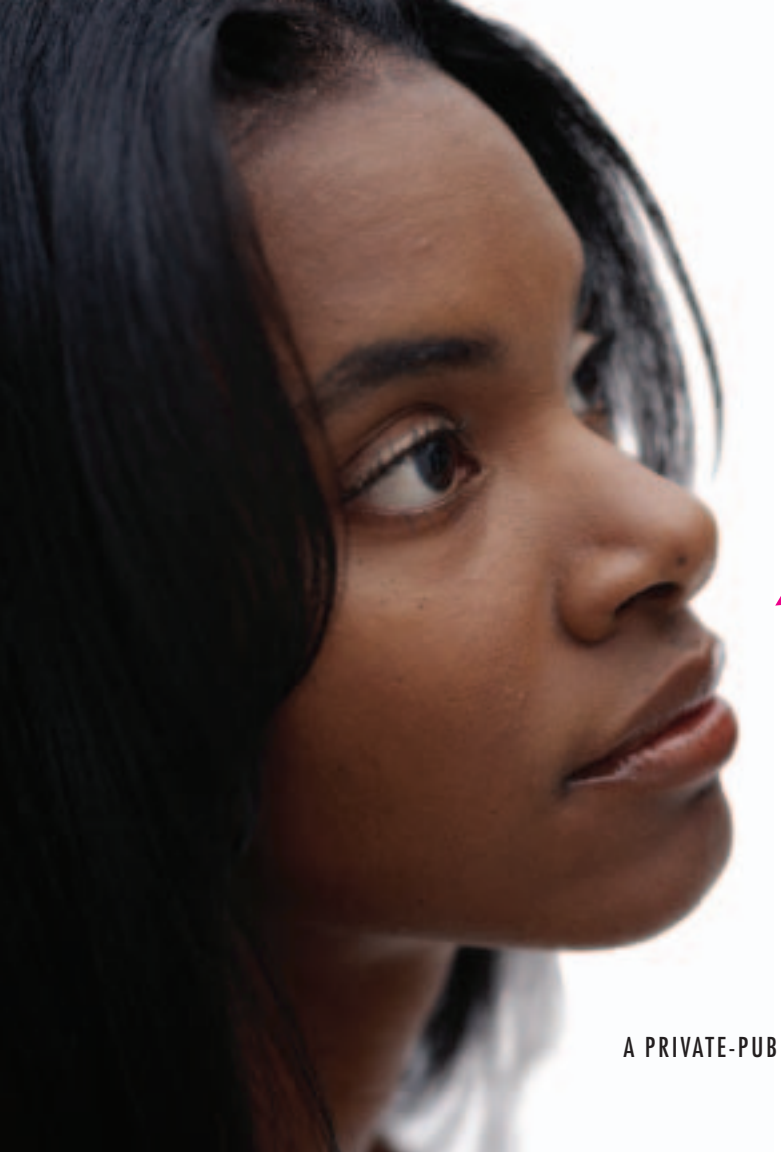


THE AVON–NCI PROGRESS FOR *patients* AWARDS PROGRAM

to support innovative research in the prevention, detection, diagnosis, and treatment of breast cancer

A PRIVATE-PUBLIC PARTNERSHIP OF THE AVON FOUNDATION & THE NATIONAL CANCER INSTITUTE

THE AVON–NCI

PROGRESS FOR *patients*

AWARDS PROGRAM

Introduction

In 2002, the Avon Foundation (AVON) and the National Institutes of Health (NIH) National Cancer Institute (NCI) announced the AVON-NCI Progress for Patients (PFP) Awards Program, a special private-public partnership to fund innovative research for preventing, detecting, diagnosing, and treating breast cancer. AVON pledged $20 million to fund breast cancer research over 5 years through a limited competition involving institutions with NCI Cancer Center Support and Specialized Programs of Research Excellence (SPORE) grants. The NCI will continue to contribute funds, conduct peer review, and monitor project progress.

The PFP Program seeks to make recent discoveries in basic science available to women at risk for breast cancer and to those who need treatment. It will capture the broadest possible range of interventions in prevention or risk assessment, breast imaging, pathology, radiation oncology, drug development, and biomarker analysis. The program goal is to increase the number of new early-phase clinical breast cancer interventions and help move promising drugs, biomarkers, and procedures into phase III clinical trials.

