

CDMRP

II. Breast Cancer Research Program

TRAILBLAZING

Vision

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

The Breast Cancer Research Program (BCRP) has managed over **\$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 blazing a trail toward the eradication of breast cancer.

BCRP Making Headlines



- ❖ **Molecular Atlas Provides New Tool for Understanding Estrogen-Fueled Breast Cancer**
Dana-Farber Cancer Institute Press Release, October 2, 2006
- ❖ **Fox Chase Cancer Center Researchers Identify Key Gene That May Be a Marker of Breast Cancer Metastasis**
Fox Chase Cancer Center News Release, April 23, 2007
- ❖ **Hamilton College Researchers Discover New Molecules with the Potential to Treat Breast Cancer**
Hamilton College News Release, May 4, 2007
- ❖ **Combined Screening Approach Leads to Discovery of Gene Linked to Breast Cancer**
Dana-Farber Cancer Institute News Release, June 14, 2007
- ❖ **Mayo Clinic-Led Study Improves Breast Cancer Risk Prediction in Women with Atypia**
Mayo Clinic, Rochester News Release, June 29, 2007
- ❖ **Biodesign Institute Leads Innovative Project to Prevent Breast Cancer, \$7.5 Million Department of Defense Award Ramps Up ASU, Mayo Clinic Collaboration to Develop Cancer Vaccine**
Mayo Clinic, Scottsdale News Release, July 9, 2007

The Disease

Breast cancer is the most commonly diagnosed non-skin cancer in women—accounting for 32 percent of all cancers in women.

- ❖ One in eight women will develop breast cancer in her lifetime.
- ❖ It is estimated that approximately 178,480 women in the United States will be diagnosed with invasive breast cancer in 2007.
- ❖ It is estimated that approximately 62,030 women in the United States will be diagnosed with breast cancer in situ in 2007.
- ❖ While breast cancer in males is rare, it is estimated that 2,030 new cases of male breast cancer will be diagnosed in 2007.
- ❖ More than 40,000 women and men are projected to die from breast cancer this year.
- ❖ The rates of invasive and in situ breast cancer have stabilized, and the death rates from breast cancer have decreased steadily over the past few years.¹

¹ American Cancer Society, *Cancer Facts and Figures*, 2007.

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.



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 average risk, asymptomatic women may help them detect breast cancer early.

Mammography

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

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.

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.



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Program Background

In fiscal year 1992 (FY92), the Department of Defense (DOD) BCRP was established 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 their family members. The following year, grassroots advocates led by the National Breast Cancer Coalition influenced public policy, which led to an FY93 congressional appropriation of \$210M for peer-reviewed breast cancer research. As success of the program and persistent advocacy efforts followed, Congress continued to appropriate

targeted funds to the BCRP totaling approximately \$2.09B through FY07 (see Figure II-1, BCRP Funding History). Throughout this time, the program has been a forerunner in filling the unique needs and gaps of the scientific and advocacy communities into specific award mechanisms, as depicted in Figure II-2.



Frances M. Visco, Esq.
National Breast Cancer Coalition
BCRP Integration Panel
Executive Committee Member-at-Large

“The National Breast Cancer Coalition is enormously proud of its role in the creation and continuation of the BCRP. This is a unique program for many reasons; we think the most significant reason is that breast cancer consumers are given the opportunity to collaborate at all levels of the program including review panels. We, along with clinicians and scientists, and the military, are working to shape some of the most innovative breast cancer research in this country.”

