



## III. Breast Cancer Research Program

**Vision:** To eradicate breast cancer.

**Mission:** To foster new directions, address neglected issues, and bring new investigators into the field of breast cancer research.

**Appropriations for Peer Reviewed Research:** \$1.218B in FY92–01, \$150M in FY02, and \$150M in FY03 in congressional funds; \$5.5M in FY99–FY01, \$1.5M in FY02, and \$2.2M in FY03 from the Stamp Out Breast Cancer Act

**Funding Summary:** 3,217 awards from the FY92–01 appropriations; 454 awards from the FY02 appropriation; ~325 awards anticipated from the FY03 appropriation

*...shaping the future of health care  
to prevent, control, and cure diseases.*



# Breast Cancer Research Program

## *The Disease*

Cancer of the breast is the most commonly diagnosed non-skin cancer in women. One out of every eight women will develop breast cancer in her lifetime. In 2003, approximately 211,300 women in the United States will receive a diagnosis of invasive breast cancer and 55,700 women will be diagnosed with breast cancer in situ. In addition, although male breast cancer is rare and accounts for less than 1 percent of all breast carcinomas in the United States, about 1,300 new cases of breast cancer will be diagnosed in men this year. Breast cancer is the second leading cause of death in women. Approximately 39,800 women and 400 men are projected to die from breast cancer this year.<sup>1</sup>

## *Program Background*

The Department of Defense (DOD) Breast Cancer Research Program (BCRP) was established in fiscal year 1992 (FY92) by Appropriations Conference Committee Report No. 102-328, which provided \$25 million (M) for research on breast cancer screening and diagnosis for military women and family members. In 1993, grassroots advocates led by the National Breast Cancer Coalition influenced public policy, which led to a FY93 \$210M congressional appropriation for peer reviewed breast cancer research. The U.S. Army Medical Research and Materiel Command sought the advice of the National Academy of Sciences (NAS) to develop a sound investment strategy for the FY93 congressional appropriation. An NAS Institute of Medicine committee thoroughly studied the major considerations and issued a report that outlined a two-tier review process and investment strategy for the \$210M appropriation. (See Section I for additional details on these two recommendations.) This two-tier review process and annual investment strategy was implemented by the BCRP and subsequently adapted by other Congressionally Directed Medical Research Programs (CDMRP).

The BCRP is the second largest funder of extramural breast cancer research in the world. From FY92 to FY03, the BCRP has managed almost \$1.52 billion (B) to fund peer reviewed breast cancer research. Through FY02, 3,671 awards have been made across the categories of research, training/recruitment, and research resources.

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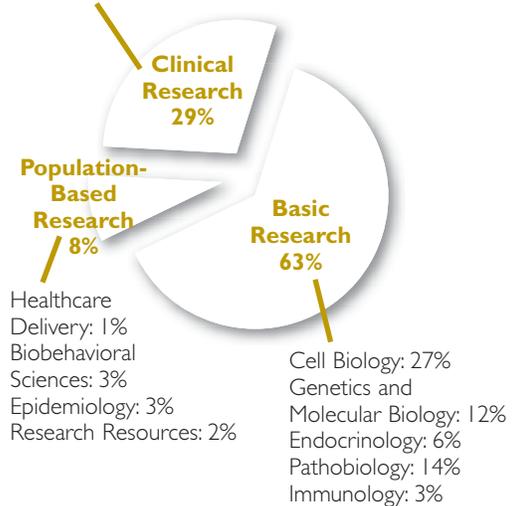
<sup>1</sup> American Cancer Society - Cancer Facts and Figures 2003.

## The Fiscal Year 2002 Program

In FY02, Congress appropriated \$150M for peer reviewed breast cancer research. The BCRP continued to emphasize innovative, high-risk/high-gain research; training new investigators; and support for translational research. In FY02, 3,323 proposals were received, and 454 were funded. Table III-I provides a summary of the award categories and mechanisms in terms of number of proposals received, number of awards made, and dollars invested. As illustrated in Figure III-I, the portfolio of research supported by the FY02 BCRP is diverse.

