THE AVON—NCI
PROGRESS FOR
patients
AWARDS PROGRAM

A CURE IN THE MAKING

A PRIVATE-PUBLIC PARTNERSHIP OF
THE AVON FOUNDATION,
THE FOUNDATION FOR NIH, AND
THE NATIONAL CANCER INSTITUTE

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, which is a 501(c)(3) public charity, pledged $20 million over a 5-year period to fund breast cancer research. This groundbreaking collaborative effort between AVON and NCI, in partnership with the Foundation for the National Institutes of Health, is implemented through a competition limited to institutions with NCI Cancer Center Support and Specialized Programs of Research Excellence (SPORE) grants. The NCI continues to contribute funds, conduct peer review, and monitor project progress.

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.

To date, the PFP Program has awarded 41 grants to projects through administrative supplements to SPORE grants and Cancer Center Support grants. PFP 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. From 2003 through 2005, 13 additional projects for SPORE investigators and 24 for investigators at NCI-designated cancer centers were funded.

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. Since 1992, AVON Breast Cancer Crusade programs in more than 50 countries have raised and awarded more than $400 million to fund access to care and finding a cure for breast cancer. As a leading advocate for women's health, AVON expects the PFP Program to further its mission of helping to reverse health care disparities and accelerating 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 Foundation for NIH was established by the United States Congress to support the NIH mission of improving health through scientific discovery. Guided by a board of directors composed of distinguished leaders in biomedical research, philanthropists, and business leaders, the Foundation for NIH works to advance research by linking the generosity of private-sector donors and partners to NIH programs.

On March 1, 2006, the NCI received proposals from breast SPORE investigators and investigators at NCI-designated cancer centers. The proposed projects

SUMMARY OF AWARDS 2002–2005			
	Projects	Participating Institutions	Total Funding
Treatment Studies	23	19	$ 11,949,290
Prevention Studies	6	7	$ 2,958,442
Early Detection, Diagnosis, Prognosis, and Prediction Studies	12	17	$ 7,944,257

encompass clinical trials (early detection, chemo-prevention, treatment, targeted therapies, vaccine therapy, chemotherapy, diagnosis, prognosis, bio-marker-based risk prediction, and prevention) and biomarker validation studies. These proposals will be reviewed in May 2006 and the most promising will be funded in summer 2006. Through this partnership, the NCI expects to issue calls for additional applications in 2007.

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 research-ers 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 *Need Help?* link to instant message with a CIS cancer infor-mation specialist.

For more information about the Avon Foundation and its women's health and empowerment programs, visit www.avonfoundation.org or call 1-866-505-AVON. Information about the Foundation for the National Institutes of Health is available at www.fnih.org.

Clinical Trials

PREVENTION STUDIES

A Phase II Study of Lovastatin in Women at High Risk for a New Breast Cancer (funded 2005)

*Judy Garber, M.D., Breast Cancer SPORE at Dana-Farber/
Harvard Cancer Center*
*Vered Stearns, M.D., Breast Cancer SPORE at Johns Hopkins
University*

Cholesterol-lowering drugs called statins have shown activity against breast cancer in preclinical studies. In this prevention trial, 50 women who have completed treatment for cancer in one breast, which puts them at elevated risk for cancer in the other breast, will receive lovastatin daily for 24 weeks. Researchers will then examine blood tests, mammograms, and breast biopsies for changes in markers associated with statin activity or breast cancer risk. Changes in markers for risk may not be evident after only 24 weeks, but investigators anticipate finding signs of statin activity: more "good" cholesterol (HDL), less "bad" cholesterol (LDL), and a decline in two established cancer biomarkers—cumulative methylation and protein kinase B activation. The identification of surrogate markers for anti-cancer activity may represent an important advance

for prevention trials, which generally have far fewer patients and shorter durations than needed to give results the most desirable statistical power.