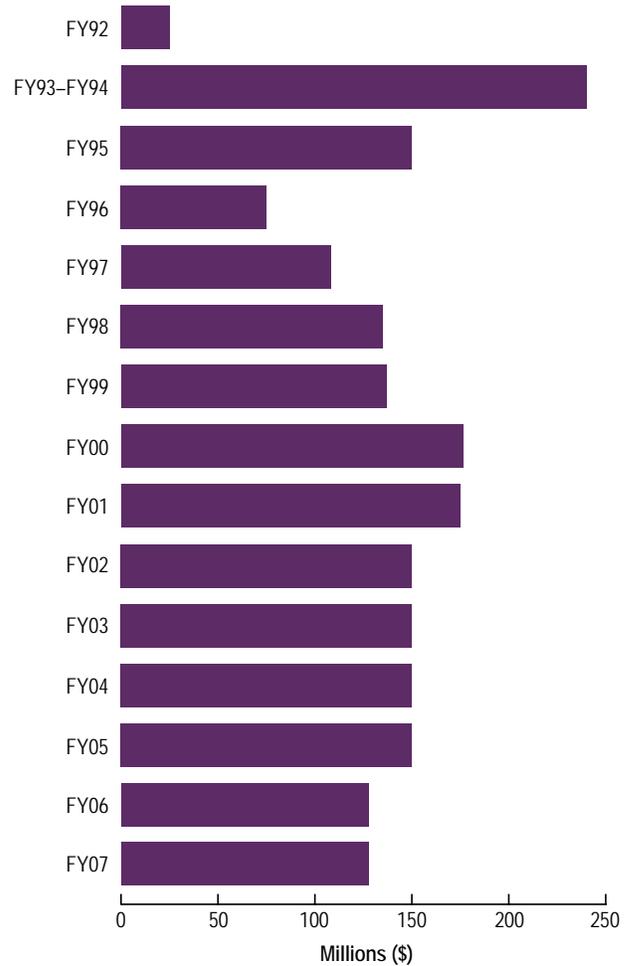


Figure II-1. BCRP Funding History

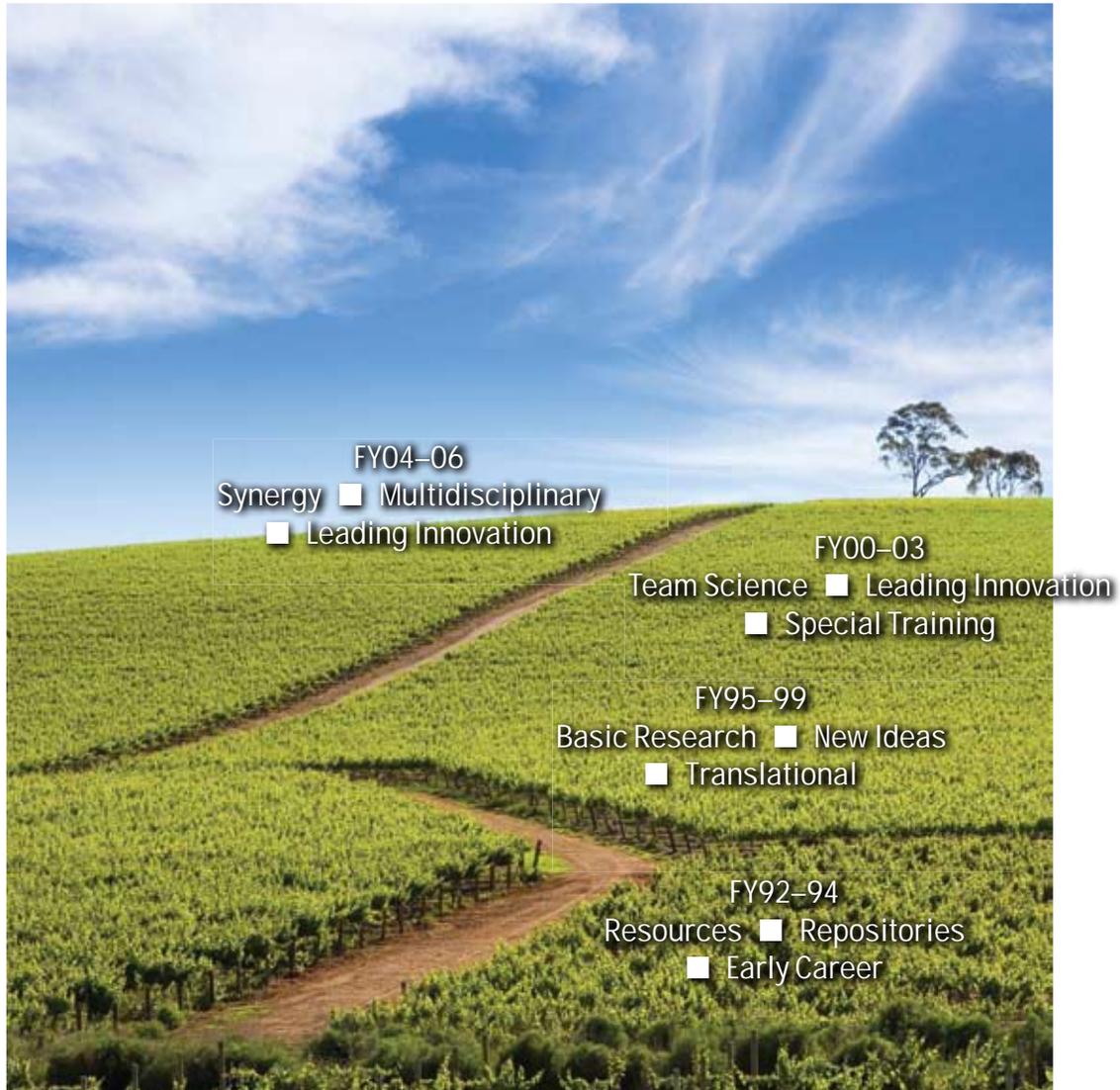


Figure II-2. Sampling of BCRP Award Mechanisms over the Years

BCRP Award Mechanisms: Filling Research Gaps and Creating New Paths

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.

Blazing the Trail

The BCRP has embraced an ambitious vision—to eradicate breast cancer. The realization of this vision requires many people working collectively together. Thus, the success of the BCRP can be attributed to the combined knowledge and dedication of many

people—from scientists and research managers to those ultimately affected by the disease. The integrated efforts of the best people are making a difference in the war against breast cancer.

Consumer Advocates

The BCRP is a pioneer in the inclusion of breast cancer survivors (consumer advocates) in every aspect of the research process. Consumer advocates have become an important force within the program as they participate as active members of the BCRP Integration Panel (IP); the peer review process, with more than **585 consumer advocates** having served on peer review panels for the BCRP since its inception; and the research process by aiding in patient recruitment, public education, and advising researchers.

The BCRP was the first program within the Congressionally Directed Medical Research Programs (CDMRP) to include consumer advocates in the research process. The overwhelming success of this precedent has influenced not only the other programs within the CDMRP to follow suit but other funding agencies as well. Additional details about consumer involvement can be found in Section I, Overview.



Gail E. Baird
FY07 BCRP Consumer Peer
Reviewer

“When people ask me why I continue to be so involved, my answer is simple...I believe. I believe the answers to cancer lie in research. Through the commitment of dedicated scientists, breakthroughs will occur. Through my advocacy and involvement, I believe I can impact how Congress funds the war on cancer. And if I reach one person a day with a cancer message, I have done my job.”



Lori Kerans
FY04-07 BCRP Consumer Peer
Reviewer

“The DOD BCRP experience of working with some of the most prominent scientists in the country has allowed me to better understand and appreciate the important role of research in the work to find a cure for breast and other types of cancers. Like breast cancer patients, the great scientific minds are housed in bodies of all shapes, sizes, ages, and races. These people are dedicating their professional lives to finding a cure for cancer; we are all on the same team!”

Peer Review Panel Members

BCRP peer review panels are composed of highly qualified investigators from scientific and clinical disciplines as well as consumer advocates. Peer review panels are organized by scientific discipline and specialty areas. The primary responsibility of the scientific peer review panel is to provide unbiased, expert advice on the scientific and technical merit of proposals submitted to the BCRP. 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, over **4,000 scientists, clinicians, and consumer advocates** have brought their expertise to the BCRP scientific peer review process. Further details about peer review appear in Section I, Overview.



Lauren S. Gollahon, Ph.D.
Texas Tech University
FY97–07 Peer Reviewer

“I believe wholeheartedly in the mission of the CDMRP BCRP. It was the first program to truly solicit innovative high-risk, high-gain research projects. It is their example that NIH followed.”



Beverly Canin
FY01–07 Consumer Peer
Reviewer

“Some scientists have said they believe consumer reviewers should be included in peer reviews everywhere and most now acknowledge consumers’ expertise as survivor/advocates. They understand the relationship is an essential component for achieving effective translational impact.”



Kevin Brown, Ph.D.
University of Florida
FY03–07 Peer Reviewer

“As a breast cancer researcher, I find participation in the BCRP peer review process keeps me in touch with the cutting edge of the field, and interaction with consumer reviewers reinforces the unmet needs within the patient community. As a scientist, I applaud the mission of the BCRP to fund innovative lines of investigation that may promise to provide tangible breakthroughs in our understanding or treatment of this disease.”

Integration Panel Members

The BCRP IP is composed of visionary and innovative scientists, clinicians, and consumer advocates. The IP members use their expertise to propose the annual program vision, develop cutting-edge investment strategies that meet the needs of the research and consumer communities, and recommend the most meritorious and programmatically relevant proposals for funding (for more information about the functions of the IP, see Section I, Overview).