AVON has been a steadfast ally in supporting breast cancer research and care for under-served populations, sponsoring local and national initiatives that have raised funds in 50 countries through the Avon Foundation Breast Cancer Crusade. As a leading advocate for women's health, AVON expects the PFP Program to further its mission to help reverse health care disparities and accelerate critical research in breast cancer prevention, detection, and treatment.

The NCI is dedicated to eliminating cancer suffering and death, and has a long history of conducting and supporting breast cancer research. The AVON-NCI PFP awards help minimize delays in conducting new and promising phase I and II clinical trials, and risk assessment and biomarker validation studies.

Nineteen projects have been awarded to date through administrative supplements to SPORE grants and Cancer Center Support grants. The PFP Program supports these projects for up to 2 years. Funding for the first four projects

went to SPORE investigators in 2002. These initial grant supplement awards included all areas of clinical investigation important to breast cancer, including prevention, detection, diagnosis, prognosis, and treatment. In 2003, another four projects for SPORE investigators and 13 for investigators at NCI-designated cancer centers were funded.

On March 1, 2004, the NCI received proposals for 13 projects from breast SPORE investigators and 19 from investigators at NCI-designated cancer centers. The projects encompass clinical trials (early detection, chemoprevention, treatment, targeted therapies, vaccine therapy, chemotherapy, diagnosis, prognosis, biomarker-based risk prediction, and prevention) and biomarker validation studies. The proposals will be reviewed in May 2004 and the most promising will be funded in summer 2004. Through this partnership, the NCI expects to issue calls for additional applications in 2005.

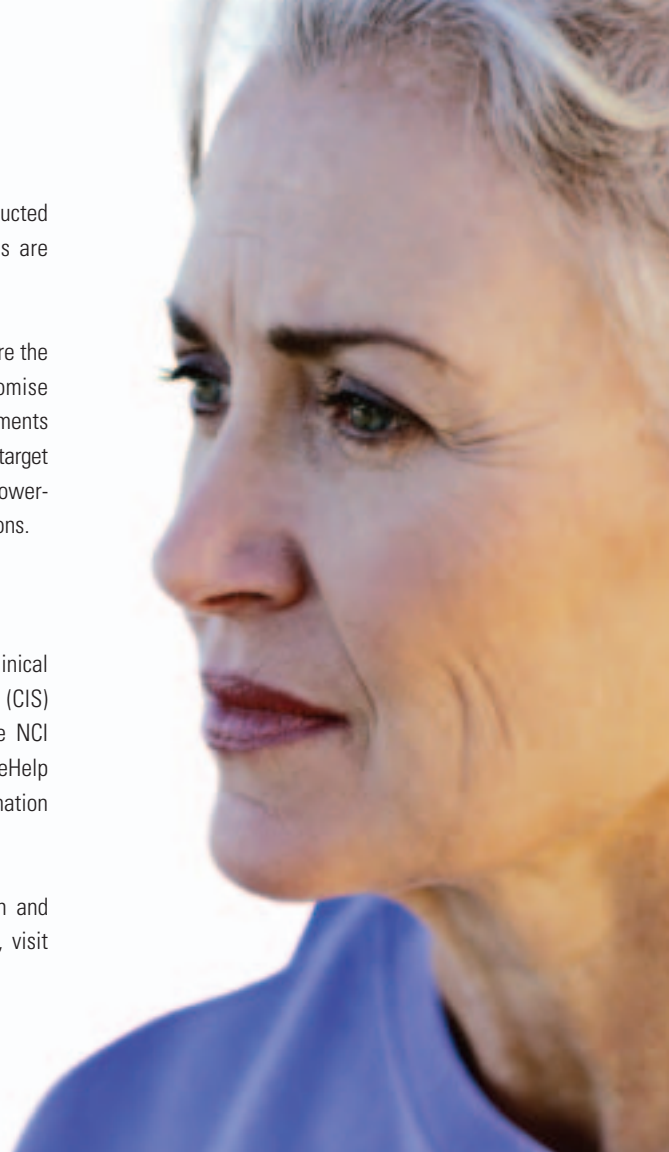
This special private-public partnership encourages creative, productive collaboration among investigators and demonstrates the potential to quickly make new and effective interventions available to women. A formal evaluation of the PFP awards program will be conducted when the program has matured and the studies are completed.

