DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

Report to Congress:

Use of Funds Received for Semipostal Stamp for Breast Cancer Research

Fiscal Year 2010

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Introduction

In December 2007, Congress reauthorized the Stamp-Out Breast Cancer Act, which extends the authority of the U.S. Postal Service to issue a semipostal stamp to raise funds for breast cancer research. A provision of this law, Public Law 110-150, requires that the National Institutes of Health (NIH) and the Department of Defense each submit to Congress and the GAO an annual report concerning the use of any amounts received from the sale of the stamps, including a description of any significant advances or accomplishments, during the year covered by the report, that were funded, in whole or in part, with such amounts. In fulfillment of that requirement, the following report has been prepared by the National Cancer Institute (NCI), National Institutes of Health (NIH), Department of Health and Human Services.

This is the seventh report issued on the Semipostal Stamp for Breast Cancer Research. The first 4 reports were issued working in conjunction with the Government Accountability Office (GAO). For those reports, NIH provided information for the *GAO Report to Congressional Subcommittees: U.S. Postal Service, Agencies Distribute Fund-raising Stamp Proceeds and Improve Reporting*, GAO-08-45. Reports are now issued directly by NIH and are available on NCI's Web page at the following URL: http://obf.cancer.gov/contribute/cr-stamp.htm.

Background

Breast cancer is the second most common cancer among women (after skin cancer) and the second leading cause of death after lung cancer. An estimated 207,090 women in the United States were diagnosed with breast cancer in 2010, and about 39,840 women have died from the disease during 2010. Since 1998, added support for breast cancer research has come from funding through the highly successful Stamp Out Breast Cancer Act. The breast cancer research stamp is offered through the United States Postal Service as an alternative to a First Class postage stamp. The Stamp Out Breast Cancer Act, initially enacted in 1997, stipulates that 70 percent of the proceeds from the stamp surcharge be directed to the National Institutes of Health for breast cancer research and 30

percent to the Department of Defense for the same purpose. The Stamp Act was reauthorized in 2007, extending the sales period through 2011.

In November 1998, NCI began receiving Breast Cancer Research stamp proceeds from the United States Postal Service. Since then, NCI has allocated the proceeds—totaling $48.8 million, with $34.2 million obligated at the end of Fiscal Year 2010—through four different programs. Initially, proceeds from the stamp were used to award 87 grants under the Insight Awards to Stamp out Breast Cancer initiative. From 2003 to 2008, NCI used proceeds to award 37 grants under the Exceptional Opportunities in Breast Cancer Research initiative and also to fund an aspect of the Trial Assigning Individualized Options for Treatment (TAILORx) in 2006. In recent years, the Institute has used its share of the proceeds to fund research through the Breast Pre-Malignancy Program and other intramural programs. Each program was selected by NCI senior leadership for its potential to make significant progress against breast cancer. In 2010, three grants were awarded in response to a new Request for Applications (RFA) in the area of estrogen receptor-negative breast cancer biology in various racial and ethnic groups. In the sections that follow, these programs are discussed in detail. Of the remaining proceeds of $14.6 million, $13.2 million will be obligated on the existing programs within the next few years. Additionally, there is $1.4 million available for NCI leadership to allocate to either existing programs or new ones.

NCI is awarded Breast Cancer Stamp funds twice annually in May and November of each fiscal year. The table below lists annual award amounts since the inception of the program.

FY	**Total**
1999	$4,150,210.00
2000	$3,101,033.00
2001	$5,556,224.67
2002	$3,594,619.80
2003	$5,175,938.00
2004	$4,813,994.00
2005	$4,372,191.62
2006	$4,467,540.23
2007	$3,006,105.81
2008	$4,855,539.01
2009	$3,403,204.50
2010	$2,344,610.59
Total	**$48,841,211.65**

Breast Cancer Programs

Insight Awards to Stamp Out Breast Cancer (2000-2002)

The Insight Awards to Stamp Out Breast Cancer program was designed to support research grants considered high risk, with the potential for high reward. One of the central aims of this initiative was to challenge existing paradigms and to develop new methodologies and technologies in breast cancer research. An unprecedented 403 applications for the new grants were received. Using funds from the proceeds made available via the Breast Cancer Stamp Act, NCI awarded 87 Insight Awards totaling $9.5 million to extramural research investigators located at universities and medical schools across the country.

The grant awards, affiliations, and funding information are listed in Appendix 1.

Exceptional Opportunities in Breast Cancer Research (2003-2008)

Under the Exceptional Opportunities in Breast Cancer Research program, NCI used the stamp proceeds to support high-quality and peer-reviewed breast cancer grant applications that were outside the funding ability for NCI in the current fiscal year. Through this initiative, NCI provided grant support for a maximum of four years to 35 Exceptional Opportunities Awards, totaling $12.5 million. Breast cancer research benefited from the Institute's ability to expand its research portfolio and focus on the many critical areas of breast cancer by supporting these additional grants.

The grant awards, affiliations, and funding information are listed in Appendix 2.

Trial Assigning Individualized Options for Treatment (TAILORx) (2006)

In 2006, NCI used the proceeds from the sale of Breast Cancer Stamps to support an early-phase breast cancer clinical trial and to support research within the new Trans-NCI Breast Pre-malignancy Research Program.

The Trial Assigning Individualized Options for Treatment (TAILORx) is designed to determine which patients with early-stage breast cancer would be more likely to benefit from chemotherapy and, therefore, reduce the use of chemotherapy in those patients who are unlikely to benefit. TAILORx is using a molecular profiling test (a technique that examines many genes simultaneously) to aid clinical decision making. The trial will determine whether this test can be used to spare women unnecessary treatment with toxic chemotherapy. Data based on evaluation of tumors from patients whose long-term outcome is known (patients who participated in previous trials) suggest that chemotherapy is not likely to provide substantial benefit to women who are at very low risk of recurrence. The goal of TAILORx is to determine the most effective current

approach to cancer treatment, with the fewest side effects, for women with early-stage breast cancer by using a validated diagnostic test developed by Genomic Health, Inc., in collaboration with the National Surgical Breast and Bowel Project, a network of cancer research professionals. The test is being provided free to all patients who meet the eligibility requirements for the study.

In fiscal year 2006, NCI awarded $4.5 million to Genomic Health, Inc., to offset the costs of testing. The trial completed accrual in October 2010; there were almost 10,000 patients who had their tumors tested. The patients will be followed for at least five years following treatment.

Trans-NCI Breast Pre-Malignancy Program (2006-present)
The Trans-NCI Breast Pre-Malignancy Program represents a comprehensive program in breast cancer pre-malignancy research that includes the areas of prevention, etiology, biology, diagnosis, and molecular epidemiology. The program consists of both NCI researchers located on the NIH campus in Bethesda and Frederick, Maryland, and extramural research programs, which support research under way in universities, medical schools, hospitals, and research institutions across the country. This provides an opportunity to create a collaborative and integrated scientific program across NCI divisions and centers, and to synergistically reach new discoveries and interventions.