QM-MSP, Ki-67, and Cytomorphology of RPFNA Specimens from High-Risk Women (funded 2005)

*Carol Fabian, M.D., Breast Cancer SPORE at University
of Alabama at Birmingham/University of Kansas*
*Saraswati Sukumar, Ph.D., Breast Cancer SPORE at
Johns Hopkins University*

This study will evaluate options for improving the accuracy of instruments that are widely used to assess breast cancer risk by applying new techniques to reduce some of the variance inherent in subjective pathology reviews. Using specimens obtained by a form of fine needle aspiration (FNA) from 200 women at high risk for breast cancer, investigators will compare results with or without laser-assisted microdissection—a process of selecting specific cell types from tissue samples—in analysis of key genes by quantitative multiplexed methylation-specific (QM-MSP) polymerase chain reaction. They will also document QM-MSP data and expression of the protein Ki-67, a marker of active tumor growth, for different cell types. In addition to providing a

better understanding of how to achieve the best results with the QM-MSP assay, this information will shed light on the possible role of QM-MSP scores and Ki-67 levels in determining risk for breast cancer and serving as surrogate markers of clinical impact in prevention studies.

Grape Seed Extract, a Natural Aromatase Inhibitor (funded 2004)

Melanie Palomares, M.D., M.S., City of Hope National Medical Center & Beckman Research Institute

This phase I clinical trial will examine the effects of grape seed extract (GSE), an inexpensive natural product or "neutriceutical," on breast cancer in postmenopausal women at increased risk for the disease. The goal of the investigation is to study the effect of GSE, associated with aromatase-inhibiting properties, on serum estrogen levels in these women. In addition, it is proposed to gather preliminary dose information for this compound to determine bioavailability and evaluate safety and tolerability in humans. Prevention of breast cancer with use of GSE without serious side effects in postmenopausal women could have significant public health implications.

Effect of Aspirin on Mammographic Density (funded 2004)

Mary Anne Rossing, M.D., Ovarian Cancer SPORE at Fred Hutchinson Cancer Research Center

This clinical trial is the first to investigate whether aspirin, a nonsteroidal anti-inflammatory drug (NSAID), affects breast density. Women whose mammograms show dense breasts have a heightened risk of developing breast cancer. Regular use of NSAIDs appears to reduce breast cancer risk for reasons not yet understood. Before conducting prevention trials of NSAIDs,

researchers hope to learn whether these drugs alter the density of breast tissue, which may explain their prevention properties. In this randomized trial, 144 women with elevated breast density will take either a regular-strength aspirin or a placebo daily for 6 months. Additionally, they will be tested for genes that metabolize aspirin to clarify any role such genes may have in determining breast density. This information may help identify women who are candidates for breast cancer prevention therapy featuring aspirin.

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

Victoria Seewaldt, M.D., Breast Cancer SPORE at 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., Breast Cancer SPORE at Northwestern University

Helen Krontiras, M.D., Breast Cancer SPORE at University of Alabama at Birmingham

Saraswati Sukumar, Ph.D., Breast Cancer SPORE at 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 biomarkers that could be used to monitor the effectiveness of chemopreventive agents against breast cancer.

TREATMENT STUDIES

Phase II Trial of Cetuximab Alone and in Combination with Carboplatin in ER-Negative, PR-Negative, HER-2 Non-Overexpressing Metastatic Breast Cancers (funded 2005)

Lisa A. Carey, M.D., Breast Cancer SPORE at University of North Carolina at Chapel Hill

Andres Forero, M.D., Breast Cancer SPORE at University of Alabama at Birmingham

Anne-Renee Hartman, M.D., Breast Cancer SPORE at Dana-Farber/Harvard Cancer Center

Minetta Liu, M.D., Lombardi Comprehensive Cancer Center at Georgetown University

Cynthia Ma, M.D., Siteman Comprehensive Cancer Center, Washington University School of Medicine

Paul Kelly Marcom, M.D., Breast Cancer SPORE at Duke University

Mothaffar Fahed Rimawi, M.D., Breast Cancer SPORE at Baylor College of Medicine

Hope Rugo, M.D., University of California, San Francisco Comprehensive Cancer Center & Cancer Research Institute

This study will investigate the effect of cetuximab (Erbitux®), a monoclonal antibody that inhibits epidermal growth factor receptor (EGFR), in women with the basal-like breast cancer (BBC) subtype. The current prognosis for women who have this phenotype is poor. Although

BBC generally lacks high levels of three proteins targeted by several existing therapies—estrogen receptors, progesterone receptors, and HER2—it does overexpress EGFR. In this multi-institution trial, 100 patients will receive either cetuximab, followed by the standard anticancer drug carboplatin if the disease progresses, or an initial cetuximab-carboplatin combination. After gathering data on response and clinical end points such as survival, investigators hope to see better results for cetuximab, alone or in combination, than those reported for previous studies of single-agent EGFR inhibitors in an unselected patient population.