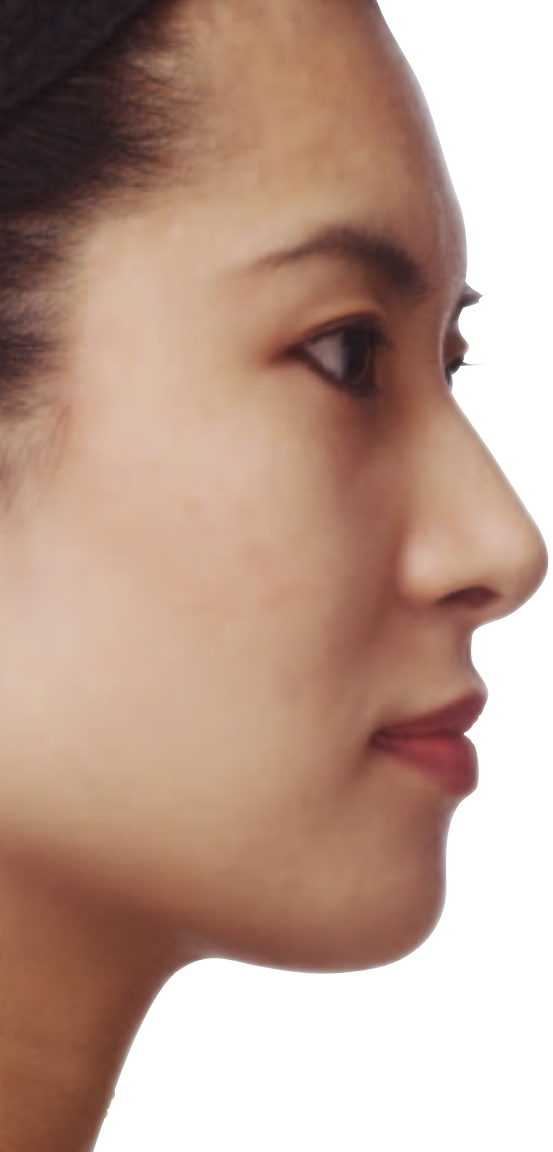
Exciting breakthroughs await scientists who explore the complex pathways of the cell, tapping the promise implicit in gene therapy, and aiming curative treatments directly at diseased cells. By allowing researchers to target breast cancer more quickly, the PFP Program is a powerful catalyst for advancing breast cancer interventions.

INFORMATION

For more information about breast cancer and clinical trials, call the NCI Cancer Information Service (CIS) at 1-800-4-CANCER (1-800-422-6237) or visit the NCI Web site at www.cancer.gov and click on the LiveHelp icon to instant message with a CIS cancer information specialist.

For more information about the Avon Foundation and its women's health and empowerment programs, visit www.avonfoundation.org, or call 212-282-5666.





Clinical Trials

PREVENTION STUDIES

Markers of Short-Term Breast Cancer Risk in Fine-Needle Aspiration (funded 2003)

Victoria Seewaldt, M.D.

Breast Cancer SPORE, Duke University

This study is looking for biological markers that predict short-term breast cancer risk so doctors can identify women who are most likely to benefit from preventive therapy, and identify their response to chemoprevention drugs. The researchers are trying to determine if the loss of expression of a gene called retinoic acid receptor-beta-2 (RARβ2) can be used to predict breast cancer risk in women at high risk for breast cancer. This extended pilot study tests the feasibility of using the presence of a chemical activity called RARβ2-promoter methylation in specimens taken from breast fine-needle aspiration as a chemoprevention marker. Studies conducted with these high-risk women could immediately help prevent breast cancer by identifying patients who have active RARβ2 signaling pathways and may be candidates for chemoprevention with vitamin A derivatives called retinoids. Women whose pathways are inactive may be appropriate candidates for other kinds of intervention.

Surrogate End Points in Prevention Studies and Ductal Lavage (funded 2003)

Seema A. Khan, M.D.; Helen Krontiras, M.D.; Saraswati Sukumar, Ph.D.

Breast Cancer SPOREs:
Northwestern University, University of Alabama at Birmingham, and Johns Hopkins University

In this phase I study, investigators are evaluating the molecular effects of tamoxifen, a medication that interferes with estrogen activity, as a chemopreventive agent in repeat breast epithelial cell samplings from milk ducts of the breasts (ductal lavage). The researchers evaluate genes that may be associated with cancer progression and identify protein patterns that are associated with risk or treatment. The study, at Northwestern Memorial Hospital and the University of Alabama at Birmingham, will include women who are at increased risk of breast cancer or who have been diagnosed with duct carcinoma *in situ* or small invasive cancers. Another participating institution, Johns Hopkins, will perform the molecular

analyses. This study could potentially identify surrogate (substitute) biomarkers that could be used to monitor the effectiveness of chemopreventive agents against breast cancer.