The NCI Breast Pre-Malignancy Program consists of six research components supporting research on pre-malignant lesions, cancer prevention techniques, and methods for detecting breast cancer or pre-cancers earlier. The program involves work on characterization and imaging of breast cancer stem cells, the biology of breast pre-malignancy, molecular epidemiology of mammographic density, strategies to improve accuracy of mammography interpretation, the evaluation of decision-making approaches used by women recruited for chemoprevention trials, molecular target identification (biomarkers), imaging, and translational research. In fiscal year 2006, NCI provided support to 6 extramural grants under the program for a total of $853,000 and funded intramural research projects at NCI totaling $371,000. In fiscal year 2007, NCI provided support to 1 extramural grant under the program totaling $115,000, and research studies within the NCI intramural program received $484,000 in total funding. In fiscal year 2008, NCI provided support to 3 extramural grants under the program for a total of $1,016,000 and funded intramural research projects at NCI totaling $491,000. In fiscal year 2009, NCI provided support to 3 extramural grants under the program for a total of $1,364,000 and funded intramural research projects at NCI totaling $509,000. In fiscal year 2010, NCI provided support to 7 extramural grants for a total of $2,482,000.

The grant awards, affiliations, and funding information are listed in Appendix 3.

A Study to Evaluate Different Decision-Making Approaches Used by Women Known to be at High Risk for Breast Cancer – 5U10CA037377-25 (Norman Wolmark)

The objective of this study is to describe the influence of social, environmental and psychological factors (sociality of medication intake, life-events, understanding of prevention, and the clinical situation) on the decision of women at risk for breast cancer for taking chemoprevention agents. Secondary objectives are to understand the implications and influences on decision making that a diagnosis of being at risk for breast cancer has for women, to develop a survey that identifies the factors that influence the decision-making process, and to understand the factors that hinder women from taking chemoprevention for breast cancer.

Background/Rationale: Chemoprevention trials have demonstrated an ability to reduce estrogen-receptor-positive breast cancer by over 70 percent. Advances in molecular medicine and increasingly better risk assessment tools for breast cancer are leading to better predictors of individual breast cancer risk. Women considered at risk for breast cancer have more options from which to choose, including regular or tailored screening, elective prophylactic mastectomy or oophorectomy, tamoxifen, and raloxifene. Women with a breast cancer risk of 1.7 percent or higher as calculated by the modified Gail model (6) are eligible to take the FDA-approved Selective Estrogen Receptor Modulator (SERM), tamoxifen. Raloxifene, another SERM, which until recently was mainly used to prevent and treat osteoporosis, is now also FDA approved for breast cancer risk reduction in postmenopausal women with osteoporosis (not requiring a 1.7-percent or higher Gail score) and in postmenopausal women at increased risk of invasive breast cancer with a 1.7-percent or higher Gail score.

Women who face the decision of taking a SERM may receive a statistical risk-benefit analysis of the different health outcomes by their physicians. All women who are given the option to take either tamoxifen or raloxifene will take an initial survey after the information session to assess recall and understanding of their risk. If a woman has made a decision, she will receive a second survey within one week. Undecided women will receive a survey between 3-6 months post clinic. At selected sites, the consultation session will be observed using video records. These women and their physicians will participate in an in-depth interview. Participants will also complete a baseline survey.

Qualitative and quantitative studies consistently show that most women in the general population are not willing to take any risks for a disease they may never get. This is clearly one reason why SERM use for breast cancer risk reduction is low. Women who take a SERM have a higher personal breast cancer risk perception and are more likely to have had an abnormal breast biopsy. Most women who—from a statistical standpoint—would benefit from SERM use do not take the medication. One study suggests that individuals are unlikely to take prevention medications that are associated with risks for all cancers. This risk aversion seems specific to cancers since prevention medications for cardiovascular diseases, such as statins, are widely used today.

Studies in sociology and anthropology show that the views of what is important in decision-making differ between physicians and patients. What is important from a medical point of view (i.e., risks/benefits of treatment) is not necessarily important from a patient's point of view. Decisions are made in real life with real consequences. Decisions take place in a social environment in which behaviors have specific meanings. For example, prescribed medicines and the patient's social surroundings are used by the patient to judge the seriousness of disease. This sociality of medication intake influences the decision as much or even more as adherence due to efficacy or side effect profiles of a drug regimen.

Status: Part I—Survey development and implementation is in progress. The NSABP Foundation, Inc., is working to refine the data flow between the University of Michigan and the NSABP. The investigators are analyzing the conjoint analysis to determine under what conditions a woman would be willing to take chemoprevention drugs. This method is used to evaluate patients' preferences in care situations in which there is more than one medically justifiable treatment option.

Part II—Observations and in-depth interviews began November 30, 2010.

Multi-parameter Monitoring of Breast Cancer Progression and Therapeutic Response - 5R01CA135650-02 (Anna Moore and Zoravka Medarova)
In the past year, Drs. Moore and Medarova have made progress towards the goal of specific aim 1, which is to investigate if µMUC-1 is a marker of breast tumor progression. They are investigating the differential accumulation of a µMUC-1 targeted imaging probe (MN-EPPT) in progressive stages of human breast lesions as a function of µMUC-1 availability, and using differential accumulation to monitor non-invasively and quantitatively the progression from pre-malignancy to advanced malignancy. Their first-year results showed a predictable pattern of µMUC-1 expression and cellular and tissue distribution with the progression of

human breast tissue from normal epithelium to metastatic disease. In year 2, they documented possible aberrant μMUC-1 in adjacent normal tissue from breast cancer patients; thus, μMUC-1 may be a very early marker of tumorigenesis relevant for progression prediction. They banked breast tissue samples representative of disease progression from the NCI Cooperative Human Tissue Network. These include tissues from 7 different patients: non-neoplastic breast epithelium from healthy subjects (n = 4); non-neoplastic adjacent normal breast epithelium from breast cancer patients (n = 14); ductal carcinoma in situ (DCIS) (n = 4); invasive ductal adenocarcinoma, stage I (n = 4), stage II (n = 7), and stage III (n = 1); and metastatic carcinoma, stage IV (n = 6). Quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) on these samples established the relative expression of the muc-1 gene. Their results suggest that MUC-1 is up-regulated with emerging transformation and in adjacent normal tissue of patients with breast cancer.

This likely represents a field effect of carcinogenesis, suggesting that MUC-1 is a very early marker of transformation. In addition, the new results indicate that MUC-1 expression peaks in early-stage disease but levels off, or is reduced, in more invasive stages. Although the expression of the MUC-1 antigen may be lower in more invasive forms of breast cancer, the levels of under-glycosylation may be more dramatic. This indicates a two-stage process of initial up-regulation of the antigen, followed by replacement of heavily glycosylated forms of MUC-1 with under-glycosylated forms. Under-glycosylation of MUC-1 enhances tumor cell binding to selectins and extravasation into the bloodstream; thus they hypothesize a transition to post-translational modification of MUC-1 in more invasive stages. They also observed increased μMUC-1 in adjacent normal tissue from patients with breast cancer relative to normal tissue from patients without a history of breast cancer, and increased abundance of μMUC-1 in all stages of disease relative to normal tissue. This pattern reflects the absolute expression of the muc-1 gene and the level of antigen under-glycosylation. They also documented that under-glycosylation is especially pronounced in metastatic samples.