Assessment of Immune Responses to an Autologous Breast Cancer Vaccine (funded 2005)

Karen S. Anderson, M.D., Dana-Farber/Harvard Cancer Center

Cancer vaccines are under investigation as a means of harnessing and amplifying the body's immune system for treatment rather than prevention. This phase I trial will look at the safety, side effects, and antitumor activity of patient-specific vaccines in 20 women with advanced breast cancer. Investigators will produce vaccines using genetically engineered tumor cells that secrete granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine that augments immune response. Such tumor-specific vaccines have been shown to generate potent and specific tumor response in mouse tumor models. Along with specified indicators of tumor response, the study will assess the antigenic targets of B- and T-lymphocyte responses to pinpoint antigens involved in destruction of breast cancer for further study.

A Phase I Study of Herceptin®/CCI-779 in HER2-Positive Metastatic Breast Cancer (funded 2005)

Gerburg Wulf, M.D., Ph.D., Breast Cancer SPORE at Dana-Farber/Harvard Cancer Center

The current outlook for women with HER2-positive (HER2+) breast cancer is poor. Trastuzumab (Herceptin®) is a standard first-line therapy for HER2+ metastatic disease, but most women who respond to the drug become resistant to it over time. Earlier research implicated the P13 kinase (P13K) pathway in the development of resistance and found that impeding this pathway enhanced trastuzumab's anticancer activity. Hoping to bolster the efficacy of trastuzumab by shutting down resistance-related signals, scientists will combine it with CCI-779 (temsirolimus), which inhibits the mTOR component of the P13K pathway. The study will enroll 22 women with HER2+ metastatic breast cancer previously treated with trastuzumab. This phase I trial will focus on safety and tolerated dose levels. If patients tolerate the initial weekly regimen of trastuzumab and CCI-779, the CCI-779 dose will be increased. Improving the effectiveness of trastuzumab with this combination may eventually lead to a better prognosis for this population.

A Phase I/II Trial of BAY 43-9006 and Anastrozole in Patients with Metastatic Breast Cancer (funded 2005)

Peter F. Lebowitz, M.D., Ph.D., Lombardi Comprehensive Cancer Center at Georgetown University

This study will address the challenge of disease resistance in hormone-sensitive breast cancer, which grows when exposed to estrogen or progesterone. The compound BAY 43-9006 (Sorafenib®) targets two separate resistance pathways, one of which regulates angiogenesis, the formation of new blood vessels that support

tumor growth. In phase I, BAY 43-9006 and anastrozole (Arimidex®), a hormonal agent in the aromatase inhibitor (AI) family, will be given to women with metastatic breast cancer who have had AI treatment and progressive disease with hormonal therapy. Phase I will identify a recommended dose. Phase II will test for evidence of antitumor activity by measuring relevant biomarkers, including one for angiogenesis. The research team hopes to see clinical benefit from a two-drug approach designed to make breast tumors more responsive to hormonal agents.

Optimizing EGFR as a Therapeutic Target in Breast Cancer (funded 2005)

Angela DeMichele, M.D., M.S.C.E., Abramson Cancer Center of the University of Pennsylvania

When a kinase such as epidermal growth factor receptor (EGFR) is overexpressed in a significant subset of breast tumors, it may become a treatment target because overexpression can flag tumor dependence on that molecule. Although EGFR is an established target in oncology, clinical results with an EGFR inhibitor in breast cancer have been disappointing. More recent data suggest that for EGFR, activation rather than overexpression may be the key factor in tumor dependence and response to treatment. This phase

II study proposes to identify and evaluate markers of EGFR activation as a better predictor of response to anti-EGFR agents in order to improve the patient selection criteria for this type of therapy. Investigators will administer lapatinib (GW572016), which inhibits EGFR and ErbB2 kinase, for 14 days to 36 women with early breast cancer. They will then analyze specimens for several measures of response.