EGFR Pathway Modulation in DCIS (funded 2003)
Christina I. Truica, M.D.
The Vanderbilt-Ingram Cancer Center at Vanderbilt University

In this study, researchers are investigating Iressa® (ZD1839)—a chemotherapy medicine originally used to treat non-small cell lung cancer—for use in ductal carcinoma *in situ* (DCIS), an early-stage breast cancer that expresses epidermal growth factor and its receptor, called EGFR, in a high proportion (50% to 80%) of cases. The researchers identify optimal biological markers of EGFR inhibition and correlate those changes with biological end points like cell growth and programmed cell death. Cell samples are analyzed before and after treatment for proteins that ZD1839 specifically regulates. Data collected in this study will help doctors design future large chemoprevention trials that test ZD1839 in women who are at high risk of breast cancer.

TREATMENT STUDIES

Biological Markers in Breast Cancer Treated by Neoadjuvant Chemotherapy (funded 2003)
Alphonse Taghian, M.D., Ph.D.
Breast Cancer SPORE,
Dana-Farber Harvard Cancer Institute

In this study, investigators are trying to find a correlation between specific genes and the response of breast cancer cells to the anticancer drugs doxorubicin and paclitaxel. Results of this study may eventually allow doctors to use such genetic markers to help choose the best neoadjuvant therapies (treatments like chemotherapy or radiation that are given before the primary treatment) for each patient. In this treatment trial, investigators use tumor biopsy samples and specific genes to measure the response to doxorubicin and paclitaxel. They use conventional clinical results (end points) and magnetic resonance imaging (MRI) to measure the response, and they use gene array techniques to evaluate a tumor's genetic fingerprint and correlate clinical end points to other markers. The investigators are addressing an important problem—why some tumors respond to certain chemotherapy agents and others do not. By studying the effect of single-agent chemotherapy given before primary treatment, they will be able to evaluate the impact of the chemotherapy agent directly on the tumor.

Response to Preoperative Therapy in Breast Cancer (funded 2003)
Vered Stearns, M.D.
Breast Cancer SPORE, Johns Hopkins University

In this pilot study, investigators are working to identify surrogate markers of response or resistance to the chemotherapy drug docetaxel for use in future trials where docetaxel will be combined with new drugs. Findings from this study could significantly improve breast cancer treatment and long-term prognosis. Forty women with newly diagnosed breast cancer receive four cycles of docetaxel every 14 days. Core breast biopsies are taken before they start the drug, 1 week after the first cycle, and during surgery. Researchers correlate changes in cell growth and programmed cell death and other changes with the response to docetaxel. This study may identify response markers that can be used to monitor treatment of breast cancer with docetaxel and other chemotherapy drugs.

Phase I Study of Docetaxel/STI571 in Breast Cancer (funded 2003)

Antonio C. Wolff, M.D.

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University

This treatment clinical trial will evaluate the drug effects of combining the chemotherapy drug docetaxel with a receptor tyrosine kinase inhibitor called STI571 in patients with locally advanced and metastatic breast cancer. The greatest potential of this and similar drug combinations might be to control residual disease, but careful drug studies must first rule out any harmful drug interactions and examine potential biomarkers. The purpose of this early-phase clinical trial is to evaluate the drug profile of STI571 and docetaxel in combination. Among other effects, the study will evaluate the response rate, duration, and time to treatment failure in patients on the combined drugs.

Phase I Study of Telomerase Peptide Vaccination for Patients with Advanced Breast Cancer (funded 2003)

Robert H. Vonderheide, M.D., D.Phil.

The Abramson Cancer Center at the University of Pennsylvania

In this immunotherapy clinical trial, researchers want to know if a protein called telomerase reverse transcriptase (hTERT) can work as an effective immune target in breast cancer cells. The researchers will determine whether it is safe to vaccinate advanced breast cancer patients with increasing doses of hTERT administered under the skin, and assess the effect of vaccination with hTERT 1540 peptide on tumor response. Patients with advanced breast cancer are vaccinated against the hTERT 1540 peptide with drugs that enhance the treatment (adjuvants). Careful immunological monitoring is conducted before and after vaccination to measure the potency of the hTERT 1540 peptide and the effectiveness of the adjuvants.