The FY02 BCRP program offered three research award mechanisms for investigators to explore innovative questions in breast cancer; Concept, Exploration, and Idea Awards. Collectively, 276 awards were made to foster innovation in breast cancer research. Six training/recruitment award mechanisms were offered to promote training and mentoring of breast cancer researchers, and collectively 170 awards were made. (Additional

Complementary and Alternative Medicine: 1%  
 Clinical and Experimental Therapeutics: 17%  
 Detection and Diagnosis: 9%  
 Primary Prevention: 2%



**Figure III-I. FY02 BCRP Portfolio by Research Area**

**Table III-I. Funding Summary for the FY02 BCRP**

Category and Award Mechanism	Number of Proposals Received	Number of Awards	Investment
<b>Research</b>			
Biotechnology Clinical Partnership	3	1	\$3.9M
Concept	1,440	154	\$17.6M
Clinical Translational Research	15	3	\$9.0M
Exploration	200	20	\$4.4M
Idea	1,084	102	\$47.8M
<b>Research Resources</b>			
Collaborative-Clinical Translational Research	3	0	0.0
Breast Cancer Center of Excellence Awards	10	3	\$19.6M
<b>Training/Recruitment</b>			
Clinical Research Nurse	24	11	\$1.9M
HBCU/MI Partnership Training	5	2	\$1.8M
Physician-Scientist Training	18	6	\$3.0M
Predoctoral Traineeships	227	82	\$7.1M
Postdoctoral Traineeships	238	62	\$10.3M
Undergraduate Summer Training Program	12	7	\$1.1M
<b>Innovator</b>	44	1	\$3.0M
<b>Total</b>	<b>3,323</b>	<b>454</b>	<b>\$130.5M</b>



information on the Undergraduate Summer Training Program Award can be found in the box story on page III-11.) The program continued to build research resources through Breast Cancer Center of Excellence Awards (3 awards). Finally, one Innovator Award was made to provide an accomplished and visionary researcher the funding to pursue groundbreaking breast cancer research, and one Biotechnology Clinical Partnership Award was made to establish a partnership with a biotechnology company to perform two clinical trials. (See related box stories on both awards.)

### *The Vision for the Fiscal Year 2003 Program*

Congress again appropriated \$150M to continue the BCRP in FY03. Nine award mechanisms were offered (all of which were previously established by the program) to continue the BCRP's investment in innovation, training, and translational research. A total of 1,543 proposals was received, as detailed in Table III-2, and approximately 325 awards are expected. Appendix B, Table B-1 summarizes the congressional appropriations and the investment strategy executed by the BCRP for FY02–03.



**Table III-2. Award Mechanisms Offered and Proposals Received for the FY03 BCRP**

<b>Category and Award Mechanism</b>	<b>Number of Proposals Received</b>
<b>Research</b>	
CTR	16
Idea	935
<b>Research Resources</b>	
Breast Cancer Center of Excellence Awards	12
<b>Training/Recruitment</b>	
Clinical Research Nurse	13
HBCU/MI Partnership Training	2
Physician-Scientist Training	10
Predocctoral Traineeships	272
Postdoctoral Traineeships	269
<b>Innovator</b>	14
<b>Total</b>	<b>1,543</b>

## *Scientific Outcomes and Advances*

The BCRP research portfolio comprises many different types of projects, including support for innovative ideas, facilitation of clinical trials, and training of breast cancer researchers. The following projects represent a sample of the many exciting developments that are resulting from research funded by the BCRP.

### **Tumor-Mediated Formation of Lymphatic Vessels:**

#### **Building Roads Out**

#### **Mihaela Skobe, Ph.D., Mt. Sinai School of Medicine**

Over the last decade, considerable attention in the field of cancer research has focused on angiogenesis, or formation of new blood vessels. Current drug design strategies have centered on ways to hold this process in check, thereby limiting or eliminating the blood supply to tumors. BCRP Concept awardee, Dr. Mihaela Skobe, has discovered that angiogenesis is not the only vessel formation process occurring in the tumor microenvironment. Lymphangiogenesis, or formation of lymphatic vessels, is also an active process mediated by tumors. This finding is significant because the lymphatic system is the main conduit by which breast cancer metastasis occurs. Historically, controversy has existed as to whether tumor lymphangiogenesis occurs; however, work from Dr. Skobe's lab puts this debate to rest. The group has also discovered that a specific protein, called VEGF (vascular endothelial growth factor)-C, appears to be involved. When breast tumor cells that overproduce this protein are implanted into mice, lymphangiogenesis within the tumors increases, as well as the incidence of metastasis to the lymph nodes and lungs. Additionally, increased lymphangiogenesis means more metastasis, further underscoring the importance of the lymphatic vessel system in tumor cell dissemination. This novel discovery has important implications since it offers a new target for therapy development to control the spread of breast cancer.