They also made progress toward the goal of aim 2, which is to investigate if MN-EPPT, the μMUC-1 targeted imaging probe, can monitor μMUC-1 as a marker of breast cancer progression. Having established a pattern of μMUC-1 expression using μMUC-1 specific antisera, they used MN-EPPT to look for these changes. They stained tissue microarrays (TMAs) with MN-EPPT and examined the sections under fluorescence microscopy. MN-EPPT accumulation and distribution in these tissue sections confirmed the expected availability of μMUC-1 based on their studies in years 1 and 2.

Publication:
Medarova Z, Rashkovetsky L, Pantazopoulos P, Moore A. Multiparametric monitoring of tumor response to chemotherapy by noninvasive imaging. *Cancer Res*, 2009 Feb 1;69(3):1182-9. Epub 2009 Jan 13. PMID: 19141648

Characterizing the Evolution of Pre-malignant Tissues at High Risk for Malignancy - 5 R01 CA135626-02 (Thea Tlsty and Ella Jones)
Drs. Tlsty and Jones reported progress on specific aim 1, which is designed to identify surface epitopes for human breast epithelial and stromal cells in basal-like pre-malignancies, and to characterize functional alterations that predict progression to malignancy. Using gene expression profiling, they identified 4 candidate cell surface biomarkers associated with basal-like pre-malignancies. Expression of these markers could be associated with high probability for progression to invasive tumors (in contrast to subsequent DCIS). One of these candidates, the 5'-ecto-nucleotidase, CD73, is validated; under way is validation of the three other markers in three HMEC/vHMEC matched sets by qRT-PCR and Western blot analysis. Progress on the other three aims of this study are outlined below.

Specific aim 2–Validating the efficacy and specificity of cell surface targets *in vitro* and *in vivo* using optical imaging: An anti-CD73 antibody optimized for optical imaging to detect vHMECs and basal-like breast tumors *in vivo* was generated. Conjugation with Alexa Fluor 680 (AF680) at a dye:antibody ratio of 1.7-2.5 produced an effective optical probe with strong affinity for CD73. As few as 300,000 vHMECs can be detected with the anti-CD73-AF680 probe *in vitro* using Fluorescence Molecular Tomographic (FMT) imaging. They tested the probe *in vivo* using a mouse xenograft model and bioluminescent imaging by transducing several tumor cell lines with luciferase-expressing retrovirus; however, they observed disparate levels of bioluminescence. Because of their concern that they would not be able to validate implantation with bioluminescent imaging, they used a CD73 breast cancer cell line (MDA-MB-453) in addition to vHMECs; all lines co-express GFP and luciferase. They then investigated whether the anti CD73-AF680 probe could discriminate three basal and three luminal breast cancer cell lines. The basal cell lines had statistically significantly higher signals than the luminal ones. Their optimized probe can detect vHMECs both *in vitro* and *in vivo*, validating the use of CD73 as a targeting group and opening the way for its use to understand further the behavior of these cells *in vivo*. Anti CD73-AF680 also shows promise as a probe to discriminate between basal and luminal tumors. Now that they have successfully produced stably

transduced vHMECs and MDA-MB-453 cells, they will use them in mouse xenograft experiments to study the behavior of the vHMECs *in vivo*.

Specific aim 3—Developing clinical imaging agents for detection of basal-like DCIS in breast tissue: 2B4, which binds to CD73 was identified as a potent scFV. The investigators attempted to label 2B4 with a PET isotope to have a clinically relevant probe. To date, two different 18F prosthetic groups were used; however, they saw no evidence of successful radio-labeling. They are switching to a different technique that has been useful in other experiments. If they are successful, they will assess whether the radio-labeling affects the binding of 2B4 to CD73 and test the probe in mouse xenograft models.

Specific aim 4—Develop and apply functional imaging to identify lesions (basal-like DCIS) that are associated with progression to invasive tumors: COX-2 was previously identified as a likely biomarker of invasive tumor potential in patients with DCIS. Generation of a novel 'turn-on' chemosensor able to detect COX-2 via a significant increase in fluorescence is in the final stage. The probe is based on a self-immolative trigger designed around the structure of aspirin, which acetylates the 2 COX isoforms *in vivo*. Significant progress has been made toward producing this sensor via the synthesis of a key intermediate that will ensure selectivity for COX-2 over COX-1. Generation of the 'turn-on' functionality will complete the synthesis of the initial test probe. This compound is the first reported fluorogenic COX-2 probe. The development of an effective COX-2 imaging agent would be invaluable to observe the progression of malignancy and to identify lesions that are likely to progress to invasive malignancies.

The Biology of Estrogen Receptor-Negative Breast Cancer in Various Racial and Ethnic Groups (U01): RFA-CA-09-026

The purpose of this funding opportunity announcement (FOA) was to promote the systematic study of the biology of estrogen receptor (ER)-negative human breast cancers, the characterization of their molecular features, and the signaling pathways and networks that support their growth, as well as to identify differences in the biology of ER-negative breast tumors among racial and ethnic groups. The information gained will be crucial in developing early detection and intervention strategies. This initiative supports studies on the basic biology of ER-negative breast cancers, and delineation of differences that exist between ER-positive and ER-negative breast cancers; the identification of the subtypes or heterogeneity that exist within ER-negative breast cancers; and the determination of whether the biology of ER-negative breast tumors differs across racial and ethnic groups. In order to address these goals, NCI solicited applications from

collaborative teams of interdisciplinary investigators focused on characterizing the biologic drivers—including genetic, epigenetic, molecular, and cellular factors—of ER-negative human breast cancer development and progression.

The NCI committed $10 million in total costs over the course of 5 years, utilizing the Stamp Fund, to award up to 3 collaborative projects. In 2010, the NCI received 20 applications in response to this solicitation. Applications were reviewed in May 2010 by a Special Emphasis Panel, and the top 3 grant applications that were identified as highly meritorious were funded in September 2010. Listed below is a brief scientific summary of the grants.

Kay Huebner (1U01CA154200) and colleagues from the Ohio State University will generate micro RNA profiles of triple negative breast cancers in order to categorize them into distinct subtypes. They will evaluate normal, premalignant, and malignant human breast tissues from a large cohort of clinically annotated samples in order to identify alterations in signaling pathways as well as potential novel therapeutic targets. The study was evaluated as being clinically very significant since triple negative cancers (which are Estrogen Receptor (ER)-negative, Progesterone Receptor (PR)-negative and HER2-negative) are highly prevalent among women of African ancestry. Breast cancers that are ER-positive and/or HER2-positive can be treated with drugs that specifically target them and have a good prognosis. Targeted therapy is not possible with ER-negative or triple negative breast cancers; these tumors do not respond well to chemotherapy and have poor prognosis.

Michael Clarke (1U01CA154209) and his team from Stanford University will use single cell genomics technology to define the cell of origin of the normal human breast epithelium. They have already identified a set of promising core group genes that allows them to stratify the different populations of cells, and they will build on this work. They will use the same technology to look at the cell of origin for triple negative breast cancers from Caucasians, Hispanics, and African Americans. They will test the hypothesis that there could be differences in the normal cellular hierarchy of the mammary epithelium of ethnic groups, which may be the reason why there is a difference in the tumors that arise from different populations.