Adenovirus p53-Infected Dendritic Cell Vaccine for Breast Cancer (funded 2003)

James E. Talmadge, Ph.D.;

Dmitry I. Gabrilovich, M.D., Ph.D.

The Eppley Cancer Center at the University of Nebraska Medical Center and the Moffitt Cancer Center and Research Institute at the University of South Florida

This immunotherapy study proposes to show that vaccination with adenovirus-p53–transfected dendritic cells can induce a p53-specific T-cell response whose extent depends on the timing of vaccination relative to primary cancer therapy. The researchers examine whether cancer vaccination should occur early, during primary cancer therapy, before T-cell polyclonality—which increases the efficiency of the immune response to invading organisms—is lost, or after primary therapy, when T-cell polyclonality may be lost but when T cells responding to the vaccine are no longer exposed to the toxic primary cancer therapy. T-cell polyclonality is critical to a therapeutic response because it provides a broad response against multiple antigens and a more effective immune response. The researchers directly compare

adenovirus-p53 vaccination during primary therapy to adenovirus-p53 vaccination after surgery, chemotherapy, and radiotherapy.

ZD1839 in Tamoxifen-Resistant Metastatic Breast Cancer (funded 2003)

Gary N. Schwartz, M.D.

The Norris Cotton Cancer Center at the Dartmouth-Hitchcock Medical Center

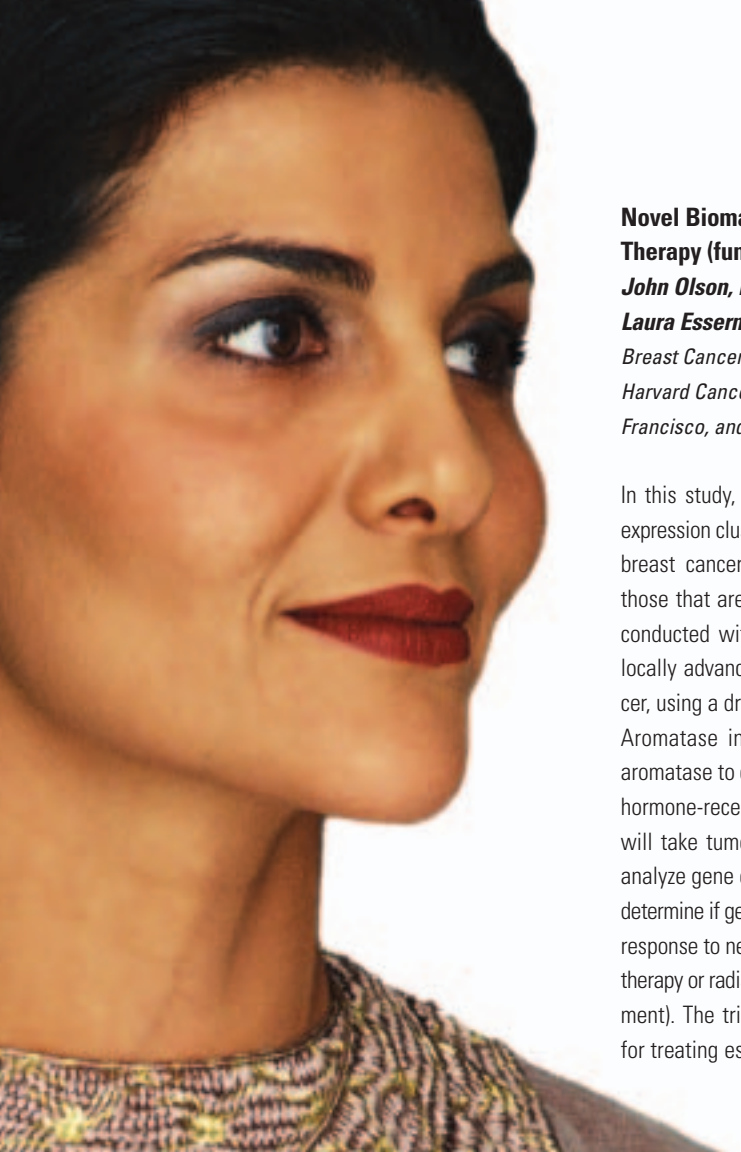
This study will show whether the drug ZD1839, an epidermal growth factor receptor-specific receptor tyrosine kinase inhibitor, can reverse newly acquired resistance to tamoxifen, a cancer medication that interferes with estrogen activity. Researchers will compare the clinical activity of combined ZD1839 and tamoxifen to the activity of ZD1839 alone. They will also validate imaging scans of lesions and plasma DNA assays as early indicators of a response to ZD1839, assess a potential drug interaction between tamoxifen and ZD1839, and, in some patients, biopsy metastatic lesions before and after ZD1839 treatment to show continued signal activity. This study will lay the groundwork for future trials of combinations of endocrine therapy and signaling inhibitors in breast cancer patients. The approach could make endocrine therapy much more effective in curing and treating early-stage and advanced breast cancers.