For additional reading about this work, please refer to the following publications:

- ◆ Skobe M et al. 2001. Induction of tumor lymphangiogenesis by VEGF-C promotes breast cancer metastasis. *Nature Med.* 7:192–198.
- ◆ Swartz MA and Skobe M. 2001. Lymphatic function, lymphangiogenesis, and cancer metastasis. *Microscopy Res.* 55:92–99.



"Many measure achievements by numbers. In the battle against Breast Cancer, it is not about numbers but about the lives of our mothers, our daughters, our sisters. It's about transforming despair into hope. Our program strives to push the frontiers of science forward to discover the gene, the protein, or the drug that will lead to a new therapy or, ultimately, a cure. We always remember, though, it isn't about the science—how many published papers—but about saving someone's mother, sister, or daughter."

Donna M. Kimbark, Ph.D.  
Grants Manager  
Breast Cancer Research Program



- ◆ Cassella M and Skobe M. 2002. Activation of lymphatic vessels in cancer. *Ann. NY Acad. Sci.* 979:120–130.
- ◆ Podgrabska S et al. 2002. Molecular characterization of lymphatic endothelial cells. *Proc. Natl. Acad. Sci. USA* 99:16069–16074.

**Alternative Medicines Open New Doors in Traditional Breast Cancer Research: Targeted Therapy for Tumor Angiogenesis and Cancer**  
**Mamoru Shoji, M.D., Dennis C. Liotta, Ph.D., and James P. Snyder, Ph.D., Emory University**

A resurgent interest in age-old remedies for ailments has spurred the medical research community to explore alternative methods of treatment. Therapies exploiting the properties of curcumin, the active ingredient in the spice turmeric, have shown increased promise in the last few years. Recently, researchers reported curcumin has a marked antitumor effect on cancers of the skin, colon, prostate, and breast. One method by which curcumin works is through blocking the synthesis of factors involved in a process called angiogenesis, the generation of new blood vessels. This mechanism of action cuts off the blood supply to the tumor cells, which leads to cell death. Drs. Shoji, Liotta, and Snyder of Emory University (Atlanta, Georgia) are developing synthetic analogs of curcumin for delivery specifically to tumors of the breast and to the blood vessels that nourish the tumors. In their ongoing study, a curcumin analog has been linked chemically to a carrier molecule that targets breast cancer cells and tumor-associated blood vessels (vascular endothelial cells). The synthetic complex kills the tumor but does not kill normal breast cells and normal blood vessels (vascular endothelial cells) in tissue culture. Results demonstrate an astounding ten-fold potency in antitumor activity over the chemotherapeutic agent cisplatin. The outcome suggests that by using a carrier-tagged analog of curcumin, tumor cells and the blood vessels that feed tumors can be selectively attacked and killed, overcoming toxic effects of other nonspecific anticancer and antiangiogenic agents. While tumor-directed therapies have the potential of decreasing the side effects of chemotherapy regimens, alternative medicines give a fresh look to an ever-pressing problem. The marriage of these two approaches may be a powerful new tool in the fight against breast cancer.