FY07 BCRP IP Members

Graham Casey, Ph.D. (Chair), The Cleveland Clinic Lerner Research Institute

Karin Decker Noss (Chair-Elect), Virginia Breast Cancer Foundation

H. Kim Lyerly, M.D. (Chair Emeritus), Duke Comprehensive Cancer Center

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

M. Carolina Hinestrosa, M.A., M.P.H., Nueva Vida

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

Mark Pegram, M.D., University of Miami

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



Graham Casey, Ph.D.
The Cleveland Clinic Lerner Research Institute
FY07 BCRP Integration Panel Chair

"I feel very honored to serve on the Integration Panel of the Department of Defense-supported Breast Cancer Research Program that constantly strives to challenge the research community to think creatively, encourages the best and brightest into the field, and aims to address unmet needs in breast cancer research. This program is an active partnership between consumers and scientists that has one goal in mind, the eradication of breast cancer."



Karin Decker Noss
Virginia Breast Cancer Foundation
FY07 BCRP Integration Panel Chair-Elect

"I have been involved with the DOD Breast Cancer Research Program for over 10 years now and am so impressed by what the program has been able to accomplish. As a consumer advocate and someone living with metastatic breast cancer, I believe I have personally benefited from some of the research. Also, I very much admire and respect the scientists with whom I have served on peer review and the Integration Panel and believe that together we are making a difference."

Scientific Community

Renowned scientists and clinicians, as well as extraordinary researchers early in their careers, are exploring the cutting edge of science to eradicate breast cancer. To date, more than **4,400 scientists and clinicians** have been funded by the BCRP. The scientific community has and will continue to be a driving force in the quest to cure breast cancer. The remainder of this section highlights just a sample of BCRP-supported advances and their promise to achieve the program’s vision of eradicating breast cancer.

Richard M. Neve, Ph.D.
FY06–07 Peer Reviewer
Lawrence Berkeley National Laboratory

“The CDMRP maintains a high standard of excellence through self-assessment and peer review. 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.”

Joy Simha
FY06 BCRP Ad Hoc Consumer Programmatic Reviewer

“I believe that [the scientific community] is committed to finding a cure. It is a very difficult challenge that needs to be met; however, it will take so much more than just commitment. We need to think out-of-the-box to find the answer to this killer.”



Trailblazing toward the eradication of breast cancer...through innovation

Concept Awards

Designed to pursue serendipitous observations and explore innovative, untested ideas relevant to breast cancer



Cahit Evrensel, Ph.D.
University of Nevada

Immune Response Augmentation Utilizing Biocompatible Magnetic Fluids

FY06 Concept Awardee Dr. Cahit Evrensel, University of Nevada, Reno, will examine the efficacy of using biocompatible biodegradable magneto-rheological fluids (MRF) as a means of augmenting immune responses to breast cancer. MRF are suspensions of iron-based particles in a carrier medium. Dr. Evrensel will work in collaboration with colleagues in chemical and

mechanical engineering, microbiology, and immunology to develop the biocompatible MRF technology and evaluate its response to externally applied magnetic field and its biological effect on breast tumor growth. MRF may represent a novel means of inducing cell death in tumors and potentiating antitumor responses to breast cancer.



Mark Rasenick, Ph.D.
University of Illinois, Chicago

Breast Tumor Growth

Dr. Mark Rasenick of the University of Illinois, Chicago received an **FY06 Concept Award** to study the interaction between G protein-coupled receptors, particularly the estrogen receptor GPR30, and alteration of lipid rafts by omega-3 fatty acids. The omega-3 fatty acids are found in fish oils and have been postulated to play a role in the chemoprevention of breast cancer. Dr. Rasenick is studying the interaction of GPR30 and omega-3 fatty acids and its effect on regulating the growth of breast cancer cells. Knowledge of alterations of G-protein signaling through omega-3 fatty acids may provide insight into the development of chemopreventive and therapeutic agents for breast cancer.



Jennifer Sims-Mourtada, Ph.D.
(second from left) and colleagues
RadioMedix, Inc.

Facilitating Early Therapeutic Intervention

Increasing evidence suggests that breast cancer cells that have metastasized to the bone exhibit characteristics similar to stem cells. Dr. Jennifer Sims-Mourtada of RadioMedix, Inc., an **FY06 Concept Award** recipient, proposes to identify “stem cell-like” cancer cells that would facilitate early therapeutic intervention to prevent tumor recurrence and metastasis of breast cancer cells. Toward this goal Dr. Sims-Mourtada is taking advantage of secreted ligand, sonic hedgehog in the hedgehog signaling pathway, to develop a radiolabeled ligand as an imaging agent. The hedgehog signaling pathway is a classic stem cell signaling pathway that is often aberrantly activated in breast cancer cells. Development of a novel radiolabeled hedgehog ligand as an imaging agent would allow for real-time noninvasive detection of activated stem cell pathways in breast cancer cells and the potential for early breast cancer intervention to control the disease.

Idea Awards

Support highly innovative, high-risk, high-reward research that ultimately could lead to critical discoveries or major advancements in breast cancer



Sarah Blair, M.D.
University of California,
San Diego Moores Cancer
Center

Real-Time Evaluation of Tumor Margins

Dr. Sarah Blair, recipient of an **FY05 Idea Award**, is part of a team at University of California, San Diego Moores Cancer Center that is developing a device to provide surgeons intraoperative evaluation of tumor margins and a real-time result on the presence or absence of cancer cells during breast cancer surgery. Currently, there is no convenient method for rapid detection of tumor cells at surgical margins. The new device would be used in the operating room to directly test tissue removed from the breast for altered protein expression and nuclear size. The team hopes to have a highly sensitive and selective test for surgical margins for up to 90 percent of patients.



Sherry Chow, Ph.D.
University of Arizona

Localized Delivery of a Cancer Preventive Agent

FY06 Idea Award recipient Dr. Sherry Chow, University of Arizona, is conducting a pilot clinical study to deliver high levels of limonene to the breast by topical breast massage in healthy premenopausal women. Limonene is a major component in citrus oils, and studies in laboratory animals showed that oral consumption of limonene increased tumor latency during the initiation and progression of mammary carcinogenesis. However, the effective oral dose determined in animal studies converts to a human dose that is not feasible for long-term usage. In the proposed study, breast tissue bioavailability of limonene following topical massage application will be determined from nipple aspirate fluid and serum. This pilot study could be the first to demonstrate the feasibility of localized delivery of a cancer preventive agent to breast cancer cells, paving the way for the development of other localized forms of therapy.