Research from Celina Kleer's (1U01CA154224) group at the University of Michigan will provide new information on the polycomb protein EZH2 that is associated with silencing of genes. The investigators have data to show that this protein is specifically increased in triple negative breast cancers and that increased expression of EZH2 increases the number of luminal progenitors. This

is significant since luminal progenitors are considered the cell of origin for triple negative tumors. They will examine the mechanism by which EZH2 operates and assess the clinical utility of EZH2 overexpression as biomarkers of prognosis in a unique cohort of triple negative breast cancers from Caucasian, African American, and Western African women.

PARP Inhibition in BRCA Mutation Carriers—A Pilot Study—3U10 CA037403-25S1 (Robert Comis)
The primary objective of this study is to determine the effect of an oral poly (ADP-ribose) polymerase (PARP) inhibition drug, Olaparib, on select biomarker modulation in tissue and blood from a high risk of breast cancer BRCA1/2 mutation carrier cohort. This study will evaluate the percent change in Poly (ADP-ribose) (PAR) before and after the treatment. These percent changes will be compared in a 100-mg dose vs. placebo arm, a 400-mg dose vs. placebo, and a 100-mg dose plus 400-mg dose combined vs. placebo arms. Secondary objectives of this study are to evaluate safety and tolerability of Olaparib at two dose levels; the modulation of other biomarkers (gamma-H2-AX, cyclin D1, aldehyde dehydrogenase (ALDH1), estrogen and progesterone receptors) before and after treatment; and to perform a comprehensive biomarker analysis on biopsy and surgical tissues.

Data were presented at the 2009 American Society of Clinical Oncology from two studies in which PARP inhibitors were given to women previously treated for metastatic breast cancer. In the first study, 86 women with a history of triple negative breast cancer received Gemcitabine and carboplatin with or without an intravenous PARP inhibitor (inhibitor BSI-201). The clinical response rate was 52 versus 12 percent in favor of the BSI-201 combination (RECIST criteria Complete +Partial responses stable disease). The nature of adverse events did not differ between the 2 treatment arms. In the second study, 54 BRCA1/2 mutation carriers with previously treated metastatic breast cancer received oral PARP (Olaparib) at 400 mg and 200 mg in a phase II proof-of-concept study. The overall response rate was 41 percent (CR +PR). These studies confirm the activity of PARP in mutation carriers and among triple negative breast cancer patients whose biological features are similar with BRCA1 mutation carriers.

This phase II randomized trial will enroll 100 women with known BRCA1/2 mutations who have chosen prophylactic mastectomies. Participants will undergo core needle biopsy for tissue acquisition at baseline and post drug prior to mastectomy. Women will be randomized to take 23 weeks of an oral PARP inhibitor or placebo.

Background/Rationale: Women with mutations in BRCA1/2 are well suited for prevention approaches. It is estimated that this population has a 27- to 85-percent lifetime risk of developing breast cancer and a 15- to 40-percent risk of developing ovarian cancer. An impressive number of BRCA mutation carriers have genetic tissue abnormalities that do not alter phenotype but establish a molecular basis for assessing and monitoring risk. Current prevention options, which include prophylactic surgery, aggressive surveillance, and/or chemoprevention measures, do not completely eliminate a mutation carrier's risk of cancer. Substantial advancements are necessary to reduce the cancer burden in this high-risk population of women.

PAR is the product of PARP 1 and 2 enzymatic activities. Levels of PAR can be directly assayed by immunohistochemical staining. There are a number of compounds currently in clinical development that directly inhibit PARP-1 in a dose-dependent manner. Therefore, as PARP-1 is inhibited, a significant decrease in PAR levels after treatment is expected to be observed. Previous studies have reported between a 30- and 95-percent reduction in PAR.

Status: The study concept has been approved by NCI's Division of Cancer Prevention and the Eastern Cooperative Oncology Group. The protocol is near activation and awaiting the details of the drug distribution by Astra Zeneca.

Breast Radiology Evaluation and Study of Tissues (BREAST) Stamp Project
Mammographic breast density, a radiologic measure of the amount of non-fatty breast tissue, is one of the strongest established risk factors for sporadic breast cancer. However, the mechanisms that mediate the breast cancer risk associated with high mammographic density are poorly understood. NCI researchers performed a feasibility study aimed at identifying molecular epidemiologic factors related to high mammographic density in partnership with the University of Vermont (UVM), an NCI Breast Cancer Surveillance Consortium (BCSC) site. The pilot, funded through an award from the Stamp Act Fund, enrolled 250 women between the ages of 40 to 65 years from 2007-2009. These participants underwent a radiologically-guided biopsy for clinical indications (unrelated to density); provided responses to a risk factor questionnaire; and donated blood, buccal cells, and tissues.

NCI scientists in collaboration with UVM researchers successfully completed the pilot study of mammographic density within the project timeline of approximately 18 months. Based on the success of the pilot, researchers extended the study with intramural funding through June 2010, resulting in a total accrual of 466 women. Preliminary data demonstrate collection of a questionnaire from 100 percent of

participants, buccal cells from 97 percent, blood from 75 percent, fixed tissue from biopsies from 97 percent, and frozen tissue from almost half the participants who underwent surgical resection for an abnormal radiologically-guided biopsy. This study provides the opportunity to relate questionnaire data, serum measures, and molecular analysis of tissues to elevated mammographic density and specific histopathologic diagnoses, as well as to explore different algorithms to improve the prediction of density measures.

Scientific Advances: Mammographic density has been analyzed primarily as a single, global area measurement for each breast. However, while elevated density is a strong risk factor, it is neither highly sensitive nor specific for cancer. In addition, cancer develops from focal lesions, suggesting that more sophisticated assessment of regional measures of density might provide added information. Thus, a novel component of this study has been the development of different methods for assessing regional variation of mammographic density. Researchers are currently refining methods for measuring density in defined regions of interest (ROI) in the breast, including tissues surrounding the biopsy target. This will provide information on whether high density around a suspicious lesion is related to pathologic diagnoses and whether this suggests that local density reflects a field effect surrounding precancerous lesions and early screen-detected cancers. Scientists are extending this work to evaluate whether density varies by quadrant to assess the hypothesis that high density in the upper outer quadrants is related to the substantially higher incidence of cancer in this region of the breast compared with other quadrants. Researchers will also compare density around the biopsy target with a mirror ROI in the contralateral breast and evaluate whether density confers a better measure of risk if assessed following subtraction of the density contributed by the central breast tissue below the nipple, a region where only 1 percent of cancers arise. Results for global and regional density are being related to histologic evidence of lobular involution and biomarkers in serum (hormones and growth factors) and in tissues, reflecting both the state of the epithelium and stroma. These hypothesis-generating analyses will identify markers that are related to high density as well as markers that are associated with cancer and its precursors.

Participants' data will also be linked to 10 years of prospective follow-up collected through the existing UVM BCSC infrastructure, providing a future resource for assessing factors associated with temporal changes in mammographic density. Furthermore, the infrastructure developed for this project may enable the researchers to evaluate determinants of volumetric mammographic density in a group of nearly 10,000 women under age 50 years. Pilot work funded through the intramural research program to demonstrate the feasibility of a proposed study

design for collecting saliva samples for germline DNA and questionnaires from these women is ongoing. Given that the density data for these women was collected as part of the original BREAST Stamp protocol, this new project, if successful, will leverage the original investment of resources and provide useful information about risk assessment among younger women.