Monitoring Breast Cancer Angiogenesis During rhuMab-VEGF (Avastin®) Treatment (funded 2003)

James K.V. Willson, M.D.

The Case Comprehensive Cancer Center

In this NCI-Cancer Therapy Evaluation Program clinical trial, investigators are evaluating the effect of an angiogenesis (new blood vessel formation) inhibitor called bevacizumab (also called rhuMAb VEGF, and Avastin®) in patients with locally advanced breast cancer who are receiving preoperative chemotherapy with the chemotherapy drug docetaxel. The researchers are working to show that adding bevacizumab, which inhibits blood vessel formation, to docetaxel, which interferes with cancer cell growth, will enhance the response of breast cancer compared with docetaxel alone. This clinical trial and related studies will offer valuable insight into the biologic activity of angiogenesis inhibitors in breast cancer and will help researchers design future angiogenesis-based studies.



Novel Biomarkers for Aromatase Inhibitor Therapy (funded 2002)

John Olson, M.D., Ph.D.; Lyndsay N. Harris, M.D.; Laura Esserman, M.D., M.B.A.; Lisa A. Carey, M.D.

Breast Cancer SPOREs: Duke University, Dana-Farber Harvard Cancer Institute, University of California, San Francisco, and University of North Carolina at Chapel Hill

In this study, researchers are trying to identify a gene expression cluster that can be used to distinguish forms of breast cancer that respond to estrogen therapy from those that are resistant. A phase II clinical trial will be conducted with 90 postmenopausal women who have locally advanced estrogen-receptor-positive breast cancer, using a drug called letrozole, an aromatase inhibitor. Aromatase inhibitors limit the ability of the enzyme aromatase to create estrogen—a major growth factor in hormone-receptor-positive breast cancers. Researchers will take tumor biopsies before and after therapy, and analyze gene expression profiles. Study results will help determine if gene expression profiles can predict a patient's response to neoadjuvant therapy (treatments like chemotherapy or radiation that are given before the primary treatment). The trial could identify a new predictive marker for treating estrogen-receptor-positive breast cancer.

Antiangiogenic Therapies for Breast Cancer (funded 2002)

Harold J. Burstein, M.D., Ph.D.

Breast Cancer SPORE,
Dana-Farber Harvard Cancer Institute

This phase II clinical trial will test the effectiveness and toxicity of a new breast cancer treatment that combines the chemotherapy drug vinorelbine with the anti-angiogenic (reduces the growth of new blood vessels) drug bevacizumab in women who have metastatic stage IV breast cancer. Findings from the study could help researchers design better ways to use anti-angiogenic drugs and may create new approaches to breast cancer treatment. This study could significantly improve treatment strategies for late-stage breast cancer.

EARLY DETECTION, DIAGNOSIS, PROGNOSIS, & PREDICTION STUDIES

Biomarkers, Breast Density, and Risk-Reduction Perspectives (funded 2003)

Michael F. Press, M.D., Ph.D.;
Jeffrey N. Weitzel, M.D.
The Norris Comprehensive Cancer Center at
the University of Southern California and the City of Hope
National Medical Center & Beckman Research Institute

Based on previous studies, a regimen of combined drugs that includes gonadotropin releasing hormone (GnRHa); deslorelin, a drug that inhibits the growth of malignant cells; and partial replacement of testosterone and a form of estrogen called 17 beta-estradiol should reduce breast cancer risk by one-third if used for 5 years and by 70% if used for 15 years. In this risk phase II biomarker trial, researchers are studying the GnRHa regimen in unaffected premenopausal women who have a *BRCA* gene abnormality (group 2), including women who plan to have a risk-reducing bilateral mastectomy in 6 months or more (group 1). Mammograms, breast imaging (with magnetic resonance imaging), and breast biopsies are taken before the study and after at least 6 months on the GnRHA regimen, before mastectomy (group 1), or after 10 months of the regimen (group 2). Imaging studies are correlated with tissue comparisons and immunohistochemical and expression microarray studies of tissues. Quality of life and perspectives about risk-reduction options are measured at the beginning of the study, after 6 months of the GnRHA regimen, and 4 months after surgery (group 1) or another 4 months of the regimen (group 2). The women in group 1 will have a unique perspective, having experienced a hormonal chemoprevention regimen and risk-reduction surgery.