Trailblazing toward the eradication of breast cancer...through creative individuals and visionary leadership

Innovator Awards

Encourage accomplished, creative individuals with a history of innovation and visionary leadership to pursue their most innovative plans that could lead to the eradication of breast cancer



Stephen Johnston, Ph.D.
Arizona State University

Developing a Prophylactic Breast Cancer Vaccine

Dr. Stephen Johnston, Arizona State University, recipient of an **FY06 Innovator Award**, has organized an interdisciplinary team of scientists and clinicians to mount a multiprong effort to identify antigens that could be used in a prophylactic breast cancer vaccine. It is well established that cancers make aberrant proteins that the immune system has not seen before. Current dogma suggests that

immune protection is tumor specific and each tumor is personal. However, Dr. Johnston and colleagues have evidence that challenges this dogma. The proposed study is based on the hypothesis that there are “foreign” peptides commonly generated by different breast tumors. These peptides may be the basis of a prophylactic breast tumor vaccine that would prevent breast cancer before it occurred.



Joe Gray, Ph.D.
Lawrence Berkeley National Laboratory,
University of California

Early Detection of Metastasis-Prone Breast Cancers

Dr. Joe Gray of the Lawrence Berkeley National Laboratory, University of California, is a leader in the development of new methods and technologies that propel both basic and translational breast cancer research forward into the clinic. Dr. Gray was awarded an **FY06 Innovator Award** to lead a group of multidisciplinary scientists in the development of new breast imaging technologies that improve digital mammography, positron emission tomography and/or magnetic resonance imaging, and histopathological evaluation. These state-of-the-art technologies may ultimately improve breast cancer detection and screening, identify signatures of breast cancer subtypes, provide new molecular information, and improve histological evaluations, leading to better clinical outcome for breast cancer patients.



Era of Hope Scholar Awards

Provide support to talented, early-career scientists who have demonstrated that they are the “best and brightest” in their fields



Peter Lee, M.D.
Stanford University

Immunology, Systems Biology, and Immunotherapy of Breast Cancer

Recent evidence implicates the host immune response as having a significant role in altering disease progression in cancer, but this interplay between the immune response and tumor cells is poorly understood. Striving to find novel immunotherapy methods, Dr. Peter Lee of Stanford University, recipient of an **FY05 Era of Hope Scholar Award**, is studying the dynamics between breast cancer and the immune response through an integrative systems approach. He and an exceptional research team are currently searching

for immune cell dysfunction within tumor sites and tumor-draining lymph nodes. They have made significant progress in developing methods of recovering and analyzing immune and tumor cell specimens from patient samples. Dr. Lee’s team will apply these newly developed techniques to discover new insights into immune evasion by breast cancer cells and novel diagnostic tools/potential therapeutic strategies for breast cancer that are directed at the biology of tumor-draining lymph nodes.

Trailblazing toward the eradication of breast cancer...through multidisciplinary and synergistic approaches

Breast Cancer Center of Excellence Awards

Support synergistic, highly integrated multidisciplinary teams of the highest caliber scientists, clinicians, and consumer advocates who work together to solve a major problem in breast cancer



V. Craig Jordan, Ph.D.
Fox Chase Cancer Center

A New Paradigm for Antihormonal-Resistant Breast Cancer Cells

FY05 Center of Excellence Award recipient

Dr. V. Craig Jordan of the Fox Chase Cancer Center and collaborators Drs. Anton Wellstein and Anna Riegel from Georgetown University and Dr. Heather Cunliffe from Translational Genomics are exploring ways to reactivate estrogen receptor-alpha breast tumors that are unresponsive to antihormonal therapy. Preliminary evidence suggests that breast tumors that are deprived of estrogen when exposed to low doses of estrogen therapy will undergo apoptosis, and remaining cells will become sensitive to antihormone treatment. Dr. Jordan is coordinating a complementary and multidisciplinary research team to identify proteins and pathways

involved in estrogen receptor-mediated apoptosis from clinical samples and laboratory models to better understand the mechanism of resistance. Drs. Ramona Swaby, Lori Goldstein, and Mary Daly of Fox Chase Cancer Center will conduct clinical trials employing low-dose estrogen therapy in patients with antihormonal-resistant breast cancer, a majority of whom are unresponsive to traditional hormonal therapy. Dr. Nancy Davidson, Johns Hopkins University, will be a collaborator on the clinical trials. Results from these investigations may establish a new therapeutic paradigm for breast cancer treatment and avoid complications with cytotoxic combinations of chemotherapy.

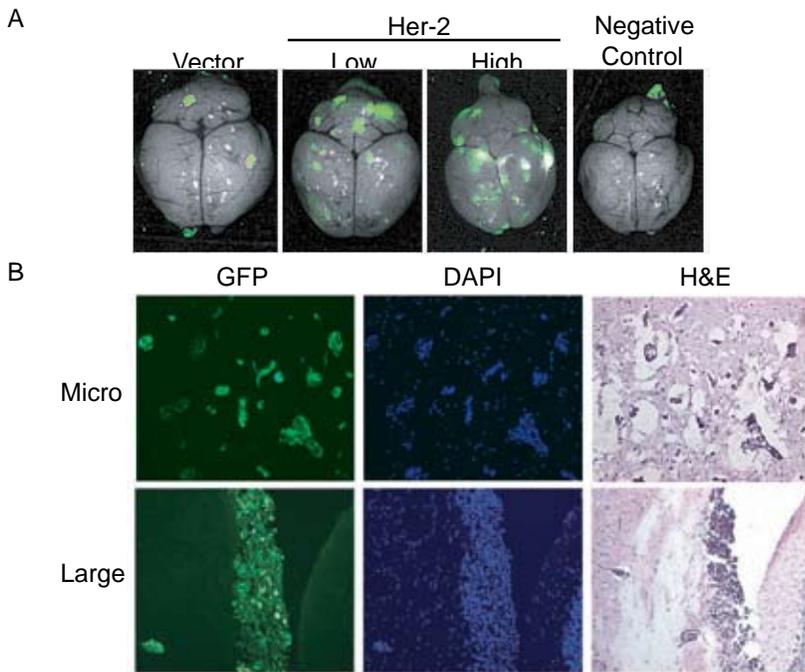


Patricia S. Steeg, Ph.D.
National Cancer Institute

Brain Metastases of Breast Cancer

FY05 Center of Excellence Award recipient Dr. Patricia S. Steeg, National Cancer Institute (administered by the TRUE Foundation), is coordinating an extensive study of 16 different investigators all studying brain metastases of breast cancer. This project has made monumental progress within its first year, including establishing a tissue core and developing a quantitative brain metastasis mouse model. Dr. Steeg is working to identify molecular pathways that functionally contribute to

brain metastases including Her-2, VEGF, and STAT3. The role of the blood-brain barrier (BBB) is under study to determine the extent to which it impedes drug delivery and how this can be overcome. Dr. Steeg is also studying the efficacy of many preclinical compounds against brain metastasis (e.g., SAHA, Lapatinib, and JSI-124), along with efficient delivery methods (BBB) disruption, synergy with radiation therapy, and ability to cross the blood tumor barrier.