AIM-Assessing and Improving Mammography Study
Jointly funded by the National Cancer Institute (Year 1) and the American Cancer Society (ACS) (Years 2 & 3), the Assessing and Improving Mammography (AIM) study was launched in August 2006. The overarching goal of the research is to improve radiologists' interpretive skills by rigorously evaluating factors that influence performance measures, and designing and testing strategies to improve performance in a national sample of 321 radiologists from the NCI-funded BCSC. The investigators have developed a testing method with a computerized testing system that displays high quality images on a portable computer. This was used in a baseline assessment.

The investigators have developed and implemented two interventions to improve interpretive abilities and developed several manuscripts. The first intervention is an instructor-led, in-person intervention and the second is a self-paced DVD. In addition, there is a post test assessment using both clinical performance data and a specially designed test set that is separate from the baseline test. One manuscript focuses on cut-point criteria for low interpretive performers of screening mammography[1] while another paper has examined the influence of volume on interpretive performance.[2] Several other papers are in analysis and write-up phases on topics including the influence of time spent and confidence on interpretive accuracy, agreement among experts when interpreting a test set, and agreement among community radiologists when interpreting a test set. Other manuscripts will be developed as study outcome data become available.

The study investigators have achieved a significant amount of progress in this complex study. Their progress has been so substantial that the ACS has agreed to fund them for a fifth year to continue their work.

Publications:
1. Carney PA, Sickles E, Monsees B, Bassett L, Brenner J, Rosenberg R, Feig S, Browning S, Tran K, Berry J, Kelly M, Miglioretti DL. Identifying Minimally Acceptable Interpretive Performance Criteria for Screening Mammography. *Radiology*, 2010; 255(2):354-61.

2. Buist DSM, Anderson ML, Haneuse SJPA, Sickles EA, Smith R, Carney PA,

Taplin SH, Rosenberg RD, Geller BM, Onega, T, Monsees B, Bassett L, Yankaskas BC, Elmore JG, Kerlikowske K, Miglioretti DL. The influence of volume on interpretive performance of screening mammography in the US. (In review.)

Other Research Initiatives Funded with Proceeds from the Breast Cancer Research Stamp

Preclinical Consortium for Brain Metastases of Breast Cancer (NCI Intramural Program)

Brain metastases of breast cancer are increasing in incidence in metastatic breast cancer patients with either HER2-positive or triple negative (estrogen and progesterone receptor negative, HER2 normal) tumors. These metastases are shielded from normal chemotherapy by a partially intact blood-brain barrier, and the use of whole brain radiation therapy (WBRT) is limited by its adverse effects on neurocognition. In an effort to improve bench-to-clinic research, a consortium of oncologists, radiation oncologists, and molecular biologists is directly comparing the results of drug or drug/radiation combinations in model systems and human clinical trials. Initial selections by members of NCI's Cancer Therapy Evaluation Program include the following.

1. The Abbott PARP inhibitor (ABT-888) combined with either radiation, capecitabine, or carboplatinum: For this combination, the drug has been approved and received from Abbott, animal protocols were finalized, and the first monotherapy experiment has been conducted. Combination studies and in vitro studies with radiation are now under way.
2. Roche gamma-secretase inhibitor (RO4929097), combined with either radiation, capecitabine, or carboplatinum: This drug has been received from Genentech, and animal use agreements are under review. In vitro studies with radiation are ongoing.
3. A wider array of "backbone" drugs will be explored so that additional combinations can be investigated.

Personalized Medicine Approach to Triple-Negative Breast Cancers (NCI Intramural Program)

Triple negative breast cancer represents one of the most challenging and deadly groups of breast cancers. Although this type of cancer accounts for a relatively small fraction of all breast cancer cases, it is responsible for a disproportionate number of breast cancer deaths. It is diagnosed more frequently in younger

women and women with Hispanic and African-American backgrounds (Reis-Filho and Tutt, 2008).

Triple negative breast cancers are defined immunohistochemically by the lack of progesterone receptor (PR), human EGF receptor 2 (HER2) and estrogen receptor (ER). As a result, this aggressive type of cancer is resistant to existing targeted treatments such as trastuzumab and hormonal treatments (Cleator, Heller, et al., 2007). Currently, the only systemic therapy available for patients with triple negative breast cancer is conventional chemotherapy, but strides are being made to find new modalities. An attractive target for therapy and imaging in triple negative breast cancer patients is EGFR, which has been shown to be expressed in 66 percent of primary tumors and 25 percent in metastatic tumor patients. Clinical trials are currently under way to test the efficacy of humanized anti-EGFR monoclonal antibodies and EGFR tyrosine kinase inhibitors (Reis-Filho et al., 2006).

Accomplishments: The initial phase of the project has focused on development of EGFR-specific imaging probes. To study the EGFR expression in vitro and its relation to HER2 expression, photo-stable and relatively simple-to-produce imaging probes for in vivo staining of EGFR and HER2 have been created. These new reagents, called Affiprobes, consist of a targeting moiety, a HER2- or EGFR-specific Affibody molecule, and a fluorescent moiety, mCherry (red) or EGFP (green). In addition, the set contains Affiprobes based on anti-Taq DNA polymerase-specific Affibody molecules (Z_{Taq}) that can be used as a negative (nonspecific) control. The results of flow cytometry and confocal microscopy experiments demonstrated high specificity of Affiprobes to their targets resulting in high signal/background ratios. Investigators have also shown that Affiprobes are able to stain both live cells and frozen tumor xenograft sections. Results suggest that Affiprobes may become an attractive alternative to chemically labeled antibodies, antibody fragments, and natural ligands for cell imaging technology. In fact, these probes have been provided to several research groups from both NIH and extramural institutions, which are using them for characterization of EGFR and HER2 expression. In the future, this type of optical probe can easily be extended for targeting other cell-surface antigens/receptors as needed. This work resulted in the following publication: Lyakhov I, Zielinski R, Kuban M, et al. *HER2- and EGFR-specific affiprobes: novel recombinant optical probes for cell imaging. Chembiochem*; 11: 345-50.

The Breast Cancer Metabolomics Project (NCI Intramural Program)
The Breast Cancer Metabolomics Project seeks to characterize metabolic profiles that precede the development of breast cancer. This will be done using metabolomics, a technique that enables the characterization of large numbers (e.g., 400 to 1,000) of metabolites within blood or urine. Metabolites that can be measured include lipids and amino acids, sex hormones, markers of energy intake and energy utilization, and many others. This breast cancer metabolic profile will be developed using plasma samples donated in 1997 by 500 women who developed breast cancer during 1998-2009, and samples donated in 1997 by 500 women who did not subsequently develop breast cancer.

Research in the area of metabolomics has accelerated rapidly within the past several years and has been especially fruitful for the development of drug toxicity biomarkers in randomized controlled studies. However, it has been applied only sparingly to observational studies, such this one. Although the observational study design is the only one that can be used, for example, to prospectively identify breast cancer biomarkers in humans, a limitation of this design is that it often yields moderate or weak effect sizes. To compensate, measurement technologies and sample processing must be exquisitely reliable, and yet many metabolomics labs struggle to attain reliable results. Therefore, the study team decided to start by thoroughly vetting the existing metabolomics technologies. This includes techniques developed and labs started since the proposal was submitted. Since receiving funds in April, the team has developed a theoretical framework for evaluating metabolomics platforms, consulted with experts about the best platform for the study, and piloted samples at three metabolomics labs.

