ebrahim Delpassand, M.D.

RadioMedix, Inc.

Dr. Ebrahim Delpassand, recipient of an FY07 Idea Award, and his colleagues will develop a novel therapeutic radionuclide

carbohydrate-based agent to use as a metabolic-targeted radiotracer for systemic radionuclide therapy. Since tumor cells are known to have accelerated metabolic pathways, Dr. Delpassand hypothesizes that a radiolabeled carbohydrate will accumulate in hypermetabolic breast cancer cells and deliver lethal radiation resulting in tumor cell death. The goal of this type of therapy is to lethally target highly metabolic tumor cells while significantly reducing the systemic toxicity associated with conventional breast cancer treatment regimens.



David Kleinberg, M.D.

Baljit Singh, M.D.

New York University School of Medicine

Dr. David Kleinberg (pictured at top), an FY06 Synergistic Idea Award recipient, has partnered with Dr. Baljit Singh (pictured at bottom) to develop a treatment that does not have antiestrogenic side effects like tamoxifen does (e.g., endometrial cancer, blood clots, and hot flashes), but that



will, nevertheless, prevent breast cancer in high-risk women. The investigators will utilize the somatostatin analog, SOM230, in this study. This drug acts by inhibiting insulin-like growth factor-1 (IGF-1) upstream of estrogen and progesterone in the breast without affecting the estrogen metabolism elsewhere, and it has the potential to be a better chemopreventive agent. A translational proof-of-principle trial in 20 premenopausal women to determine if SOM230 will cause cellular changes that reflect blockage of IGF-1 activity and, therefore, estrogen and progesterone actions (e.g., inhibition of cell division and increase in apoptosis), has started.



Timothy Clay, Ph.D.

Duke University

Dr. Timothy Clay, recipient of an FY05 Clinical Translational Research Award, will target HER2-positive metastatic

breast cancer with a novel viral vector vaccine combination. Adenovirus and alphavirus constructs will deliver the human HER2 gene and stimulate the immune system to attack the tumor. Each vaccine will be tested independently in a Phase I trial for safety and in combination with a heterologous vector prime-boost protocol in a Phase I/II trial. The combination of both vaccines should greatly enhance stimulation of immune cells to destroy cancer cells and produce antibodies to many targets on the HER2 protein, providing a “one-two punch” for the increased anti-tumor immune response detectable in breast cancer patients.



The Program Today

FY07 Summary

A congressional appropriation of \$127.5M in FY07 was directed to the BCRP. The program offered 11 award mechanisms to contribute to the program’s vision of eradicating breast cancer. A total of 3,029 proposals were received across mechanisms and 293 awards were made, as shown in Table II-1. The portfolio developed by the FY07 BCRP is depicted in Figure II-2.

Table II-1. Funding Summary for the FY07 BCRP

Categories and Award Mechanisms	Proposals Received	Awards	Investment
Innovative Research			
Era of Hope Scholar	16	5	\$19,127,067
Idea	869	69	\$31,572,653
Impact	86	0	\$0
Innovator	5	2	\$15,581,740
Innovator Research Project	8	4	\$13,986,128
Synergistic Idea	285	29	\$11,423,662
Concept	1,407	83	\$9,343,676
Training/Recruitment			
Era of Hope Postdoctoral	22	8	\$2,659,229
HBCU/MI Partnership Training	3	0	\$0
Multidisciplinary Postdoctoral	47	3	\$1,722,564
Predocctoral Traineeship	281	90	\$8,264,401
TOTAL	3,029	293	\$113,681,120