Novel Anti-Angiogenesis Therapy After Preoperative Chemotherapy for Breast Cancer (funded 2005)

Harold J. Burstein, M.D., Ph.D., Dana-Farber/Harvard Cancer Center
Kathy D. Miller, M.D., Indiana University Cancer Center

Because tumors need new blood supplies for growth, the formation of blood vessels—a process called angiogenesis—has been an area of strong research interest. Bevacizumab (Avastin®) is an antibody against vascular endothelial growth factor (VEGF), a major regulator of tumor angiogenesis. This phase II study will investigate the potential of bevacizumab in preventing breast cancer recurrences in a population at high risk: 100 women with evidence of remaining invasive disease after they have had chemotherapy but not surgery. All 100 patients will have stage II or III breast cancer and

will take bevacizumab for one year. The first 60 patients will receive only the anti-VEGF drug; the next 40 will also receive low-dose chemotherapy. The two-agent approach given to the second group, called metronomic chemotherapy, is thought to work in part through inhibition of angiogenesis. The study will test the theory that residual early-stage disease, which has not had time to establish its own blood supply, will be more susceptible to angiogenesis-inhibiting therapy than more advanced breast cancer.

Phase II Trial of CCI-779 in Breast Cancer (funded 2005)

Gini Fleming, M.D., University of Chicago Cancer Research Center

Cynthia Ma, M.D., Ph.D., Siteman Comprehensive Cancer Center, Washington University School of Medicine

Cellular signals that allow tumors to grow and metastasize travel along complex metabolic pathways. In targeted therapy, molecule-specific drugs home in on one or more links in the signaling chain to disrupt tumor-promoting messages. CCI-779 (temsirolimus), a derivative of the drug rapamycin, targets the protein called mTOR (mammalian target of rapamycin) in the PI3K/Akt signaling pathway. According to recent reports, the PI3KCA gene, which encodes for the active subunit of PI3K, is mutated in approximately 30% of breast cancers. This phase II trial will enroll 58 women with locally advanced or metastatic breast cancer profiled for PIK3CA mutations over a two-year period. Investigators will evaluate the drug's efficacy after four weekly doses and at eight-week intervals thereafter for approximately 24 weeks. In this process, they will assess mutations in the PIK3CA gene and the proteins activated in the PI3K/Akt pathway as potential markers for response to CCI-779. They also will look for correlations between PIK3CA mutations and clinical response to CCI-779 to identify women most likely to benefit from treatment with this class of agents.

Trastuzumab and Erlotinib in HER2+ Metastatic Breast Cancer (funded 2004)

Carolyn Britten, M.D., Jonsson Comprehensive Cancer Center at the University of California, Los Angeles

This phase I/II clinical trial will target two of the four cell receptors in the ErbB family, which interact in the complex signaling pathway that directs the growth and spread of malignant cells. In this study, investigators will use erlotinib (Tarceva™) to inhibit epidermal growth factor receptor (ErbB1) and trastuzumab (Herceptin®) to inhibit HER2 (ErbB2). Preclinical data demonstrated antitumor activity with an approach aimed at inactivating multiple ErbB receptors. A multidrug regimen also has shown some success in overcoming tumor resistance to trastuzumab as a single agent. Participants in the trial will be women with HER2-positive (HER2+) metastatic breast cancer. HER2+ disease is more aggressive and associated with poorer survival outlook than tumors that are negative for this protein. Favorable results will guide development of combination chemotherapy that simultaneously attacks not only these but additional targets in the same signaling pathway to improve outcomes in women with advanced HER2+ disease.

Suramin in Combination with Paclitaxel in Advanced (Stage IIIB or IV) Metastatic Breast Cancer (funded 2004)

Charles Shapiro, M.D., Ohio State University Comprehensive Cancer Center

Drug resistance is an important problem in the treatment of advanced cancers. This phase I/II clinical trial will investigate the ability of suramin to enhance the antitumor activity of paclitaxel in metastatic breast cancer by reducing resistance to this chemotherapy agent. Although suramin has little direct anticancer effect at any dose, it is known to inhibit growth factors even at nontoxic low doses. Investigators believe suramin suppresses fibroblast growth factor (FGF), a substance that may help malignant tumors withstand chemotherapy. In this study, researchers will assess whether low-dose suramin increases the sensitivity of advanced-stage breast cancer to the primary agent, paclitaxel, and will conduct assays to learn more about suramin's mechanism of action against FGF.