Since April 2010, the research team has assembled, developed a theoretical framework for the research, initiated important contacts in the extramural community, and piloted samples. The research team is now well positioned to begin the main thrust of the research proposal and is excited to see what will be found.

Maternal Pregnancy Factors and Breast Cancer Risk (NCI Intramural Program)
The Epidemiology and Biostatistics Program in the Division of Cancer Epidemiology and Genetics at NCI is pursuing a research program on the maternal and prenatal factors that contribute to the causes of cancer in the mother and offspring. Pregnancy conditions and exposures have important consequences for subsequent breast cancer risk of the mother, but the reasons for this are not understood. Often, research studies attempt to obtain information by interviewing women about their previous pregnancy complications, but women often do not know or remember features of their past pregnancies, especially if the pregnancies

occurred many years or even decades ago. For this reason, it is difficult to study pregnancy exposures.

Some States have the potential to link cancer registry to birth certificate data, and the NCI has contracted with researchers at the Fred Hutchinson Cancer Research Center in Seattle, Washington, to conduct a project, "Linked Registry Study of Maternal Pregnancy Factors and Breast Cancer Risk," in which Washington State cancer registry and birth certificate databases for 4 decades will be linked. The goal is to provide information on maternal, gestational, and neonatal factors, in particular, for pregnancy complications such as preeclampsia and gestational diabetes, which will be evaluated in relation to the offspring's breast cancer risk. Demonstration of the ability to conduct this linkage will help establish a consortium with investigators in other States in order to include a group of cases and controls as large as possible, enhancing our ability to learn how pregnancy factors affect breast cancer risk. This six-month-long project began on September 29, 2010. Progress to date includes establishment of Human Subjects Protection Committee approvals from the Washington State Department of Health. Receipt of cancer registry data will occur shortly, and data linkage will begin, using methods previously established by the investigator's team.

Conclusion

Breast cancer research has benefited from this innovative funding source. Having this additional funding has furthered our efforts to exploit the increasing knowledge of genetics, molecular biology, and immunology to develop more effective and less toxic treatments for breast cancer. Moreover, through the trans-NCI breast pre-malignancy program, made possible by Stamp proceeds, we are able to further investigations to recognize and define the attributes of pre-malignant stages of human breast cancer, which in turn may have a major effect on the detection and prevention of invasive breast cancer malignancies.

A table summarizing the major programs funded with proceeds from the Breast Cancer Research Stamp is below.

Fiscal Year(s)	Program Title	Total
2000-2002	Insight Awards	$9,442,838
2003-2008	Exceptional Opportunities in Breast Cancer Research	$12,488,716
2006	TAILORx Trial	$4,500,000
2006-present	Breast Pre-Malignancy Program	$7,684,865
2010	NCI Intramural Research Program Initiatives	$120,154
Total		**$34,236,573**

Appendix 1. Insight Awards to Stamp Out Breast Cancer Funded with Proceeds from the Breast Cancer Research Stamp

Fiscal Year	Institution	Principal Investigator	Total
2000	ALBANY MEDICAL COLLEGE OF UNION UNIVERSITY	BENNETT, JAMES A	$116,250
2000	BAYLOR COLLEGE OF MEDICINE	ROSEN, JEFFREY	$78,488
2000	BETH ISRAEL DEACONESS MEDICAL CENTER	JUNGHANS, RICHARD P	$130,500
2000	CALIFORNIA UNIVERSITY, IRVINE	BLUMBERG, BRUCE	$105,946
2000	CALIFORNIA UNIVERSITY, SAN FRANCISCO	COLLINS, COLIN C	$110,625
2000	CENTER FOR MOLECUCULAR MEDICINE AND IMMUNOLOGY/GARDEN STATE CANCER CENTER	BLUMENTHAL, ROSALYN D	$142,500
2000	CLEMSON UNIVERSITY	CHEN, WEN Y	$105,000
2000	COLUMBIA UNIVERSITY HEALTH SCIENCES	SWERGOLD, GARY D	$127,875
2000	DANA-FARBER CANCER INSTITUTE	KUFE, DONALD W	$126,138
2000	FOX CHASE CANCER CENTER	RUSSO, JOSE	$126,866
2000	GEORGETOWN UNIVERSITY	WONG, LEE-JUN C	$116,950
2000	HADASSAH UNIVERSITY HOSPITAL	VLODAVSKY, ISRAEL	$61,000
2000	HAWAII UNIVERSITY	GOTAY, CAROLYN C	$101,000
2000	ILLINOIS UNIVERSITY	WESTBROOK, CAROL A	$116,475
2000	INSTITUTE FOR CANCER RESEARCH	YEUNG, ANTHONY T	$126,866
2000	HENRY M. JACKSON FOUNDATION	LECHLEIDER, ROBERT J	$74,000
2000	THOMAS JEFFERSON UNIVERSITY	SAUTER, EDWARD R	$117,851
2000	LONG ISLAND JEWISH MEDICAL CENTER	SHI, Y ERIC	$116,616
2000	VIRGINIA MASON RESEARCH CENTER	NELSON, BRAD H	$47,250
2000	MASSACHUSETTS GENERAL HOSPITAL	HABER, DANIEL A	$129,500
2000	MASSACHUSETTS UNIVERSITY, AMHERST	JERRY, D JOSEPH	$115,125
2000	MELBOURNE UNIVERSITY	THOMPSON, ERIK W	$75,000

Fiscal Year	Institution	Principal Investigator	Total
2000	MOUNT SINAI SCHOOL OF MEDICINE	KRETZSCHMAR, MARCUS D	$125,387
2000	NEW YORK STATE UNVERSITY	MUTI, PAOLA C	$77,000
2000	PENNSYLVANIA UNIVERSITY	LEMMON, MARK A	$118,875
2000	PENNSYLVANIA UNIVERSITY	RADICE, GLENN L	$118,875
2000	PITTSBURGH UNIVERSITY	NICHOLS, MARK D	$112,500
2000	SCHEPENS EYE RESEARCH INSTITUTE	D'AMORE, PATRICIA A	$121,500
2000	UTAH UNIVERSITY	GRISSOM, CHARLES B	$112,125
2000	VERMONT UNIVERSITY	KRAG, DAVID N	$113,250
2000	WAKE FOREST UNIVERSITY	SHELNESS, GREGORY S	$108,750
2000	YALE UNIVERSITY	ZHANG, HUI	$122,625
2001	ALBANY MEDICAL COLLEGE OF UNION UNIVERSITY	BENNETT, JAMES A	$116,250
2001	BAYLOR COLLEGE OF MEDICINE	ROSEN, JEFFREY	$109,322
2001	BETH ISRAEL DEACONESS MEDICAL CENTER	JUNGHANS, RICHARD P	$130,500
2001	CALIFORNIA UNIVERSITY, IRVINE	BLUMBERG, BRUCE	$112,800
2001	CALIFORNIA UNIVERSITY, SAN FRANCISCO	COLLINS, COLIN C	$110,625
2001	CALIFORNIA UNIVERSITY, IRVINE	RADANY, ERIC H	$112,800
2001	GARDEN STATE CANCER CENTER	BLUMENTHAL, ROSALYN D	$142,500
2001	CLEMSON UNIVERSITY	CHEN, WEN Y	$105,000
2001	COLUMBIA UNIVERSITY HEALTH SCIENCES	FISHER, PAUL B	$127,875
2001	COLUMBIA UNIVERSITY HEALTH SCIENCES	SWERGOLD, GARY D	$127,875
2001	DANA-FARBER CANCER INSTITUTE	GARBER, JUDY E	$128,750
2001	DANA-FARBER CANCER INSTITUTE	KUFE, DONALD W	$125,862
2001	FOX CHASE CANCER CENTER	RUSSO, JOSE	$126,133
2001	GEORGETOWN UNIVERSITY	BYERS, STEPHEN W	$116,550