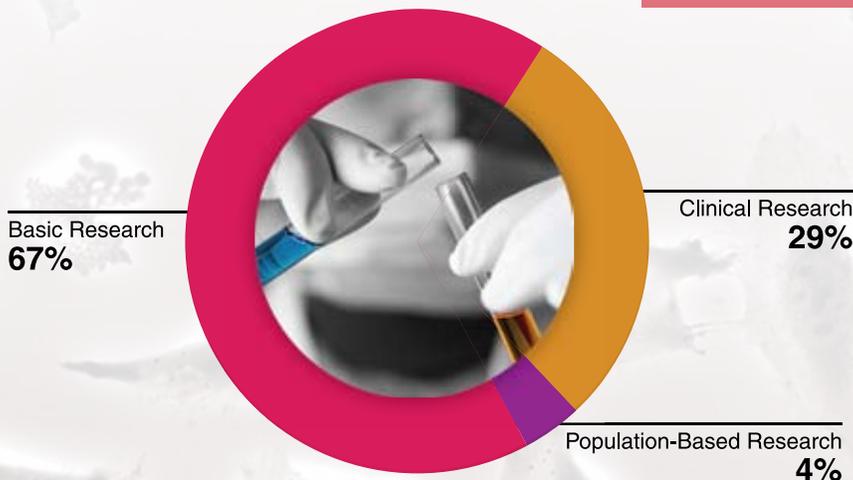
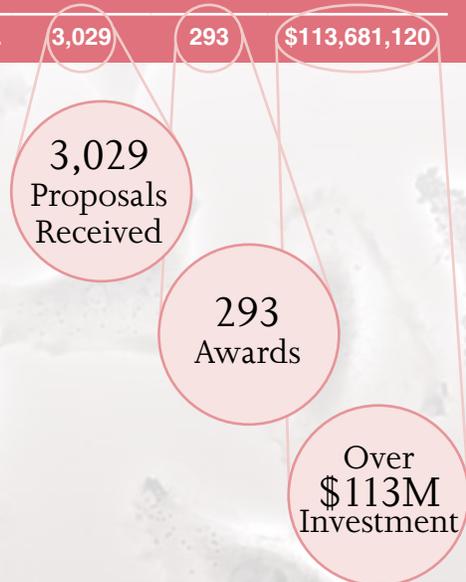


Figure II-2. FY07 BCRP Portfolio by Research Area



The Vision for FY08

Congress appropriated \$138M to continue the BCRP in FY08. Nine award mechanisms were offered to contribute to the program's vision of eradicating breast cancer. These mechanisms span three categories: clinical research, innovative research, and training/recruitment, as illustrated in Table II-2. A total of 1,775 proposals were received, and 175 awards have been recommended for funding to date. The congressional appropriations and investment strategy executed by the BCRP for FY07 and FY08 are summarized in Appendix B, Table B-1.

Table II-2. Award Mechanisms Offered and Proposals Received for the FY08 BCRP

Categories and Award Mechanisms	Proposals Received
Clinical Research	
Clinical Translational Research	11
Innovative Research	
Era of Hope Scholar	10
Idea	980
Impact	60
Innovator	7
Synergistic Idea	328
Training/Recruitment	
Era of Hope Postdoctoral	44
HBCU/MI Partnership Training	4
Predoctoral Traineeship	331
TOTAL	1,775

The BCRP Team

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Program Manager

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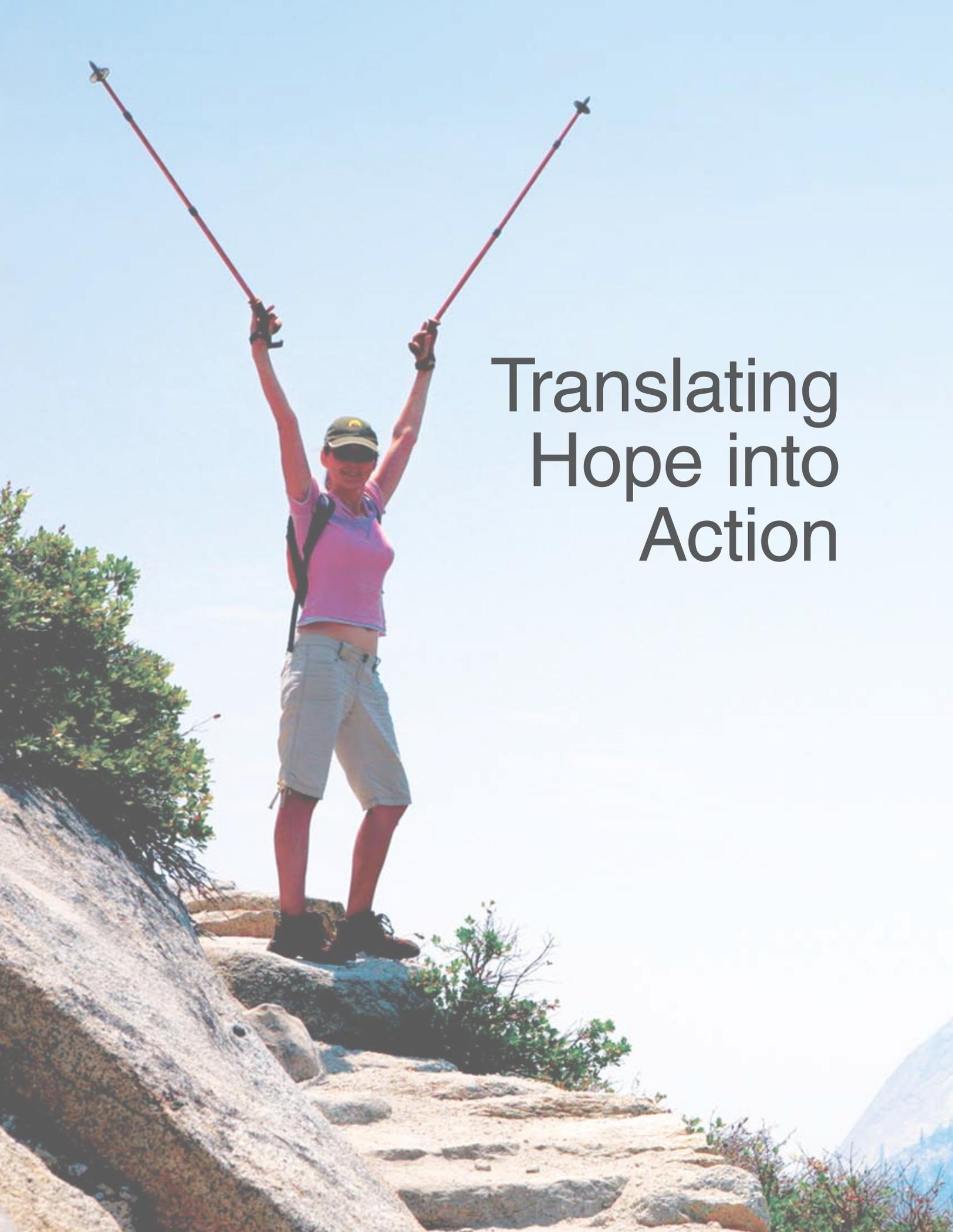
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Herbert Avila, Ph.D.
Peer Review Coordinator
SRA International