231-BR xenograft model system for quantification of breast cancer brain metastases. EGFP-labeled 231-BR brain-seeking cells were injected into the left cardiac ventricle of BALB/c nude mice, and brain metastases were determined 4 weeks later. A, Ex vivo whole-brain images were captured using the Maestro 420 in vivo Spectral Imaging System. Representative images from each group are shown. Negative control is a representative image from a mouse that did not receive an injection of tumor cells. Autofluorescence is routinely noted on the periphery of the tissue. B, Histologic images representative of micrometastases and large brain metastases. Left, EGFP fluorescence; middle, DAPI-stained nuclei; right, H&E-stained images in a successive section. Magnification, 200.

Multidisciplinary Postdoctoral Awards

Encourage development of research expertise in two or more diverse disciplines to enhance the training of future innovators at the forefront of breast cancer research



Eva Balint, M.D.
Stanford University

Vitamin D, Breast Cancer, and Bone Health

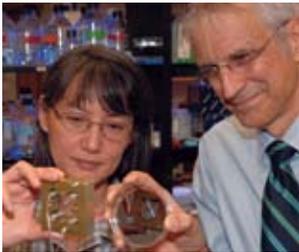
FY06 Multidisciplinary Postdoctoral Award

recipient Dr. Eva Balint of Stanford University will combine her background in endocrinology with training in oncology and epidemiology to become a physician-scientist with a career in translational research. She will examine the effects of oral administration of high doses of vitamin D with aromatase inhibitors. Using a mouse xenograft model of breast cancer, Dr. Balint will assess the effectiveness of high doses of vitamin D in the presence or absence of anastrozole on tumor growth,

patterns of gene expression, and bone turnover. Additionally, Dr. Balint will conduct a clinical trial involving postmenopausal women with breast cancer who are being treated with aromatase inhibitor to determine the effect of escalating doses of vitamin D on serum calcium levels and reduction in aromatase inhibitor-mediated side effects in bone and muscle. Ultimately, the combined action of vitamin D and aromatase inhibitors could lead to suppression of breast cancer cells, decreased risk of cancer progression, and improved patient outcome.

Synergistic Idea Awards

Support highly innovative, high-risk, high-reward research by two independent investigators who bring their unique expertise together to address a central problem in breast cancer research from synergistic and complementary perspectives



John Wikswo, Ph.D. and Jin Chen, M.D., Ph.D.
Vanderbilt University

Modeling the Tumor Microenvironment

FY06 Synergistic Idea awardee Dr. John Wikswo of Vanderbilt University and Dr. Jin Chen are leading a multidisciplinary team of cancer and vascular biologists, biophysicists, and engineers in the development of a Perfused Breast Tissue Bioreactor (PBTB) system using standard microfabrication and microfluidic techniques. In this system, normal and breast cancer cells will be co-cultured with a perfusive endothelial capillary network and/or a controlled, highly porous filter for cell separation and perfusion. The PBTB recapitulates a controlled tissue microenvironment in which tumor cells

are surrounded by tissue matrix, microvascular endothelial cells, and stromal cells/fibroblasts and are capable of chemical sensing, thereby making the system suitable for studying breast cancer cell growth, angiogenesis, and metastasis. The novel and highly innovative PBTB system to be developed and optimized may provide a vehicle in which drugs aimed at disrupting angiogenesis and metastasis could be screened or discovered, and resected tumors/cells from patients could be studied to provide individualized medicine tailored to the breast cancer patient.

Trailblazing toward the eradication of breast cancer...through clinical advances

Clinical Translational Research Awards

Sponsor innovative research that will result in substantial improvements over current approaches to breast cancer chemoprevention and/or therapy by accelerating the progression of promising new findings in preclinical breast cancer research from the laboratory to the clinic



William Gillanders, M.D. (left) and colleague
Washington University, Saint Louis

Mammaglobin A Vaccine to Prevent Breast Cancer Recurrence

Dr. William Gillanders, recipient of an **FY05 Clinical Translational Research Award**, Washington University in Saint Louis, is leading a team of scientists studying the mammaglobin-A gene. Mammaglobin-A is overexpressed in almost all breast cancers, making it an attractive target for a breast cancer vaccine. The gene's exclusive expression in normal breast epithelium and breast cancer decreases the risk of autoimmunity. Additional studies determined from analysis of

blood samples from breast cancer patients that these patients harbor circulating T cells that are capable of recognizing and destroying breast cancer cells, suggesting that mammaglobin-A is recognized by the immune system. Dr. Gillanders and colleagues are developing a DNA vaccine to target mammaglobin-A. This vaccine is designed to elicit an antitumor immune response in breast cancer patients and may ultimately find clinical application in breast cancer treatment and prevention.



Mary Nora Disis, M.D.
University of Washington

HER2 Intercellular Domain Peptide Vaccine in Combination with Trastuzumab

FY03 Clinical Translational Research Award

recipient Dr. Mary Nora Disis, University of Washington, is leading a team of scientists in a Phase II clinical trial of HER2 intercellular domain (ICD) peptide vaccine in combination with trastuzumab (humanized monoclonal anti-HER-2/neu antibody) in patients with advanced stage HER2-positive breast cancer. The goal of the combination therapy is to generate long-term immunity through stimulation of tumor-specific T cells. The vaccine elicits an immune response in which the body's immune system destroys remaining cells left after therapy, thereby preventing breast cancer relapse and potentially improving survival. In a Phase I trial, administration of the vaccine in women with breast cancer showed that the vaccine was safe

and immunogenic with T cell-mediated immunity that lasted over 5 years. In addition, the small number of patients receiving the vaccine began to develop immunity against other tumor antigens/cancer proteins (epitope spreading) without signs of autoimmunity. Dr. Disis and collaborators at Seattle Cancer Care Alliance and Breastlink, Inc. are actively screening and enrolling patients in the Phase II trial. If the combined HER2 ICD and trastuzumab therapy proves successful at increasing patient survival, preventing breast cancer relapses, and increasing immunity against other tumor antigens, Dr. Disis' study may lead to a randomized Phase III trial that compares the vaccine in combination treatment versus standard treatment alone.