Fiscal Year	Institution	Principal Investigator	Total
2001	GEORGETOWN UNIVERSITY	DICKSON, ROBERT B	$116,600
2001	GEORGETOWN UNIVERSITY	WONG, LEE-JUN C	$116,400
2001	HADASSAH UNIVERSITY HOSPITAL	VLODAVSKY, ISRAEL	$61,000
2001	HAWAII UNIVERSITY, MANOA	GOTAY, CAROLYN C	$101,000
2001	JOHNS HOPKINS UNIVERSITY	FEDARKO, NEAL S	$122,750
2001	ILLINOIS UNIVERSITY	WESTBROOK, CAROL A	$116,475
2001	INSTITUTE FOR CANCER RESEARCH	YEUNG, ANTHONY T	$126,133
2001	HENRY M. JACKSON FOUNDATION FOR THE ADVANCEMENT OF MILITARY MEDICINE	LECHLEIDER, ROBERT J	$74,000
2001	THOMAS JEFFERSON UNIVERSITY	SAUTER, EDWARD R	$85,657
2001	LONG ISLAND JEWISH MEDICAL CENTER	SHI, Y ERIC	$117,050
2001	VIRGINIA MASON RESEARCH CENTER	NELSON, BRAD H	$47,250
2001	MASSACHUSETTS GENERAL HOSPITAL	HABER, DANIEL A	$127,500
2001	MASSACHUSETTS UNIVERSITY, AMHERST	JERRY, D JOSEPH	$112,323
2001	MEDICAL DIAGNOSTIC RESEARCH FOUNDATION	CHANCE, BRITTON	$92,500
2001	MELBOURNE UNIVERSITY	THOMPSON, ERIK W	$75,000
2001	MINNESOTA UNIVERSITY, TWIN CITIES	SHEAFF, ROBERT J	$111,375
2001	MISSOURI UNIVERSITY	SAUTER, EDWARD R	$33,491
2001	MOUNT SINAI SCHOOL OF MEDICINE OF NEW YORK UNIVERSITY	KRETZSCHMAR, MARCUS D	$127,125
2001	NORTHWESTERN UNIVERSITY	JORDAN, VIRGIL C	$110,250
2001	PENNSYLVANIA UNIVERSITY	LEMMON, MARK A	$118,875
2001	PENNSYLVANIA UNIVERSITY	RADICE, GLENN L	$118,875
2001	PITTSBURGH UNIVERSITY	NICHOLS, MARK D	$112,500
2001	SCHEPENS EYE RESEARCH INSTITUTE	D'AMORE, PATRICIA A	$121,500

Fiscal Year	Institution	Principal Investigator	Total
2001	STANFORD UNIVERSITY	CONTAG, CHRISTOPHER H	$119,597
2001	UTAH UNIVERSITY	GRISSOM, CHARLES B	$112,500
2001	UNIVERSITY OF VERMONT AND STATE AGRICLTURAL COLLEGE	KRAG, DAVID N	$113,250
2001	WAKE FOREST UNIVERSITY	SHELNESS, GREGORY S	$108,375
2001	WAYNE STATE UNIVERSITY	FERNANDEZ-MADRID, FELIX R	$111,750
2001	WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH	WEINBERG, ROBERT A	$116,250
2001	YALE UNIVERSITY	ZHANG, HUI	$122,625
2002	CALIFORNIA UNIVERSITY, IRVINE	RADANY, ERIC H	$112,800
2002	COLUMBIA UNIVERSITY HEALTH SCIENCES	FISHER, PAUL B	$122,799
2002	DANA-FARBER CANCER INSTITUTE	GARBER, JUDY E	$128,375
2002	FOX CHASE CANCER CENTER	RUSSO, JOSE	$4,300
2002	GEORGETOWN UNIVERSITY	BYERS, STEPHEN W	$116,400
2002	GEORGETOWN UNIVERSITY	DICKSON, ROBERT B	$116,400
2002	JOHNS HOPKINS UNIVERSITY	FEDARKO, NEAL S	$122,625
2002	MEDICAL DIAGNOSTIC RESEARCH FOUNDATION	CHANCE, BRITTON	$103,350
2002	MINNESOTA UNIVERSITY, TWIN CITIES	SHEAFF, ROBERT J	$111,375
2002	WAYNE STATE UNIVERSITY	FERNANDEZ-MADRID, FELIX R	$111,750
2002	WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH	WEINBERG, ROBERT A	$116,238
Total	**Insight Awards to Stamp Out Breast Cancer**		**$9,515,828**

Appendix 2. Exceptional Opportunities in Breast Cancer Research Funded with Proceeds from the Breast Cancer Research Stamp

