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 Breast Cancer Research:**
- $1.368B in FY92–02
- $150M in FY03
- $150M in FY04
- $7M in FY99–02, $2.2M in FY03, and $1.1M in FY04 from the Stamp Out Breast Cancer Act

**Funding Summary:**
- 3,671 awards from the FY92–02 appropriations
- 402 awards from the FY03 appropriation
- ~140 awards anticipated from the FY04 appropriation

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**The Disease**

Cancer of the breast is the most commonly diagnosed non-skin cancer in women, accounting for 32% of all cancers in women. One out of every eight women will develop breast cancer in her lifetime. Breast cancer is second only to lung cancer as the leading cause of death in women. In 2004, approximately 215,990 women in the United States will receive a diagnosis of invasive breast cancer and approximately 59,390 women will be diagnosed with breast cancer in situ. In addition, although male breast cancer is rare and accounts for less than 1% of all breast carcinomas in the United States, about 1,450 new cases of breast cancer will be diagnosed in men this year. More than 40,000 women and approximately 400 men are projected to die from breast cancer this year.¹

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**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 an 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 were 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. The program is also a recognized leader in innovative program management. (See the box story on page III-5 for an example of how one unique BCRP award mechanism is accelerating advances in breast cancer research.) From FY92 to FY04, the BCRP has managed almost $1.67 billion (B) in peer reviewed research in an effort to accelerate medical discovery and eradication of breast cancer. Through FY03, 4,073 awards have been made. Appendix B, Table B-1 summarizes the congressional appropriations and the investment strategy executed by the BCRP for FY03–04.

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The Fiscal Year 2003 Program

In FY03, 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 FY03, 2,857 proposals were received, and 402 were funded. Table III-1 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-1, the portfolio of research supported by the FY03 BCRP is multidisciplinary.

The FY03 BCRP offered 10 award mechanisms to support research with the potential to impact and change the course of science in breast cancer. Two research award mechanisms, Concept and Idea Awards, were offered for investigators to boldly explore novel questions in breast cancer. Collectively, 245 awards were made to foster innovation in breast cancer research. Four training/recruitment award mechanisms were offered to promote the training and mentoring of future leaders in breast cancer research: 106 awards were made. One of the training/recruitment award mechanisms, the Historically Black Colleges and Universities/Minority Institutions (HBCU/MI) Partnership Training Award, reflects the BCRP’s continued commitment to addressing the health disparity associated with breast cancer and breast cancer treatment. (See the related box story on page III-7 for further details about this mechanism and the corresponding partnerships that have been developed.) Additionally, the program continued to build research resources through the Breast Cancer Center of Excellence Awards. Four awards were made in this mechanism to leading institutions across the nation in an effort to support pioneering, multi-institutional approaches to the acceleration of research progress in breast cancer. Finally, two Innovator Awards were made, one to Dr. Judah Folkman of Children’s Hospital, Boston, Massachusetts and the other to Dr. Stephen Elledge of Brigham and Women’s Hospital, to provide accomplished and visionary researchers with the funding to pursue groundbreaking breast cancer research.

The Vision for the Fiscal Year 2004 Program

Congress again appropriated $150M to continue the BCRP in FY04. Eight award mechanisms were offered to sustain the BCRP’s investment in innovation, training, and translational research. Six of these award mechanisms were previously established by the BCRP (Predoctoral Traineeships, Multidisciplinary Postdoctoral, HBCU/MI Partnership Training, Idea, Innovator, and Breast Cancer Center of Excellence Awards). Two of the mechanisms were new to the...
program in FY04 to fill unique niches, the Era of Hope Scholar Award and the Center of Excellence Pilot Award. The intent of these new mechanisms is highlighted as follows:

- The Era of Hope Scholar Award was designed to offer early-career gifted scientists the opportunity to challenge the status quo and implement a vision that may ultimately lead to the eradication of breast cancer. Award recipients were required to demonstrate that they are the best and brightest in their field as well as show a strong potential for leadership in breast cancer research.