**Advancing Breast Cancer Diagnosis through New Imaging Techniques**  
**L. Dean Chapman, Ph.D., Illinois Institute of Technology**

Breast cancer survival can be highly dependent on detection and therapeutic intervention. By enhancing present imaging techniques, it is hoped that tumors may be detected during the earliest stages of development and that these advanced imaging techniques could decrease the need for invasive diagnostic procedures such as needle biopsy. A novel technique called Diffraction Enhanced Imaging is being studied for its usefulness in breast cancer diagnosis. Dr. L.D. Chapman of the Illinois Institute of Technology (Chicago, Illinois) co-developed this method in medical imaging and is now applying it to breast cancer studies. By expanding the capabilities of Diffraction Enhanced Imaging, more information has been extracted, thus leading to improved imaging of the complex tissue matrix making up the breast. This new technique allows for high-contrast images to be acquired by using refracted and scattered x-ray beams in addition to the absorption of conventional mammography. These advances in medical imaging will actually permit a dose reduction of x-rays since the optimization of the refraction and scatter contrast occur where absorption (or delivered dose) is low. Additionally, these studies show a correlate of Diffraction Enhanced Imaging with conventional histology diagnosis from breast biopsy samples. This technical development holds new promise for early detection of breast cancer.

Further information about this research appears in the following publications:

- ◆ Dilmanian FA, Zhong Z, Ren B, et al. 2000. Computed tomography of x-ray index of refraction using the Diffraction Enhanced Imaging method. *Phys. Med. Biol.* 45(4): 933–946.
- ◆ Pisano ED, Johnston RE, Chapman D, et al. 2000. Human breast cancer specimens: Diffraction Enhanced Imaging with histologic correlation improved conspicuity of lesion detail compared with digital radiography. *Radiology* 214(3): 895–901.
- ◆ Hasnah MO, Zhong Z, Oltulu O, et al. 2002. Diffraction enhanced imaging contrast mechanisms in breast cancer specimens. *Med. Phys.* 29(10): 2216–2221.

**FY02 Biotechnology Clinical Partnership Award Recipient**

The Biotechnology Clinical Partnership Award was designed in FY02 by the BCRP to facilitate clinical trials in breast cancer; and Dr. Olaf G. Wilhelm was the first recipient of this award. Dr. Wilhelm is co-founder and CEO of Willex AG, Munich (Germany), a biopharmaceutical company dedicated to the development of novel cancer therapies for the treatment of solid tumors. Dr. Wilhelm will be using this award to clinically evaluate the use of WX-UK1, an inhibitor of urokinase-type plasminogen activator (uPA), for the treatment of breast cancer. uPA is a tumor-related enzyme involved in metastasis and serves as a prognostic biomarker for breast cancer. WX-UK1 has been shown to reduce tumor growth and prevent metastasis in animal models.

Dr. Wilhelm will be performing two clinical trials (Phase I and Phase 2) using WX-UK1 in collaboration with the Fox Chase Cancer Center in Philadelphia, Pennsylvania and believes this research will move us one step closer to preventing the spread of primary breast cancer in high-risk patients.



"The DOD program has specialized in finding those new, 'out-there' innovative ideas, which can potentially advance the field forward in leaps, not steps. I have been particularly impressed with the Program's dedication to difficult issues, the development of synergistic research teams, and the translation of basic research findings toward the clinic."

Patricia Steeg, Ph.D., Chief,  
Women's Cancer Section,  
National Cancer Institute;  
FY03 Integration Panel Chair



### **Managing Cancer Pain through Gene Therapy**

**J. Yang, M.D., Ph.D., Presbyterian Hospital, Columbia University**

Traditional pain management for patients with advanced breast cancer has relied on the prescription of drugs such as morphine. Treatments used for chronic pain are self-limiting due to side effects and efficacy issues. Patients develop tolerance to opiates and must be prescribed larger quantities of the drug to relieve debilitating pain. Current published studies suggest a role for many intracellular molecules in mediating pain signaling. In an experimental gene therapy study by Dr. J. Yang, formerly of the University of Rochester (Rochester, New York), antisense oligonucleotides to one such molecular mediator of pain, protein kinase C-g, were shown to inhibit signaling pain pathways in the rat animal model. These 'backward' gene sequences are able to block chronic pain by silencing the active conversion of genes to their products, proteins. An analgesic effect of antisense oligonucleotides to protein kinase C-g was observed when an inflammatory pain response was present in rats. Since cancer pain is associated with a strong neuropathological signaling component in nerve cells, this study demonstrates the significance of gene therapy in inhibiting pain by blocking the production of proteins that carry pain signals. The broad therapeutic ramifications in pain management for advanced breast cancer and other chronic pain syndromes are clear.