Fiscal Year	Institution	Principal Investigator	Total
2003	CALIFORNIA UNIVERSITY	NEUHAUSEN, SUSAN L	$545,271
2003	COLUMBIA UNIVERSITY	HARLAP, SUSAN	$616,010
2003	HOPKINS JOHNS UNIVERSITY	OUWERKERK, RONALD	$154,852
2003	NORTHWESTERN UNIVERSITY	HUANG, SUI	$389,482
2003	PENNSYLVANIA UNIVERSITY	LEE, WILLIAM M	$198,759
2003	PITTSBURGH UNIVERSITY	WIENER, ERIK C	$405,009
2003	ST VINCENT'S INST	PRICE, JOHN T	$108,000
2003	TEXAS UNIVERSITY GALVESTON	LU, LEE-JANE W	$532,409
2003	TORONTO UNIVERSITY	VOGEL, WOLFGANG F	$81,000
2003	WISCONSIN UNIVERSITY	SCHULER, LINDA A.	$285,725
2004	CALIFORNIA UNIVERSITY	NEUHAUSEN, SUSAN L	$545,576
2004	COLUMBIA UNIVERSITY	HARLAP, SUSAN	$604,299
2004	JOHNS HOPKINS UNIVERSITY	OUWERKERK, RONALD	$157,176
2004	NORTHWESTERN UNIVERSITY	HUANG, SUI	$389,522
2004	PENNSYLVANIA UNIVERSITY	LEE, WILLIAM M	$198,759
2004	PITTSBURGH UNIVERSITY	WIENER, ERIK C	$410,688
2004	ST VINCENT'S INST	PRICE, JOHN T	$108,000
2004	TEXAS UNIVERSITY GALVESTON	LU, LEE-JANE W	$566,037
2004	TORONTO UNIVERSITY	VOGEL, WOLFGANG F	$81,000
2004	WISCONSIN UNIVERSITY	SCHULER, LINDA A	$254,625
2005	CALIFORNIA UNIVERSITY	NEUHAUSEN, SUSAN L	$561,474
2005	COLUMBIA UNIVERSITY	HARLAP, SUSAN	$600,585
2005	NORTHWESTERN UNIVERSITY	HUANG, SUI	$401,655
2005	PENNSYLVANIA UNIVERSITY	LEE, WILLIAM M	$198,759
2005	PITTSBURGH UNIVERSITY	WIENER, ERIK C	$423,007
2005	TEXAS UNIVERSITY GALVESTON	LU, LEE-JANE W	$550,147
2005	WISCONSIN UNIVERSITY	SCHULER, LINDA A	$254,625
2006	CALIFORNIA UNIVERSITY	NEUHAUSEN, SUSAN L	$561,838
2006	PENNSYLVANIA UNIVERSITY	LEE, WILLIAM M	$194,088
2006	PITTSBURGH UNIVERSITY	WIENER, ERIK C	$404,520
2006	TEXAS UNIVERSITY GALVESTON	LU, LEE-JANE W	$24,291
2007	CALIFORNIA UNIVERSITY	NEUHAUSEN, SUSAN L	$424,870
2007	UNIV OF TEXAS MED BR GALVESTON	LU, LEE-JANE W	$468,507
2007	PENNSYLVANIA UNIVERSITY	LEE, WILLIAM M	$188,460
2008	MASSACHUSETTS GENERAL HOSPITAL	MOORE, ANNA	$616,625
Total	**Exceptional Opportunities in Breast Cancer Research**		**$12,505,650**

Appendix 3. Breast Cancer Pre-Malignancy Program Funded with Proceeds from the Breast Cancer Research Stamp

Fiscal Year	Institution	Principal Investigator	Total
2006	BAYLOR COLLEGE OF MEDICINE	OSBORNE, C KENT	249,838
2006	DARTMOUTH COLLEGE	CARNEY, PATRICIA A	101,546
2006	GROUP HEALTH COOPERATIVE	BUIST, DIANA SM	114,226
2006	GROUP HEALTH COOPERATIVE	MIGLIORETTI, DIANA L	217,296
2006	NCI INTRAMURAL PROGRAM	VARIOUS	371,398
2006	NORTH CAROLINA UNIVERSITY	YANKASKAS, BONNIE C	90,514
2006	NSABP FOUNDATION INC	WOLMARK, NORMAN	80,000
2007	UNIVERSITY OF VERMONT	GELLER, BERTA	115,047
2007	NCI INTRAMURAL PROGRAM	VARIOUS	483,938
2008	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	TLSTY, THEA D	666,024
2008	NSABP FOUNDATION, INC.	WOLMARK, NORMAN	119,226
2008	UNIVERSITY OF VERMONT	GELLER, BERTA	230,312
2008	NCI INTRAMURAL PROGRAM	VARIOUS	491,050
2009	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	TLSTY, THEA D	640,750
2009	MASSACHUSETTS GENERAL HOSPITAL	MOORE, ANNE	598,918
2009	NSABP FOUNDATION	WOLMARK, NORMAN	123,992
2009	NCI INTRAMURAL PROGRAM	VARIOUS	508,939
2010	FRONTIER SCI & TECHNOLOGY RSCH FDN, INC	COMIS, ROBERT L	$200,000
2010	NSABP FOUNDATION, INC.	WOLMARK, NORMAN	$97,000
2010	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	TLSTY, THEA D	$634,250
2010	MASSACHUSETTS GENERAL HOSPITAL	MOORE, ANNA	$94,933
2010	OHIO STATE UNIVERSITY	HUEBNER, KAY	$548,311
2010	STANFORD UNIVERSITY	CLARKE, MICHAEL	$553,639
2010	UNIVERSITY OF MICHIGAN AT ANN ARBOR	KLEER, CELINA G	$353,718
Total	**Breast Cancer Pre-Malignancy Program**		**$7,684,865**

Glossary of Terms

BRCA1 - A gene on chromosome 17 that normally helps to suppress cell growth. A person who inherits certain mutations (changes) in a BRCA1 gene has a higher risk of getting breast, ovarian, prostate, and other types of cancer.

BRCA2 - A gene on chromosome 13 that normally helps to suppress cell growth. A person who inherits certain mutations (changes) in a BRCA2 gene has a higher risk of getting breast, ovarian, prostate, and other types of cancer.

BSI-201 - A substance being studied in the treatment of breast cancers caused by mutations (changes) in the BRCA1 and BRCA2 genes. It is also being studied in the treatment of other types of cancer. It blocks an enzyme involved in many functions of the cell, including the repair of DNA damage. DNA damage may be caused by normal cell actions, UV light, some anticancer drugs, and radiation used to treat cancer. BSI-201 may cause cancer cells to die. It is a type of poly (ADP-ribose) polymerase inhibitor. It also is called iniparib and PARP-1 inhibitor BSI-201.

DCIS - ductal carcinoma in situ. A noninvasive condition in which abnormal cells are found in the lining of a breast duct. The abnormal cells have not spread outside the duct to other tissues in the breast. In some cases, DCIS may become invasive cancer and spread to other tissues, although it is not known at this time how to predict which lesions will become invasive. Also called intraductal carcinoma.

Extravasation - The leakage of blood, lymph, or other fluid, such as an anticancer drug, from a blood vessel or tube into the tissue around it. It also is used to describe the movement of cells out of a blood vessel into tissue during inflammation or metastasis (the spread of cancer).

Gail Model - A computer program that uses personal and family medical history information to estimate a woman's chance of developing breast cancer.

Gail Score - Indicates a woman's risk for breast cancer; calculated using the Gail Model.

HER2 - human EGF receptor 2. A protein involved in normal cell growth, it is found on some types of cancer cells, including breast and ovarian. Cancer cells removed from the body may be tested for the presence of HER2/neu to help

decide the best type of treatment. HER2/neu is a type of receptor tyrosine kinase. It also is called c-erbB-2, and human epidermal growth factor receptor 2.

MN-EPPT - a μMUC-1 targeted imaging probe.

PARP - poly (ADP-ribose) polymerase. A type of enzyme involved in many functions of the cell, including the repair of DNA damage. DNA damage may be caused by normal cell actions, UV light, some anticancer drugs, and radiation used to treat cancer. Inhibitors of one enzyme, PARP-1, are being studied in the treatment of cancer.

PARP inhibitor - poly (ADP-ribose) polymerase inhibitor. A substance that blocks an enzyme involved in many functions of the cell, including the repair of DNA damage. DNA damage may be caused by normal cell actions, UV light, some anticancer drugs, and radiation used to treat cancer. It may cause cancer cells to die. It is a type of targeted therapy.

Selectins - a family of transmembrane molecules, expressed on the surface of leukocytes and activated endothelial cells.

SERM - selective estrogen receptor modulator. A drug that acts like estrogen on some tissues but blocks the effect of estrogen on other tissues. Tamoxifen and raloxifene are SERMs.