- The Center of Excellence Pilot Award was established to support the recruitment of an integrated, multi-institutional team of world-renowned investigators to develop the foundation for a Breast Cancer Center of Excellence.

A total of 1,264 proposals were received, as detailed in Table III-2, and approximately 140 awards are expected.

**Scientific Outcomes and Advances**

The BCRP research portfolio comprises many different types of projects that are aimed at accelerating discovery and eradication of breast cancer, including support for innovative ideas, facilitation of translational research, and training of future leaders in breast cancer research. The following projects represent a sample of the extraordinary developments that are resulting from research funded by the BCRP.

**Early Life Events and the Risk of Breast Cancer**

*Mads Melbye, M.D., Staten Serum Institut, Copenhagen*

Understanding the causes of breast cancer should lead to improved methods of identifying women with the highest risk for developing this disease. Many studies point toward early developmental events in a woman’s life (including growth rates in utero, childhood, and adolescence) as influencing her risk of developing breast cancer as an adult. A team of researchers led by Dr. Mads Melbye, an FY99 Breast Cancer Research Program Idea Award recipient, took advantage of a unique opportunity to link Denmark’s high-quality nationwide registries to examine associations among birth weight, childhood and pubertal growth, and breast cancer in a large cohort of 117,415 Danish women. The height and weight of these individuals had been recorded annually during the school years. This study determined that high birth weight, being tall at 14 years of age, having a low body-mass index at 14 years of age, and showing peak growth at an early age were independent risk factors for breast cancer. Height at 8 years of age and the increase in height during puberty (8 to 14 years of age) were also associated with breast cancer. The team found no effect when adjusting for parity and age at first childbirth. In contrast to other studies, there was no correlation between age at menarche and developing breast cancer. In addition, data suggested that high body-mass index at a young age protected against breast cancer. A possible

<table>
<thead>
<tr>
<th>Category &amp; Award</th>
<th>Proposals</th>
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<tbody>
<tr>
<td>Research Idea</td>
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<td>Research Resources</td>
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<td>Center of Excellence Pilot Award</td>
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<td>Breast Cancer Center of Excellence Awards</td>
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<tr>
<td>Training/Recruitment</td>
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<td>HBCU/MI Partnership Training</td>
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<td>Postdoctoral Multidisciplinary</td>
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<td>Predoctoral Traineeships</td>
<td>302</td>
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<td>Era of Hope Scholar Award</td>
<td>26</td>
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<tr>
<td>Innovator</td>
<td>15</td>
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<tr>
<td>Total</td>
<td>1,264</td>
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An Update: The Biotechnology Clinical Partnership Award — Accelerating Research Advances through Collaborations between Academic Institutions and the Biotechnology Industry

Last year, this report highlighted the Biotechnology Clinical Partnership Award mechanism and its first recipient, Dr. Olaf Wilhelm of Wilex AG. This year, the CDMRP would like to report progress in this arena. The Biotechnology Clinical Partnership Award was established by the BCRP in FY02 to facilitate partnerships between the biotechnology industry and academic institutions to reduce the challenges related to drug development faced by many biotechnology companies and to accelerate the delivery of novel breast cancer therapeutics and chemopreventives. This funding mechanism was designed to support Phase 1/2 or Phase 2 clinical trials of new breast cancer therapeutic agents.