For additional reading about this work, please refer to the following publications:

- ◆ Wu C, Garry M, Zollo R, and Yang J. 2001. Novel targets for gene therapy in the management of pain, Part I: Strategies and methods. *Anesthesiol.* 94:1119–1132.
- ◆ Wu C, Garry M, Zollo R, and Yang J. 2001. Novel targets for gene therapy in the management of pain, Part II: Molecular targets. *Anesthesiol.* 95:216–240.

**Predictors of Follow-up after an Abnormal Mammogram**

**Alexis Bakos, Ph.D., National Cancer Institute**

An estimated 60 percent of women who have an abnormal mammogram do not return for further medical evaluation. BCRP investigator Dr. Alexis Bakos, while attending Johns Hopkins University as a graduate student, conducted this study to determine why some women with abnormal mammograms do not return for evaluative follow-up care. Cox's Interaction Model of Client Health Behavior was used as a framework. The study sample included 75 women; 44 women who returned for diagnostic follow-up and 31 women who had not returned were interviewed using a telephone survey method to determine which variables predicted follow-up care and most accurately classified women into either category. Those who returned for diagnostic follow-up after their abnormal mammogram cited four major reasons: (1) health promotion, (2) influence of family, (3) influence of others, and (4) fear as a motivator. Those who did not return for diagnostic follow-up cited six major reasons: (1) avoidance, (2) lack of health insurance coverage, (3) inconvenience, (4) stress of an illness, (5) denial of the need to return, and (6) fear as a barrier. A major outcome of this study was identifying factors related to the decision of whether to obtain follow-up care after an abnormal



**FY02 Innovator Award Recipient**

The Innovator Award was first offered by the BCRP in FY01 to provide accomplished and visionary scholars from any field of study the freedom to pursue creative, potentially groundbreaking research that could end the campaign against breast cancer. Dr. Naomi Halas of Rice University was the sole recipient of the FY02 Innovator Award. Dr. Halas is a professor of chemistry and inventor of the nanoshell, an optically active nanoparticle. This nanoparticle shows intense absorption, light scattering, and tunable emission properties that Dr. Halas believes will be ideal for breast cancer detection and treatment. Dr. Halas has developed a multidisciplinary team of researchers, including clinicians, biologists, and engineers, to exploit the unique properties of nanoshells to identify and destroy breast cancer cells. The nanoshells will be designed to specifically absorb near infrared light, light at wavelengths that penetrate several inches through human tissue. The nanoshells will be attached to proteins that specifically bind to cancerous cells. Once bound, they will be illuminated with near infrared light through the skin. The illuminated nanoshells act as highly localized heat sources that thermally destroy the cancerous cells without harming the surrounding normal tissue. Thus, these engineered nanoparticles have the potential to radically transform how breast cancer is detected and treated. Rice University recently highlighted Dr. Halas as the recipient of the Innovator Award in a news release that can be accessed on-line at <http://riceinfo.rice.edu/projects/reno/Newsrel/>



mammogram. This information can be used to design intervention strategies to increase the number of women who return for diagnostic follow-up.

### **Novel Amplification-Dependent Oncogenes in Breast Cancer Progression**

**Fergus J. Couch, Ph.D., Mayo Foundation, Rochester, Minnesota**

Dr. Fergus J. Couch and other investigators at the Mayo Foundation in Rochester have been isolating novel oncogenes from an amplification region on chromosome 17q23 because regions of gene amplification have been shown to contribute to tumor progression. Physical mapping of the amplification region yielded several peaks of gene duplication in tissue culture cells and in human breast cancer tumors. The study also showed that 42 percent of all breast tumors contained an amplification of at least one target gene and that gene amplification was also found in early-stage breast tumors. The relationship of the genes in these amplification regions to hereditary breast cancer was investigated. One gene of interest was amplified in breast tumors that exhibit BRCA1 and BRCA2 mutations, while a different gene was associated with sporadic breast cancers. The investigators set out to determine whether overexpression of the amplified gene could play an important role in tumor progression. Eight of the candidate genes were found overexpressed in human breast cancer cell lines, and four of the genes exhibited oncogenic properties. The finding of an amplification region whose genes are overexpressed in breast cancer has important implications in breast cancer prognosis and may have implications in the development of novel immunological cancer treatments.