Phase II Trial of Estradiol Therapy for Advanced Breast Cancer (funded 2004)

Lisa A. Carey, M.D., University of North Carolina Lineberger Comprehensive Cancer Center
Matthew Ellis, M.B., Ph.D., Siteman Comprehensive Cancer Center, Washington University School of Medicine
Gini F. Fleming, M.D., University of Chicago Cancer Research Center
Kelly Marcom, M.D., Duke Comprehensive Cancer Center

This study will evaluate two daily dose regimens of estradiol (E2), a natural estrogen, in advanced breast cancer. In this phase II clinical trial, 66 women will be randomly assigned to E2 at a high dose (30 mg) with proven efficacy or a less toxic "physiological" dose (6 mg). Recent data show that E2 at physiological doses has strong cancer-killing ability in estrogen receptor-positive (ER+) cell lines that have been exposed to the anti-estrogen drug tamoxifen. The study will examine several surrogate end points for efficacy and toxicity and the relationship of dose to both. Through tumor samples, researchers also will measure expression of substances

involved in apoptosis (programmed cell death) to clarify the mechanism through which E2 triggers this process. It is hoped that this study will find lower-dose E2 to be a safe and effective treatment option for women with ER+ breast cancer when anti-estrogen therapy has failed.

HER(erb) Inhibitors in Untreated Operable Breast Cancer (funded 2004)

Carlos Arteaga, M.D., Breast Cancer SPORE at Vanderbilt University
Benjamin Calvo, M.D., Breast Cancer SPORE at University of North Carolina at Chapel Hill
Helen Krontiras, M.D., Breast Cancer SPORE at University of Alabama at Birmingham
Ian Krop, M.D., Dana-Farber/Harvard Cancer Center

The principal goal of this phase II trial is to identify factors that predict response to treatment of breast cancer with erlotinib (Tarceva™) and thus improve selection of candidates for this therapy in future trials. Erlotinib, also known as OSI-774, is a promising agent that blocks epidermal growth factor receptor (EGFR), a protein implicated in the development of breast cancer that appears necessary to the progression of advanced disease. Levels of EGFR and related proteins linked to cell growth will be measured before and after exposure to erlotinib, as a means of assessing the cancer-fighting impact of the drug in women with early-stage breast cancer. Through a technology abbreviated as MALDI MS, the researchers will develop molecular profiles that could expedite development of patient-tailored therapies.

A Neoadjuvant Phase II Trial of GW572016 in Breast Cancer Patients: Biologic Correlative Study (funded 2004)

Jenny Chang, M.D., Breast Cancer SPORE at Baylor College of Medicine

This phase II trial is designed to demonstrate the effectiveness of GW572016 (lapatinib) as first-line treatment for locally advanced breast cancer. A dual-acting agent, GW572016 blocks the signaling functions of two cell-surface receptors, HER1 (also known as epidermal growth factor receptor or EGFR) and HER2. All patients in the study will have cancers that express high levels of both proteins, which are active in pathways that regulate cell survival and growth. To confirm that GW572016 does block HER1 and HER2 signaling, investigators will conduct multiple tests on tumor samples collected at several points during the study. By impeding two pathways vital to tumors, GW572016 may outperform therapies that interrupt only one signaling chain in women whose tumors overexpress both HER1 and HER2.

Targeting the hCG-beta for Breast Cancer Immunotherapy (funded 2004)

Michael Morse, M.D., Duke Comprehensive Cancer Center

Most vaccines prevent disease, but cancer vaccines are designed to recruit the body's natural defenses to attack existing disease. This immunotherapy study seeks to find out whether a fusion protein called MDX-1307, which combines two immune system-bolstering components, will produce strong antitumor responses in women with advanced breast cancer. For clinically effective immune responses, two different types of T cells—the body's major disease-fighting weapons—need to be activated. Most breast cancer vaccines activate only

one. MDX-1307 adds a substance that increases T-cell response to human chorionic gonadotropin (hCG), which triggers immune response and is expressed in up to 80% of breast cancers. In addition to safety and efficacy, this phase I trial will evaluate delivery of the therapy intravenously rather than by the more common intradermal (in or between skin layers) route. Encouraging results from this study will shape phase II research in earlier-stage breast cancer, when tumors are usually more sensitive to therapy.

A Phase II Trial of GW572016 for Brain Metastases in Patients with HER2-Overexpressing Breast Cancer (funded 2004)

Lisa A. Carey, M.D., University of North Carolina Lineberger Comprehensive Cancer Center

Minetta Liu, M.D., Breast Cancer SPORE at Georgetown University

Eric P. Winer, M.D., Breast Cancer SPORE at Dana-Farber/ Harvard Cancer Center

Women with breast cancer that has spread to the brain have few therapeutic choices beyond treatment or surgery with radiation. This phase II clinical trial will evaluate the activity of GW572016 (lapatinib) in women whose brain metastases have progressed after treatment. GW572016, a dual tyrosine kinase inhibitor, acts against epidermal growth factor receptor (EGFR) and HER2, proteins essential to the signaling process that switches on cell proliferation. GW572016 interferes with that signal, slowing or halting cell growth. All study participants will have breast primary tumors that express elevated levels of HER2. As part of this study, investigators will explore the potential of tissue and blood biomarkers and novel imaging techniques to help predict as well as gauge response to the therapy. Encouraging results with GW572016 will expand treatment options for women with advanced, HER2-positive breast cancer that has metastasized to the central nervous system.