Trailblazing toward the eradication of breast cancer...by improving quality of life



Michelle Naughton, Ph.D.
Wake Forest University

Quality of Life after Chemotherapy

Dr. Michelle Naughton and colleagues at Wake Forest University were awarded an **FY00 Behavioral Center of Excellence Award** to research various factors that affect the quality of life of breast cancer patients after diagnosis and treatment. One study assesses the menstrual cycle patterns and quality of life of young women (ages 18 to 45) diagnosed with stage I, II, or III breast cancer to detect determinants of treatment-related absence of a menstrual period. Certain chemotherapy treatment regimens and older age at diagnosis significantly affected a woman's ability to resume her menstrual cycle after several months without menstruation. While other symptoms are also being studied, over half of the women reported arm or hand swelling 36 months after surgery, with many women reporting that they had persistent swelling. Study participants also reported decreases in their quality of life

and an increase in depressive symptoms during the first months after diagnosis, but most women showed significant improvements in quality of life during the first year following treatment. A related study is examining psychosocial factors to explain age differences in health-related quality of life among women ages 18 to 85 and older diagnosed with breast cancer for the first time. An additional study is a randomized intervention trial of women during chemotherapy to determine if a tailored physical activity program with education regarding lymphedema prevention will improve the physical well-being and quality of life of these patients. The results of all of these investigations have the potential to greatly inform clinical practice and decision making and to guide interventions to improve the short- and long-term quality of life of women of all ages diagnosed with breast cancer.



Diana Tisnado, Ph.D.
University of California, Los Angeles (UCLA)

Racial and Ethnic Disparities in Breast Cancer Care

FY02 Postdoctoral Traineeship awardee Dr. Diana Tisnado of UCLA is working on understanding the racial and ethnic disparities in breast cancer care and the contribution of socioeconomic position and language barriers for Hispanic women in Los Angeles County, California. Through baseline survey data of non-Hispanic white, Hispanic English-speaking, and Spanish-speaking population and census data from 2000, Dr. Tisnado and colleagues were able to derive analytical variables on racial/ethnic composition, socioeconomic resources, and acculturation. In a patient-level analysis, they have found enduring evidence of racial/ethnic and socioeconomic disparities in respect to the breast cancer health care system. Non-white patients are prone to live in neighborhoods with fewer resources and lower rates of acculturation. Older and Hispanic Spanish-speaking women reported severe symptoms less often than other women, yet Spanish-speaking women received less help from their physicians for their symptoms. Low-income remains a barrier to the discussion and process of breast reconstruction (a measure of quality care in breast cancer). The rates of patient–physician discussions about alternative treatments and the possible positive/negative outcomes of breast cancer are relatively low, and they are highly correlated with the patients’ satisfaction with their medical care.



Scarlett Gomez, Ph.D.
Northern California Cancer Center

Impact of Discrimination on Medical Care and Quality of Life

It has been shown that the burden of breast cancer is unevenly distributed across various ethnic groups, particularly when it comes to diagnosis and treatment of the disease. Dr. Scarlett Gomez, recipient of an **FY06 Idea Award**, and her team at the Northern California Cancer Center hypothesize that racial and ethnic disparities arise from exposures to institutional-based discrimination through women’s social and physical environments within their neighborhoods. Based on this hypothesis, they are launching an innovative epidemiologic study in this little-researched area of public health. A new questionnaire will be designed to ascertain the impact of individual- and institutional-level discrimination on diagnosis and treatment. This tool will also look at the quality of life for these patients and survivors. Once validated, the questionnaire will be part of a multilevel approach incorporating individual- and neighborhood-level data. Dr. Gomez believes that the results of this novel study addressing the environmental factors of racial/ethnic disparities have the capability of ensuring equal treatment for all patients, enhancing quality of life, and improving the health and awareness for breast cancer patients and the public at large.

Trailblazing toward the eradication of breast cancer...by training a new generation of innovators

Predoctoral Traineeship Awards

Prepare promising graduate students who have a strong commitment to breast cancer research for successful and competitive careers by promoting creative approaches to training breast cancer investigators



Talya Salant, M.A.
University of Chicago

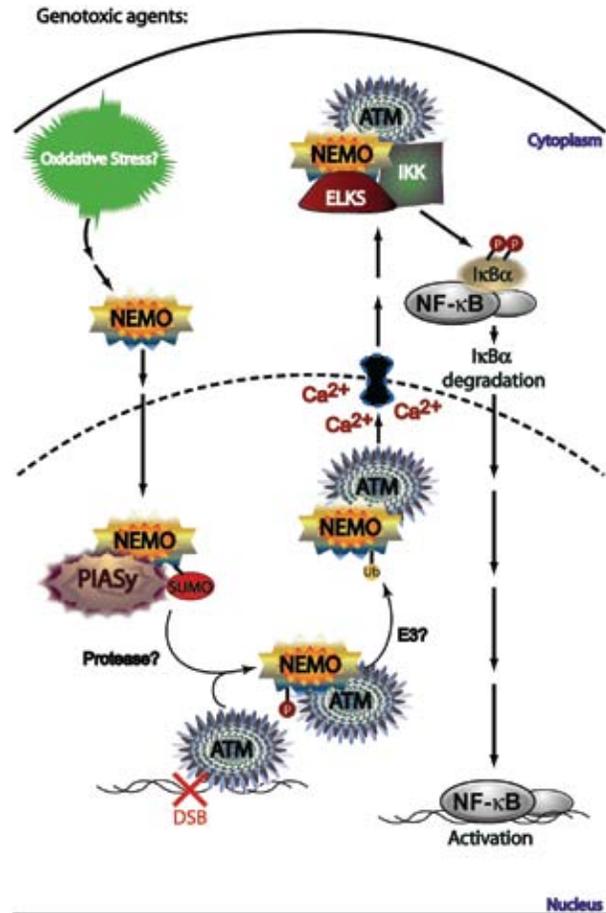
Ethnic and Cultural Dimensions of Risk Assessment

Talya Salant, an **FY03 Predoctoral Traineeship Awardee** at the University of Chicago, conducted a prospective, multisite, longitudinal study and qualitatively analyzed how “at risk” women from ethnically and socioeconomically diverse backgrounds comprehend their disease risk and how they make decisions about their preventive care. One of the major goals of this study was to determine if there is a difference between the psychological predictors of breast cancer risk perception and the actual way in which women

at high risk understand and decide on prevention options. Results from this study suggest that modified risk communication and alternatives to medication-based prevention options should be considered when treating African American women at high risk of developing breast cancer because current research methods may not consider influences such as spirituality, causal models, and competing life and health risks when measuring individual risk perception and risk prevention behaviors.