Additional information about this research can be found in the following publications:

- ◆ Sinclair CS, Adem C, Soderburg C, et al. 2002. TBX2 is preferentially amplified in BRCA1 and BRCA2 related breast tumors. *Cancer Res.* 62(13):3587–3591.
- ◆ Sinclair CS, Rowley M, Naderia A, et al. 2003. The 17q23 amplicon and breast cancer. *Breast Cancer Res. Treat.* 78(3):313–322.

## Summary

Since 1992, the BCRP has been responsible for managing almost \$1.52B in appropriations, which has resulted in 3,671 awards for FY92–02. The focus of the program spans a spectrum of research, including basic, clinical, behavioral, environmental sciences, and alternative therapy studies. The BCRP offers awards that benefit the current needs of the patient and research communities, while not duplicating efforts of other agencies. Research highlights, award data, and abstracts of funded BCRP proposals can be viewed on the CDMRP website (<http://cdmrp.army.mil>).

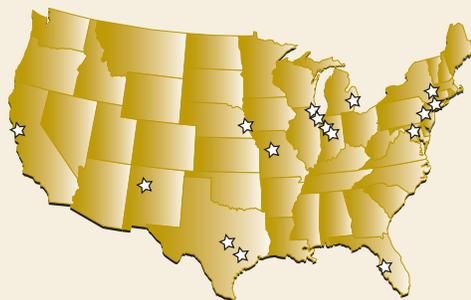


### Stimulating Talented New Investigators

A closer look at the BCRP Undergraduate Summer Training Program award mechanism reflects the program's investment in stimulating new investigators in breast cancer research. First offered in FY00, this award mechanism is intended to train talented undergraduates in breast cancer research. A total of 16 Undergraduate Summer Training Programs have been supported across the country from FY00 to FY02. These programs are providing exciting and meaningful education and training opportunities for undergraduate students at an important career decision-making point. It is anticipated that students participating in these BCRP-supported training programs will continue to contribute their talents to the field of breast cancer. Efforts are under way to track the students' future careers and the effectiveness of the program for initiating careers in breast cancer research.

### FY00-02 Undergraduate Summer Training Program Award Recipients

Albany Medical College  
Wayne State University  
University of Texas Health Science Center at San Antonio  
University of Nebraska  
University of Missouri, Columbia  
University of Chicago  
University of New Mexico  
University of Pennsylvania  
Purdue University



University of Illinois  
University of Maryland, Baltimore County  
University of South Florida  
Baylor College of Medicine  
Methodist Research Institute at Clarian Health  
E.O. Lawrence Berkeley National Laboratory/  
University of California, Berkeley  
Stevens Institute of Technology

## *Fiscal Year 2003 Integration Panel Members*

**Patricia S. Steeg, Ph.D. (Chair)**

National Cancer Institute

**Lynn M. Matrisian, Ph.D.  
(Chair Emeritus)**

Vanderbilt University School of  
Medicine

**M. Carolina Hinestrosa, M.A.,  
M.P.H. (Chair Elect)**

Nueva Vida

**Anna D. Barker, Ph.D.  
(Executive Committee)**

National Cancer Institute

**Frances M. Visco, Esq.  
(Executive Committee)**

National Breast Cancer Coalition

**Leslie Bernstein, Ph.D.**

Keck School of Medicine of the  
University of Southern California

**Laurie L. Fajardo, M.D.**

University of Iowa Health Care

**Barbara A. Given, F.A.A.N.,  
Ph.D.**

Michigan State University College  
of Nursing

**Peter A. Jones, Ph.D., D.Sc.**

University of Southern California  
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**Laurence N. Kolonel, M.D.,  
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Hawaii, University of Hawaii

**Ngina Lythcott, Dr.P.H.**

National Black Women's Health  
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**Daniel Medina, Ph.D.**

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**Abram Recht, M.D.**

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**Rosemary Rosso, J.D.**

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**Geoffrey M. Wahl, Ph.D.**

The Salk Institute for Biological  
Studies