Biological Markers in Breast Cancer Treated by Neoadjuvant Chemotherapy (funded 2003)

Alphonse Taghian, M.D., Ph.D., Breast Cancer SPORE at Dana-Farber/Harvard Cancer Center

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 at 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., 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 will 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)

Dmitry I. Gabrilovich, M.D., Ph.D., H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida
James E. Talmadge, Ph.D., Eppley Cancer Center at the University of Nebraska Medical Center

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., 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., 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)

Lisa A. Carey, M.D., Breast Cancer SPORE at University of North Carolina at Chapel Hill
Laura Esserman, M.D., M.B.A., Breast Cancer SPORE at University of California, San Francisco
Lyndsay N. Harris, M.D., Breast Cancer SPORE at Dana-Farber/Harvard Cancer Center
John Olson, M.D., Ph.D., Breast Cancer SPORE at Duke University

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.

Anti-Angiogenic Therapies for Breast Cancer (funded 2002)

Harold J. Burstein, M.D., Ph.D., Breast Cancer SPORE at Dana-Farber/Harvard Cancer Center

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

Serum Glycan Analysis in Breast Cancer (funded 2005)

Helen Chew, M.D., University of California, Davis Cancer Center

At present, no known biomarkers can reliably identify early recurrences or response to treatment in breast cancer. Previous immunochemical and proteomic analyses of promising candidates produced disappointing results. With new techniques that separate O-linked glycans (substances associated with tumors) from proteins in serum, this prospective study will be able to analyze samples directly by a sophisticated method called mass spectrometry. Researchers will examine serum glycan from 100–200 patients and, if significant differences are found, try to correlate glycan changes with recurrent disease or effect of treatment. This study may contribute to the validation of serum glycan as a biomarker and thus help to expedite treatment for women whose breast cancer returns and to direct non-responders to potentially more effective therapies.

Multiplex Analysis of *In Situ* Protein Expression to Predict Response to Herceptin® (funded 2005)

David L. Rimm, M.D., Ph.D., Yale Comprehensive Cancer Center

By accurately measuring protein expression with a new technology known as automated quantitative analysis (AQUA), researchers hope to improve on current tests used to identify probable responders to targeted biological therapies. This study will focus on predicting response to Herceptin® (trastuzumab), an important therapeutic agent in metastatic breast cancer for patients whose tumors express high levels of the protein HER2. HER2-positive disease represents nearly 30% of breast cancers. AQUA relies on algorithms that can assess microarrays—hundreds of tissue sections from different tumors arrayed on a single glass slide—with speed and accuracy superior to that of other automated technologies and without a pathologist's subjectivity. Although this study addresses Herceptin®, if AQUA is validated, the technology could be applied to many other drugs to match patients to therapies more effectively.

DNA Methylation in Serum as a Predictive Marker in Metastatic Breast Cancer (funded 2005)

Lisa A. Carey, M.D., University of North Carolina Lineberger Comprehensive Cancer Center
Antonio C. Wolff, M.D., Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University

Shutting down watchdog genes called tumor suppressors is one tactic by which cancer evades the body's natural defenses. DNA methylation is a by-product of this process. In this prospective clinical trial, researchers will examine blood samples from up to 150 women with metastatic breast cancer at three time periods—before chemotherapy with or without Herceptin® (trastuzumab), after 3–4 weeks of therapy, and after 9–12 weeks of therapy—for patterns of DNA methylation. After amassing and evaluating a panel of methylated gene markers as indicators of response to treatment, they will develop a model to gauge whether a relationship exists between patterns of DNA methylation and clinical outcomes for study participants. Decreased levels of methylated DNA may signify benefit from the treatment. If the model demonstrates predictive success, the team will conduct additional tests to assess the model's value in helping clinicians learn early during a treatment regimen which patients will benefit from that treatment on the basis of reductions in their methylated DNA.