The first award in this mechanism was made to Wilex AG, a German-based biopharmaceutical company that was developing WX-UK1 for the treatment of breast cancer. WX-UK1, a novel, non-cytotoxic, synthetic, small molecule inhibitor of the Urokinase-type Plasminogen Activator (uPA), plays a key role in primary tumor growth and tumor metastasis. Unlike existing chemotherapeutic agents, WX-UK1 disrupts the activity of a biological target that is directly connected to cancer progression. Thus, this drug offers an entirely new mechanism of action, the prevention of metastasis. Funding from this award supports a collaboration between Wilex AG and the Fox Chase Cancer Center (FCCC) in which FCCC provides the expertise needed to direct a clinical trial and the ability to accrue an appropriate number of breast cancer patients to demonstrate the efficacy of WX-UK1. As a result of this award, Wilex AG and FCCC were able to obtain Investigational New Drug status and initiate a Phase 1 clinical trial of WX-UK1 in less than 1 year. In a recent news article, Dr. Lori Goldstein, principal investigator on the clinical trial and director of FCCC's Breast Evaluation Center, was quoted as saying, “The DOD-Wilex-Fox Chase collaboration is an example of how government, private industry, and academia can work together to bring promising research from the laboratory to the clinic quicker than traditional avenues.”

Please refer to the following publications for additional information about this research:


Guilt by Association: The Complexity of Breast Cancer

Ramin Shiekhattar, Ph.D., The Wistar Institute, Philadelphia, Pennsylvania

Researchers have identified BRCA1 and BRCA2 as genes that can be changed or mutated leading to the development of breast cancer. These genes are associated with an increased risk of familial breast cancer. Proteins are synthesized from genes and carry out the instructions contained within the DNA. Alterations at the genomic level lead to a protein process gone awry. By examining protein complexes rather than just one protein, Dr. Ramin Shiekhattar and co-investigators at the Wistar Institute hope to discover novel proteins that may be associated with both familial and sporadic incidences of breast cancer. They hypothesize that proteins “guilty by association” with BRCA1 may assist in cancer progression. To analyze BRCA1 containing protein complexes, Dr. Shiekhattar and his colleagues combined modern molecular biology...
techniques with classic biochemical studies. By labeling BARD1 (a protein known to interact with BRCA1) with a molecular tag, the scientists were able to use it as a hook to fish out other proteins in the BRCA1 complex. Members of the protein complex could then be isolated by chromatography and identified using mass spectrometry. The proteins found to associate with the new complex called BRCC (BRCA1 and BRCA2 containing complex) were BRCA1, BRCA2, RAD51, BRCC36, and BRCC45. The last two proteins, BRCC36 and BRCC45, are novel proteins. Exploring the function of the complex, the researchers were able to demonstrate a ligase activity of BRCC. The complex plays a regulatory role in DNA repair by targeting proteins that are known to activate the cell proliferation cycle for degradation. By halting cell proliferation, BRCC acts as a stopgap measure to allow the cell to repair any damage to the DNA following adverse events such as ionizing radiation prior to cell division. If one protein of the complex is mutated and does not function properly, BRCC may fail in its role, thus leading to cell division without DNA repair, one step in the process of carcinogenesis. Proteins linked to the complex are therefore suspects in the development of breast cancer and are “guilty by association” according to Dr. Shiekhattar. Understanding how the proteins within the holoenzyme complex of BRCC function may lead to new insights in breast cancer research as well as new targets for future therapies. This research was made possible through an FY01 BCRP Idea Award.

Additional details about this research have been published in the following journal article:


**Bryostatins: Potential Breast Cancer Therapeutic Agents from the Sea?**

**Margo Haygood, Ph.D., University of California, San Diego**

Bryostatins, a unique family of naturally occurring compounds, are found only in the marine bryozoan *Bugula neritina*. Bryostatins work through the protein kinase C (PKC) signaling pathway to alter cellular activity unlike most chemotherapeutic drugs, which kill all rapidly growing cells in the body thereby causing serious side effects. Bryostatins also interact with many chemotherapeutic agents and enhance their effectiveness. In addition, bryostatins sensitize human breast cancer cells to the cytotoxic effects of anticancer agents, resulting in lower dose requirements and less toxicity. Finally, bryostatin 1 holds great promise for the treatment of breast cancer and for enhancing lymphocyte survival during radiation treatment. There are 19 known bryostatins, some or all of which may be valuable therapeutic agents. However, research on and development of bryostatins, including bryostatin 1, are severely limited by an inadequate supply of these compounds. Dr. Margo Haygood, a marine biologist from the University of California, San Diego, previously demonstrated that a bacterial symbiont of *B. neritina* is the source of the bryostatins. Through research funded by an FY99 BCRP Idea Award, Dr. Haygood is looking for ways to increase production of these compounds including cloning of the genes responsible for biosynthesis of these compounds, expressing these genes in a more easily cultured organism, and/or finding ways to culture the symbiotic bacteria such that large amounts of these compounds can be produced. It is expected that this work will provide an unlimited supply of the bryostatins and will also allow for the development of analogs with improved biological activity.

**Identifying the Risk of Breast Cancer Recurrence in Patients Treated with Tamoxifen**

**Dennis Sgroi, M.D., Massachusetts General Hospital**

Tamoxifen, a drug that blocks the interaction between estrogen and its receptor, is among the most widely used chemotherapeutic agents for the treatment of breast cancers that express the estrogen receptor (ER). Approximately 30% of patients do not respond to tamoxifen treatment and patients who respond initially to treatment may acquire tamoxifen resistance and eventually fail treatment. The ability to determine which patients will not respond well to tamoxifen therapy would allow earlier use of other, potentially more effective, therapies and could result in a better
Breast Cancer occurs more frequently in some racial and ethnic groups than in others and not all women who develop breast cancer have the same chance of surviving. More black women than white women, on average, die of their disease. One reason for this difference in survival is that breast cancer in black women tends to be diagnosed at a more advanced stage, when it can be treated less successfully. Disparate survival rates from breast cancer among women from different racial and ethnic groups also may be due to differences in the treatment they receive. The BCRP believes that a multilevel strategy is needed to address these health disparities, including the enhancement of the research training and capacity of minority and underserved institutions. To this end, the BCRP initiated the HBCU/MI Focused Training and HBCU/MI Partnership Training Awards in FY99. The goal of these award mechanisms is to create collaborative partnerships in which HBCU/MI faculty investigators work alongside established breast cancer researchers. The intent is to train individual scientists or establish training programs at the HBCU/MI to increase the number of HBCU/MI investigators studying breast cancer research and the disparities associated with this disease. The mentoring and experience gained through these awards should enable the HBCU/MI investigators to prepare and submit high-quality research proposals, thereby establishing a well-funded breast cancer research program at HBCU/MI. Since its inception, ten awards, involving seven HBCU/MI and nine collaborating institutions (as illustrated in the accompanying figure), have been granted to support collaborative projects in such areas as genomic and proteomic analysis of signaling pathways, antiproliferative biomarkers, diagnostic breast imaging, health disparities, and the interrelationships of hormones, diets, body size, and breast cancer.

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>HBCU/MI</th>
<th>Collaborating Institution</th>
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<tbody>
<tr>
<td>1999</td>
<td>Xavier University</td>
<td>Tulane University</td>
</tr>
<tr>
<td></td>
<td>Florida A&amp;M University</td>
<td></td>
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<tr>
<td>2000</td>
<td>Howard University</td>
<td>Georgetown University</td>
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<tr>
<td></td>
<td>Walter Reed Army Institute of Research</td>
<td></td>
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<tr>
<td>2002</td>
<td>Howard University</td>
<td>Howard University</td>
</tr>
<tr>
<td></td>
<td>Winston-Salem State University</td>
<td>Johns Hopkins University</td>
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<tr>
<td></td>
<td>Meharry Medical College</td>
<td>Vanderbilt University Medical Center</td>
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<tr>
<td>2003</td>
<td>University of Texas at Brownsville and Texas Southmost College</td>
<td>University of Texas School of Public Health at Houston</td>
</tr>
<tr>
<td></td>
<td>Morehouse School of Medicine</td>
<td>Mayo Clinic Comprehensive Cancer Center</td>
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<tr>
<td></td>
<td>Xavier University</td>
<td>Tulane Cancer Center</td>
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</table>

“The Breast Cancer Research Program continues to encourage the scientific community to focus our attention on the problem of breast cancer by providing unique funding mechanisms like the Breast Cancer Center of Excellence Awards. In my experience, it would not have been possible to bring together so many leading scientists, regardless of their location, to work on a single problem and speed progress against this devastating disease, except through this award mechanism.”