Estrogen-Related Receptor Alpha as a Novel Biomarker for Breast Cancer (funded 2003)

Janet Mertz, Ph.D.
The Comprehensive Cancer Center at
the University of Wisconsin

This study seeks to learn whether a woman's estrogen-related receptor alpha (ERRα1) status can work as a new biomarker, together with estrogen receptor alpha, the progesterone receptor, and the ErbB2 receptor, to improve doctors' ability to determine a prognosis and decide on the best treatments for breast cancers. Researchers also will look for correlations between ERRα1 status, currently assayed biomarkers, course of treatment, and patient outcome. A good correlation between ERRα1 status and some of the other parameters would justify a large-scale study to confirm whether ERRα1 is a good candidate for development as a prognosticator and predictor of therapeutic benefit from current drug treatments, and as a new drug target.

FEZ1/LZTS1 Gene Expression as a Predictor of Response to Taxol® (funded 2003)

Carlo M. Croce, M.D.
The Kimmel Cancer Center at
Thomas Jefferson University

This study seeks to determine whether loss of expression of the tumor suppressor gene *FEZ1/LZTS1* can predict a response of breast cancer to Taxol®, a trade name for the anticancer drug paclitaxel. Study results should help predict which patients will and will not respond to Taxol®. The research examines tumor tissue from 120 women with measurable primary or metastatic breast

cancer who are receiving paclitaxel treatment. A clear-cut correlation between alterations in *FEZ1/LZTS1* expression and resistance to paclitaxel could offer a useful clinical screening tool for choosing the best candidates for paclitaxel treatment.

Subareolar Injection Site for Sentinel Lymph Node Biopsy (funded 2003)

Gildy Vallarta Babiera, M.D.
The University of Texas M.D. Anderson Cancer Center

This study hypothesizes that the subareolar position of the breast (below the circular region around the nipple), as the site of injection for sentinel lymph node biopsy in women undergoing regional nodal evaluation for breast cancer, is just as accurate as the peritumoral (around or near the tumor) injection site in predicting the involvement of lymph nodes with metastasis. To test this hypothesis, the study will determine the accuracy of the subareolar injection in predicting the regional status of the lymph nodes. Then researchers will evaluate the lymphatic drainage patterns of the breasts by comparing the subareolar and peritumoral injection sites. If the subareolar injection site is shown to be just as accurate and can be used as the optimal site for sentinel lymph node biopsy procedures for breast cancer, the study will validate this new injection procedure and compare its images with those obtained by peritumoral injection.

Specific Characterization of Biomarkers Using Proteomic Analysis of Ductal Lavage and Nipple Aspirate Fluid Samples in Patients with Invasive Breast Cancer, Ductal Carcinoma *in situ,* and Atypical Ductal Hyperplasia (funded 2003)

David R. Brenin, M.D.
The Cancer Center at the University of Virginia Health Sciences Center, Charlottesville

This study seeks to further analyze previously described biomarkers that were found in the nipple aspirate fluid of women with breast cancer for use in breast cancer screening. Researchers will identify the proteins responsible for differences seen in the mass spectrometry protein signatures of fluid from breasts with cancerous or precancerous disease and breasts with no evidence of disease, to determine if the specific protein contents of breast fluid from women with invasive breast cancer, ductal carcinoma *in situ,* and atypical ductal hyperplasia are different, and to compare the effectiveness of nipple aspiration and ductal lavage in procuring adequate fluid samples for protein analysis. Ninety percent of breast cancers originate from epithelial cells that line the milk ducts of the breasts. Because it is generally believed that breast cancer begins with the slow progression of breast epithelial cells through a spectrum of changes, resulting in a clinically detectable mass or mammographic finding, it is reasonable that doctors might be able to use material from the ductal system to detect otherwise nondetectable, early-stage malignancies or premalignant conditions. The researchers hypothesize that unique proteins will be present in the ductal fluid of women with invasive breast cancer, ductal carcinoma *in situ,* and atypical ductal hyperplasia that differ from proteins in fluid from nondiseased breasts, and that there is no difference between nipple aspiration and ductal lavage in obtaining those proteins.