Markers of Short-Term Contralateral Breast Cancer Risk in Women with a History of Sporadic Breast Cancer (funded 2004)

Victoria Seewaldt, M.D., Breast Cancer SPORE at Duke University
Thea Tlsty, Ph.D., Breast Cancer SPORE at University of California, San Francisco
Lisa Yee, M.D., Ohio State University Comprehensive Cancer Center

This study will explore the value of hypermethylation, which occurs in genes associated with breast cancer, in women who have had the disease, as a molecular marker for their risk of developing cancer in the other breast. Researchers will quantify hypermethylation patterns in specimens from primary tumors and healthy cells from ipsilateral (same side as the tumor) and contralateral breast tissue, collected through a form of fine-needle aspiration. From these findings, they will assess hypermethylation as a predictor of cell abnormalities in the noncancerous tissue samples. The study also will determine whether administration of chemotherapy, specifically AC (Adriamycin® [doxorubicin]/cyclophosphamide) or AC-taxane, eliminates previously identified hypermethylation in contralateral breast tissue. Validation of hypermethylation as a biomarker will present a pharmacological target for prevention as well as treatment and monitoring of treatment effect.

Computer-Aided Diagnosis Applied to Breast MRI (funded 2004)

Nola Hylton, Ph.D., University of California, San Francisco Comprehensive Cancer Center & Cancer Research Institute
Constance Lehman, M.D., Fred Hutchinson Cancer Research Center

In this study, researchers are exploring the utility of one computer-aided diagnosis (CAD) system in conjunction with magnetic resonance imaging (MRI) for finding and assessing breast cancer. MRI's proven ability to detect breast cancer makes it a highly promising technology to complement mammography, but it is expensive, time-intensive, and flags benign as well as malignant conditions. This study is examining whether CAD can (1) improve radiologists' diagnostic accuracy in reading and reporting on MR images and (2) reduce the time they spend doing it. Novice and expert breast radiologists will review the same set of 70 MR images from women with cancerous or noncancerous lesions. If the CAD software boosts their diagnostic accuracy or cuts their time, larger studies of CAD as an adjunct to MRI may be warranted to help determine whether this technology combination has clinical value in screening for breast cancer and evaluating known or suspected cases.

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

Michael F. Press, M.D., Ph.D., Norris Comprehensive Cancer Center at the University of Southern California
Jeffrey N. Weitzel, M.D., 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

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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., University of Wisconsin Comprehensive Cancer Center

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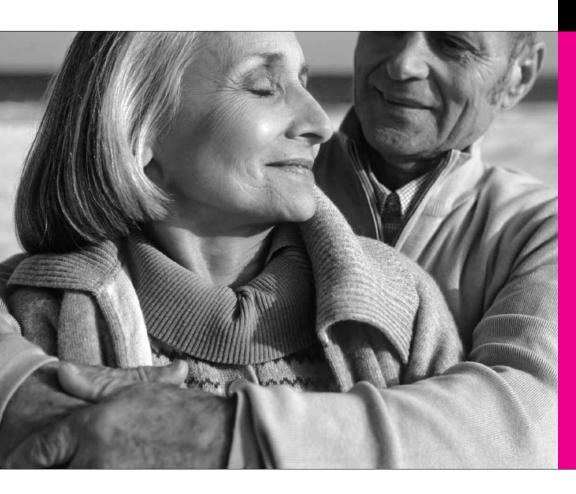
Carlo M. Croce, M.D., Kimmel Cancer Center at Thomas Jefferson University

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., 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., University of Virginia Cancer Center

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)

Mack N. Barnes, M.D., Ovarian Cancer SPORE at University of Alabama at Birmingham

Mary B. Daly, M.D., Ph.D., Ovarian Cancer SPORE at Fox Chase Cancer Center

Gordon B. Mills, M.D., Ovarian Cancer SPORE at University of Texas M.D. Anderson Cancer Center

Nicole Urban, Sc.D., Ovarian Cancer SPORE at Fred Hutchinson Cancer Research 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 2,000) 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 at 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.

For more information about breast cancer and clinical trials, call the NCI Cancer Information Service (CIS):
1-800-4-CANCER
(1-800-422-6237)

Or visit the NCI Web site at *www.cancer.gov.*
Click on the *Need Help?* link 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.*

Information about the Foundation for the National Institutes of Health is available at *www.fnih.org.*

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