Translating Hope into Action

- ❖ **HERCEPTIN®**
(Dr. Dennis Slamon)
Provided the early funding for research leading to development of monoclonal antibodies against the HER2/neu receptor.
- ❖ **SENTINEL LYMPH NODE BIOPSY** (Dr. Lorraine Tafra and Dr. Kathryn Verbanac)
Supported clinical trial testing the validity and accuracy of sentinel lymph node biopsy; current standard of care for disease staging.
- ❖ **MARGARET DYSON FAMILY RISK ASSESSMENT PROGRAM** (Dr. Mary Daly)
Evolved from BCRP funding for establishment of the Fox Chase Network Breast Cancer Risk Registry, this program serves a large urban area with a range of risk assessment, screening, and preventive services for high-risk patients and families.
- ❖ **MOLECULAR BREAST IMAGING** (Dr. Carrie Hruska)
Supported studies showing that molecular breast imaging has comparable sensitivity and specificity to magnetic resonance imaging and may be a more cost-effective alternative for women who have increased risk and dense breast tissue.

...to Achieve Our Vision

- ❖ **ATLAS TRIAL**
(Dr. Richard Peto)
Supported initiation of the Phase III clinical trial, Adjuvant Tamoxifen Longer Against Shorter, the largest breast cancer treatment trial ever undertaken that is examining the optimal duration of adjuvant tamoxifen in early breast cancer.
- ❖ **DUCTAL LAVAGE**
(Dr. Susan Love)
Supported the development of a minimally invasive diagnostic procedure for detecting precancerous and cancerous breast cells in fluid from the breast ducts.
- ❖ **CAROLINA MAMMOGRAPHY REGISTRY**
(Dr. Bonnie Yankaskas)
Funded the infrastructure for a population-based mammography registry as a resource for studying community-based screening; now a member site for the NCI Breast Cancer Surveillance Consortium.
- ❖ **3D CELL CULTURE SYSTEM AND ASSAY** (Dr. Mina Bissell)
Supported the development of a 3D culture system and assay to study breast cancer heterogeneity and the role of the tissue microenvironment in breast cancer development.
- ❖ **shRNA LIBRARIES**
(Dr. Gregory Hannon and Dr. Stephen Elledge)
Supported the development of gene silencing and genetic screening strategies to identify new potential therapeutic targets.
- ❖ **DISPARITY IN MINORITY POPULATIONS**
(Dr. Funmi Olopade)
Supported early studies examining how genetic risk factors contribute to the high incidence and mortality from breast cancer in young African American women.
- ❖ **HOMING PEPTIDES**
(Dr. Erkki Ruoslahti)
Funded the identification of homing peptides that specifically home to breast tumors and have the potential to deliver drugs or treatments to tumors with higher efficacy and reduced side effects.
- ❖ **HER2/neu VACCINE**
(Dr. Constantin Ioannides)
Funded the characterization of immunodominant epitopes in breast cancer; led to development of E75 peptide vaccine, which is now entering Phase III clinical trials.