Saraswati Sukumar, Ph.D., FY03 BCRP Breast Cancer Center of Excellence Award Recipient
prognosis for these women. However, there is currently no reliable method of predicting which ER+ patient will not respond to tamoxifen treatment.

With funding received from a FY02 BCRP Exploration Award, Dr. Dennis Sgroi of Massachusetts General Hospital is looking at the levels of expression of certain genes in breast cancer as a way of identifying prognostic categories that may guide cancer treatment choices. In a recently published study, Dr. Sgroi and his colleagues performed genome-wide microarray analysis on 60 tumor samples taken from patients who had received tamoxifen treatment for early-stage, ER+ breast cancer. Of these 60 patients, 32 remained disease-free for an average of 8 years, while 28 experienced tumor recurrence or metastasis. This study revealed that the ratio between the expression levels of two genes, HOXB13 and IL17BR, was a strong predictor of tumor recurrence. High levels of HOXB13 or low levels of IL17BR expression suggested that tamoxifen therapy would fail. Although these studies need to be validated in a larger population, it appears that this simple test will assist oncologists in deciding whether to use tamoxifen therapy or an alternative therapy in treating ER+ breast cancer patients.

Additional information pertaining to this research can be found in the following publication:


Improving the Management of Breast Cancer through Sentinel Lymphadenectomy and Detection of Molecular Biomarkers

Kathryn M. Verbanac, Ph.D., and Lorraine Tafra, M.D., East Carolina University

Sentinel lymphadenectomy (removal of only a few sentinel nodes most likely to contain disease; SL) for breast cancer is becoming the standard of care for select patients treated by experienced surgeons. This technique is a minimally invasive diagnostic procedure that is able to predict the likelihood of metastases and, thereby, avoid the morbidity associated with total lymph node removal. BCRP award recipients Drs. Lorraine Tafra and Kathryn Verbanac from East Carolina University were among the first in the world to implement SL in breast cancer patients. Their multi-institutional study to assess the accuracy of this technique in the management of breast cancer was supported, in part, through an FY97 BCRP Career Development Award. This study showed the general utility of SL and distinguished factors that play an important role (patient age, surgical experience, and tumor location) from those that are irrelevant (prior surgery, tumor size, and technetium99 timing) to SL. Drs. Verbanac and Tafra received an FY99 BCRP Clinical Translational Research Award that allowed them to expand their work on SL and evaluate molecular assays to detect breast cancer biomarkers in sentinel lymph nodes (SLN). This work has the potential for high impact in breast cancer diagnosis and treatment because current methods using histological analysis of postsurgical lymph node slices have a high false-negative rate, with ~30% of women developing recurrent disease despite histologically negative lymph nodes. In previous studies, Dr. Verbanac and colleagues identified two markers, mammaglobin (MGB) and carcinoembryonic antigen (CEA), that appear to be highly indicative of micrometastases in SLN. In the current study, reverse transcriptase-polymerase chain reaction (RT-PCR), a detection technique that is ~100 times more sensitive than routine pathology methods, is being used to detect both MAM and CEA in SL specimens. The sensitivity, accuracy, and prognostic value of the RT-PCR method is being compared to standard techniques. Though still under way, these studies suggest that RT-PCR-based detection of MGB and other biomarkers in SLN increases the identification of occult metastases over the existing methodology and may serve as a more accurate predictor of disease recurrence and patient survival.