Validation of a Breast Biomarker Panel (funded 2002)

Nicole Urban, Sc.D.; Mack N. Barnes, M.D.; Mary B. Daly, M.D., Ph.D.; Gordon B. Mills, M.D.

Ovarian Cancer SPOREs:
Fred Hutchinson Cancer Research Center, University of Alabama at Birmingham, Fox Chase Cancer Center, and University of Texas M.D. Anderson Cancer Center

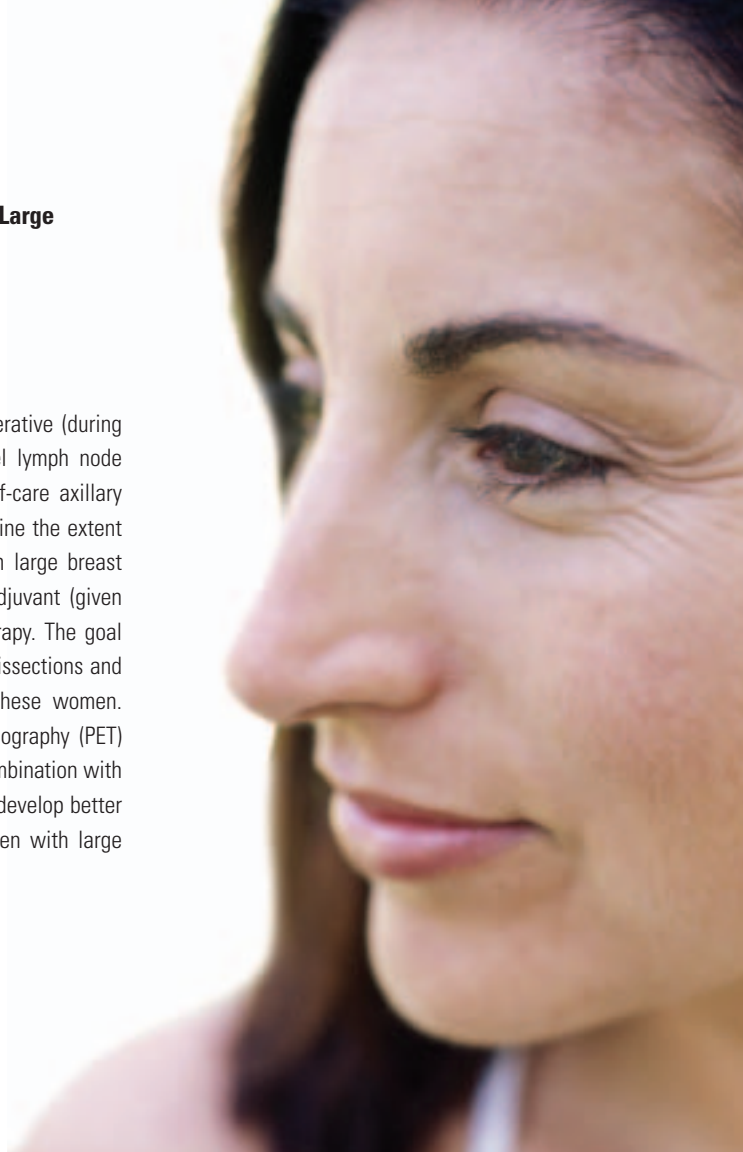
This validation study will evaluate a promising series of serum-based early-detection biomarkers for breast cancer and identify an optimal panel of these biomarkers to use as a mammography screening tool. Researchers will develop a large repository of well-characterized serum samples (more than 2000) from women who are at high risk of breast cancer (before and after malignancy is detected) and women at average risk who have normal mammograms. If the biomarkers are validated, clinicians will have a new and powerful way to detect and diagnose breast cancer.

Novel Approaches for Patients with Large Breast Cancers (funded 2002)

David W. Ollila, M.D.

Breast Cancer SPORE,
University of North Carolina at Chapel Hill

This study examines the role of intraoperative (during surgery) lymphatic mapping and sentinel lymph node removal as an alternative to standard-of-care axillary (armpit) lymph node dissection to determine the extent or progression of cancer in women with large breast cancers who will be treated with neoadjuvant (given before the primary treatment) chemotherapy. The goal is to reduce the number of lymph node dissections and improve breast preservation rates for these women. An intraoperative positron emission tomography (PET) probe will be used for the first time in combination with tissue and molecular marker analyses to develop better prognostic and predictive tools for women with large breast cancers.



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