Novel Target for Chemotherapeutic Treatment

Ms. Angela M. Mabb, University of Wisconsin-Madison received an **FY03 Predoctoral Traineeship Award** to study a novel target for chemotherapeutic treatment regimens against estrogen receptor-negative (ER-) breast cancer. In many ER- breast cancers, the transcription factor NF-κB is highly activated and exhibits inducible activation in response to DNA damaging agents. Many current therapies focus on a general inactivation of NF-κB, which causes unwanted side effects. Ms. Mabb has focused her studies on finding a molecular target that could specifically inhibit DNA damage-induced activation of NF-κB without affecting the classical activation of NF-κB, so as to reduce the side effects of this type of therapy. Ms. Mabb focused on a protein called PIASy, which is an adaptor protein necessary for NF-κB activation. Preliminary studies have shown that PIASy can specifically promote DNA damage-induced NF-κB activation. In addition, a reduction in the amount of the PIASy protein caused inhibition of NF-κB activation in response to several commonly used anticancer DNA damaging agents, and overexpression of PIASy enhanced NF-κB activation. These results suggest that PIASy could be a promising anticancer therapy for ER- breast cancer.



Model depicting the role of PIASy in genotoxic stress-induced NF-κB signaling

Historically Black College and University/Minority Institution Partnership Training Awards

Create a collaborative partnership between two or more Historically Black Colleges/Universities and Minority Institutions (HBCU/MI) faculty-level investigators and at least one established breast cancer researcher at another research institution. The award is intended to enable HBCU/MI faculty to obtain the training and experience necessary to obtain independent breast cancer research funding and to facilitate development of an ongoing breast cancer training program at the HBCU/MI.



Deodutta Roy, Ph.D.
Florida International University

Mechanisms Underlying Antiestrogen Resistance

The emergence of tamoxifen or aromatase inhibitor resistance is a major problem in the treatment of breast cancer and understanding the mechanisms by which resistance to these agents arises could have major clinical implications for preventing or circumventing it. An **FY06 HBCU/MI Partnership Training Award** to Dr. Deodutta Roy of Florida International University and Dr. Joyce Slingerland of University of Miami Braman Family Breast Cancer Institute will address how reactive oxygen species-induced redox signaling pathways in breast cancer cells may contribute to molecular mechanisms of antiestrogen resistance.



Cruz Maria Nazario, Ph.D. (pictured far right) and colleagues
University of Puerto Rico

Breast Cancer Epidemiology in Puerto Rico

The rate of breast cancer has been climbing far more rapidly among Puerto Rican women than among women in the United States. Nevertheless, there is a great deficit of minority scientists engaged in breast cancer research. To address this issue, **FY06 HBCU/MI Partnership Training Award** recipient Dr. Cruz Maria Nazario from the University of Puerto Rico is collaborating with Dr. Jo Freudenheim from the University at Buffalo to examine breast cancer risk factors in Puerto Rican women. Both childhood and adult factors will be examined including diet, lifetime physical activity, energy balance, environmental exposures, and early life and reproductive history. Members of Dr. Nazario's research team include Drs. Farah Ramirez, Imar Mansilla, and Michele Schelse-Santos.

The Program Today

Fiscal Year 2006 Summary

The FY06 congressional appropriation to the BCRP was **\$127.5M**. Awards were made across 11 different mechanisms, as shown in Table II-1, with emphasis placed on innovation, training, and clinical research. A total of **3,121 proposals** were received across mechanisms and **220 awards** were made.

The BCRP continued to identify areas of need within the scientific community and launched two new award mechanisms called the Synergistic Idea and Era of Hope Postdoctoral Awards. These awards foster new directions in innovation, challenge existing dogma/paradigms, and bring exceptional new investigators to the field of breast cancer research. The research portfolio developed by the FY06 program encompassed basic research, clinical research, and population-based research (see Figure II-2).

Table II-1. Funding Summary for the FY06 BCRP

Categories and Award Mechanisms	Proposals Received	Awards	Investment
Clinical Research			
Clinical Translational Research	11	2	\$9.1M
Innovative Research			
Concept	1,231	83	\$9.6M
Era of Hope Scholar	11	3	\$10.2M
Idea	791	62	\$29.1M
Innovator	23	2	\$14.6M
Synergistic Idea	584	43	\$30.1M
Training/Recruitment			
Era of Hope Postdoctoral	22	8	\$2.3M
HBCU/MI Partnership Training	5	4	\$5.5M
Multidisciplinary ^a Postdoctoral	166	12	\$6.4M
Predocctoral Traineeship ^a	276	1	\$0.1M
Research Resources			
Center of Excellence	1	0	0
TOTAL	3,121	220	\$117M

^a An additional 64 FY06 Predocctoral Traineeship (\$5.8M) and 6 Multidisciplinary Postdoctoral Traineeship (\$3.1M) awards were funded using BCRP FY05 appropriations.

Fiscal Year **2006**
3,121 Proposals Received
\$127.5M in Appropriations
220 Awards

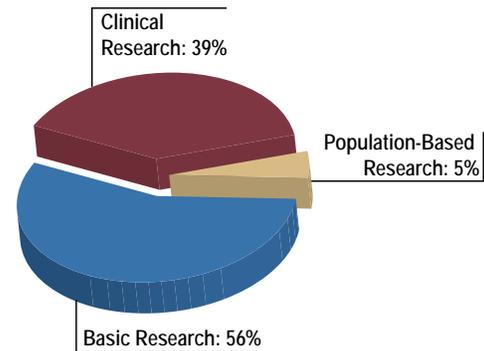


Figure II-2. FY06 BCRP Portfolio by Research Area

The Vision for Fiscal Year 2007

Congress appropriated \$127.5M to continue the BCRP in FY07. The program offered nine award mechanisms to contribute to the program’s vision of eradicating breast cancer, as illustrated in Table II-2. The Impact Award represented an original mechanism for the program as it is intended to support unique projects that do not fit existing BCRP award mechanisms yet possess a strong potential to significantly impact the prevention, detection, diagnosis, and/or treatment of the disease. A total of 1,512 proposals were received and approximately 199 awards are anticipated. The congressional appropriations and investment strategy executed by the BCRP for FY06 and FY07 are summarized in Appendix B, Table B-1.

Table II-2. Award Mechanisms Offered and Proposals Received for the FY07 BCRP

Categories and Award Mechanisms	Proposals Received
Innovative Research	
Idea	767
Synergistic Idea	285
Training/Recruitment	
Era of Hope Postdoctoral	22
HBCU/MI Partnership Training	3
Multidisciplinary Postdoctoral	47
Predocctoral Traineeship	281
Other Award Mechanisms	
Era of Hope Scholar	16
Impact	86
Innovator	5
TOTAL	1,512

Toward...