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

Breast Cancer Research Program


**Bottom Line**

Since 1992, the BCRP has provided opportunities to accelerate discovery and eradication of breast cancer. To date, the program has been responsible for managing almost $1.67B in congressional appropriations, which has resulted in 4,073 awards for FY92–03. BCRP-supported researchers are exploring revolutionary ideas and emerging trends across all areas of laboratory, clinical, behavioral, and epidemiologic research. Research highlights, award data, and abstracts of funded BCRP proposals can be viewed on the CDMRP website (http://cdmrp.army.mil).

**Fiscal Year 2004**

**Integration Panel Members**

M. Carolina Hinestrosa, M.A., M.P.H. (Chair), Nueva Vida
Patricia S. Steeg, Ph.D. (Chair Emeritus), National Cancer Institute
Frances M. Visco, Esq. (Chair-Elect), National Breast Cancer Coalition
Anna D. Barker, Ph.D. (Executive Committee, Member-at-Large), National Cancer Institute
Graham Casey, Ph.D., Lerner Research Institute, Cleveland Clinic
Mauro Ferrari, Ph.D., The Ohio State University
H. Kim Lyerly, M.D., Duke Comprehensive Cancer Center
Ngina Lythcott, Dr.P.H., National Black Women’s Health Project and Mailman School of Public Health, Columbia University
Renata Pasqualini, Ph.D., The University of Texas M.D. Anderson Cancer Center
Don Plewes, Ph.D., University of Toronto Sunnybrook & Women’s College Health Sciences Centre
William H. Redd, Ph.D., Mount Sinai-New York University Medical Center
Rosemary Rosso, J.D., Greater Baltimore-Washington Breast Cancer Group
Steven Shak, M.D., Genomic Health, Inc.
Survivor Serves as Consumer Reviewer for Department of Defense Grants

By Deanna Beyer, M.S., R.N. — Twelve year breast cancer survivor

Deanna Beyer, a breast cancer survivor and advocate, recounts her experience as a BCRP Consumer Peer Reviewer and how she impacted breast cancer research.

Those who have lived with, through, and beyond the experience of having cancer often develop a desire to help others who are newly diagnosed. This has been described as the concept of the veteran helping the rookie.

Recently, I had an opportunity to help on a broad level by serving as a Consumer Reviewer for the Department of Defense (DOD) Breast Cancer Research Program.

Several research panels met in Washington DC, in August to review more than 1,200 national and international research proposals aimed at the prevention, detection, diagnosis, and treatment of breast cancer. Proposal review includes a two-step process of scientific and programmatic review. Each scientific panel consisted of 20 scientists and two consumer reviewers...

The development of the DOD Congressionally Directed Medical Research Programs was the result of grassroots efforts and increasing public awareness. Because of this, consumer reviewers, who are advocates for issues of breast cancer, have been included on the decision-making panels. As the medical director of the program stated, “Researchers working with test tubes and slides can become somewhat removed from the human side of cancer. Consumer reviewers put a face on cancer and have an ability to put fire in the belly of researchers.”

In my own lifetime I have experienced the tremendous difference medical research has made with the treatment of breast cancer. My mother was diagnosed in 1950. At that time, treatment options were extremely limited and basically consisted of radical disfiguring surgery or benign neglect. Her disease progressed rapidly, and she died in 1952. When I was diagnosed in 1989, I benefited from tremendous progress in treatment that had been made as the result of medical research. I had multiple treatment options from which to choose, and the potential for cure was very hopeful.

Progress for future advances in the prevention, detection, diagnosis, and treatment of breast cancer continues to be very hopeful. It was very exciting to have an opportunity to have a voice in the selection of research proposals that could have a tremendous impact on the future health of women, including my own daughters and granddaughters.

* This article first appeared in the University of Michigan Comprehensive Cancer Center’s journal Progress (Winter 2002).