Herceptin

- Supported the development of monoclonal antibodies against Her-2/neu receptor (Dennis Slamon, M.D., Ph.D.)

Sentinel Lymph Node Biopsy

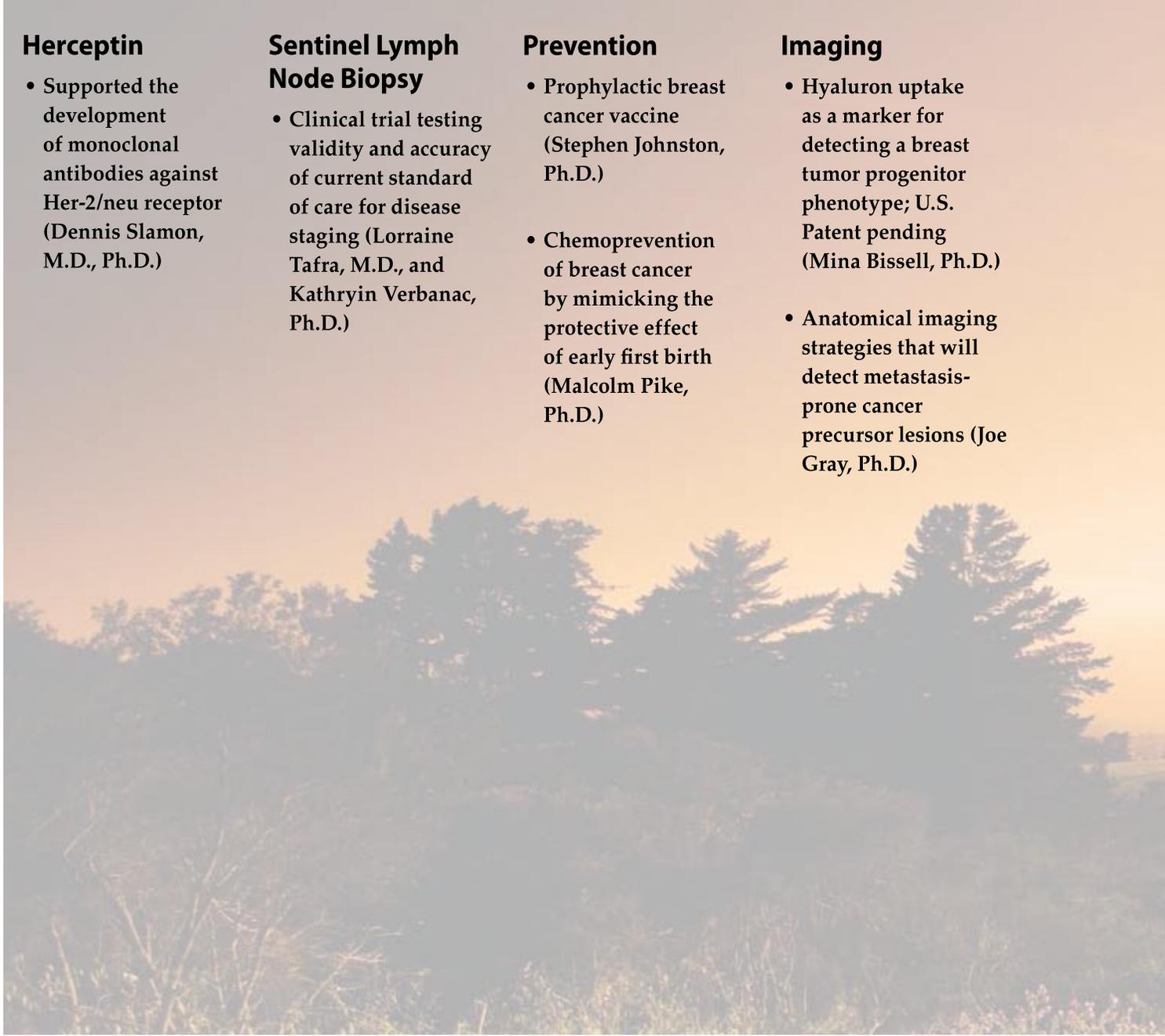
- Clinical trial testing validity and accuracy of current standard of care for disease staging (Lorraine Tafra, M.D., and Kathryin Verbanac, Ph.D.)

Prevention

- Prophylactic breast cancer vaccine (Stephen Johnston, Ph.D.)
- Chemoprevention of breast cancer by mimicking the protective effect of early first birth (Malcolm Pike, Ph.D.)

Imaging

- Hyaluron uptake as a marker for detecting a breast tumor progenitor phenotype; U.S. Patent pending (Mina Bissell, Ph.D.)
- Anatomical imaging strategies that will detect metastasis-prone cancer precursor lesions (Joe Gray, Ph.D.)



Support from the BCRP has helped lead to improvements in breast cancer diagnostics and treatment with far-reaching impact. Building on past successes through a strategy of funding innovative and progressive research and people, the BCRP portfolio holds the promise of many more advancements to come. Here is a sample of successes that mark the start of the path toward eradicating breast cancer and promising new work that may lead the journey.

New Horizons

Biobehavioral Sciences

- Exercise training to increase response to neoadjuvant therapy in operable breast cancer; Phase I–II study planned (Lee Jones, Ph.D.)
- Identifying biological and epidemiological factors that make women susceptible to weight gain after breast cancer diagnosis and treatment (Chi-Chen Hong, Ph.D.)

Nanotechnology

- Gold nanoparticles that specifically interact with breast cancer cells allowing primary and metastatic sites to be detected at earlier stages using standard imaging methods (Todd Giorgio, Ph.D.)
- Targeted nanoshells for detection, imaging, and therapy of breast cancer (Naomi Halas, Ph.D.)

Therapeutic Advances

- PTC299: suppress tumor growth by selectively inhibiting post-transcriptional VEGF production (Langdon Miller, M.D.)
- Development of legumin, a cell-impermeable therapeutic agent activated by legumin in the tumor micro-environment (Chen Liu, Ph.D.)
- A heterologous prime-boost cancer vaccine regimen to trigger antitumor immune responses in HER2+ metastatic breast cancer (Timothy Clay, Ph.D.)

Clinical Trials

- WX-UK1: inhibits urokinase-type plasminogen activator; Phase 2 clinical trial in progress (Olaf Wilhelm, M.D.)
- HER2 intercellular domain (ICD) peptide vaccine in combination with trastuzumab; Phase 2 clinical trial in progress (Mary Disis, M.D.)
- Proteomics and genomics to predict individual responses to therapeutic agents, clinical trial in progress (George Sledge, M.D.)
- Combination therapy using Herceptin and Avastin; Phase 2 clinical trial in progress (Mark Pegram, M.D.)

