IV BREAST CANCER RESEARCH PROGRAM

Cancer of the breast, the most commonly diagnosed non-skin cancer in women, accounts for 32% of all cancers in women. One out of every eight women will develop breast cancer in her lifetime, a disease second only to lung cancer as the leading cause of death in women. It was estimated that in 2005, approximately 211,240 women in the United States would receive a diagnosis of invasive breast cancer and approximately 58,490 women would be diagnosed with breast cancer in situ. In addition, although male breast cancer is rare and accounts for less than 1% of all breast carcinomas in the United States, it was projected that about 1,690 new cases would be diagnosed in 2005. More than 40,000 women and approximately 460 men were projected to die from breast cancer this year.[1]

Vision: To eradicate breast cancer.

Mission: To foster new directions, address neglected issues, and bring new investigators into the field of breast cancer research.

Appropriations for Peer Reviewed Breast Cancer Research:

- $1.518B in FY92–03
- $150M in FY04
- $150M in FY05
- $9.2M in FY99–03, $2.1M in FY04, and $1.9M in FY05 from the Stamp Out Breast Cancer Act

Funding Summary:

- 4,073 awards from the FY92–03 appropriations
- 220 awards from the FY04 appropriation
- ~150 awards anticipated from the FY05 appropriation

PROGRAM BACKGROUND

The Department of Defense (DOD) Breast Cancer Research Program (BCRP) was established in fiscal year 1992 (FY92) by Appropriations Conference Committee Report No. 102-328, which provided $25 million (M) for research on breast cancer screening and diagnosis for military women and their family members. In 1993, grassroots advocates led by the National Breast Cancer Coalition influenced public policy, which led to an FY93 congressional appropriation of $210M for peer reviewed breast cancer research. The U.S. Army Medical Research and Materiel Command sought the advice of the National Academy of Sciences (NAS) to develop a sound investment strategy for the FY93 congressional appropriation.

An NAS Institute of Medicine (IOM) committee thoroughly studied the major considerations and issued a report that outlined a two-tier review process and an investment strategy for the $210M appropriation. (See Section I for additional details on these two recommendations.) This two-tier review process and annual investment strategy were implemented by the BCRP and subsequently adapted by other Congressionally Directed Medical Research Programs (CDMRP).

Today, the BCRP is the second largest funder of extramural breast cancer research in the world. The program is also a recognized leader in innovative program management. An example of innovative program management can be seen in the BCRP's support for ground-breaking award mechanisms. For instance, the Innovator Award was first launched in FY01 to provide gifted individuals the opportunities to pursue groundbreaking research. Other mechanisms have been designed to address health disparities and build critical research resources in underserved, understudied, and underrepresented communities. The

[1] *American Cancer Society,* Cancer Facts and Figures, *2005*.

box stories on pages IV-8 and IV-11 highlight the fruits of such undertakings. Additionally, the BCRP has sponsored four multidisciplinary, scientific Era of Hope meetings (1997, 2000, 2002, and 2005) to publicly present results of DOD-funded studies. These meetings provided BCRP-funded investigators from different fields the opportunity to come together with breast cancer survivors and advocates to learn about the advances against breast cancer made since the program's inception. (Additional details about the Era of Hope 2005 can be found in the box story on page IV-5.)

From FY92 to FY05, the BCRP has managed $1.83 billion (B) in peer reviewed research to find a cure for breast cancer. Through FY04, 4,293 awards have been made. In addition, the BCRP is the recipient of 30% of the revenues from sales of the U.S. Postal Service's first-class Breast Cancer Stamp. (See the story beginning on page IV-11 for additional information about the Stamp Out Breast Cancer Act.) Appendix B, Table B-1 summarizes the congressional appropriations and the investment strategy executed by the BCRP for FY04 through FY05.

THE FISCAL YEAR 2004 PROGRAM

In FY04, Congress appropriated $150M for peer reviewed breast cancer research. The BCRP continued to emphasize innovative, high-risk/high-gain research; training of new investigators; and support for translational research. In FY04, 2,638 proposals were received, and 220 were funded. Table IV-1 provides a summary of the award categories and mechanisms in terms of number of proposals received, number of awards made, and dollars invested. Recognizing that the war against breast cancer must be fought on multiple fronts, the FY04 BCRP developed a diverse research portfolio that encompasses basic, clinical, and population-based research (see Figure IV-1).

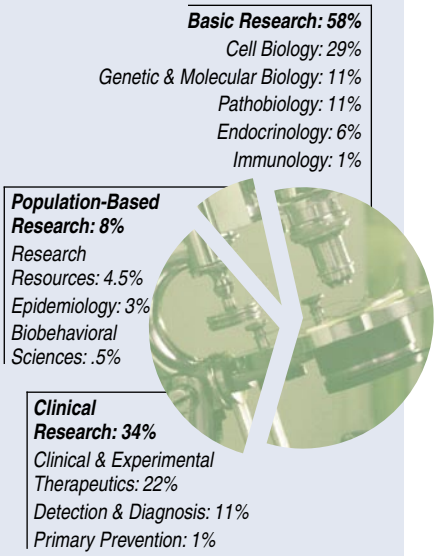


Figure IV-1. FY04 BCRP Portfolio by Research Area

The FY04 BCRP offered nine award mechanisms to support research with the potential to revolutionize the landscape of breast cancer research. Seven of these award mechanisms were previously established by the BCRP (Concept, Idea, Breast Cancer Center of Excellence, Historically Black Colleges and Universities/Minority Institutions [HBCU/MI] Partnership Training, Multidisciplinary Postdoctoral Traineeship, Predoctoral Traineeship, and Innovator) and two of the mechanisms were new to the program in FY04, the Era of Hope Scholar Award and the Center of Excellence Pilot Award. Both the Concept and Idea Awards were offered for investigators to boldly explore novel questions in breast cancer and, collectively, 126 awards were made in these two mechanisms. Three training/recruitment award mechanisms (see Table IV-1) were offered to promote the training and mentoring of future leaders in breast cancer research and 77 investigators were supported by these awards. Additionally, the

Table IV-1. Funding Summary for the FY04 BCRP

Categories and Award Mechanisms	Number of Proposals Received	Number of Awards	Investment
Research			
Concept	*1,331*	*92*	*$10.4M*
Idea	*794*	*34*	*$16.8M*
Training/Recruitment			
HBCU/MI Partnership Training	*4*	*2*	*$2.8M*
Multidisciplinary Postdoctoral	*111*	*9*	*$3.4M*
Predoctoral Traineeship	*302*	*66*	*$5.9M*
Research Resources			
Breast Cancer Center of Excellence	*4*	*2*	*$24.5M*
Center of Excellence Pilot	*8*	*1*	*$0.1M*
Other Award Mechanisms			
Era of Hope Scholar	*69*	*10*	*$34.7M*
Innovator	*15*	*4*	*$27.6M*
Total	*2,638*	*220*	*$126.2M*

program continued to build research resources through the Breast Cancer Center of Excellence Awards and the Center of Excellence Pilot Awards; three awards were made in these mechanisms at leading institutions across the nation in an effort to support pioneering, multi-institutional approaches to accelerating research progress in the critical areas of breast cancer prevention, detection, diagnosis, and/or treatment. The Era of Hope Scholar Award was launched in FY04 to fill a unique niche for early-career gifted scientists who have the potential to challenge the status quo and implement a vision that may ultimately lead to the eradication of breast cancer; 10 of these awards were made. Finally, four Innovator Awards were made to provide accomplished and visionary researchers with the funding to pursue groundbreaking breast cancer research. The recipients of this prestigious award were Dr. Malcolm Pike of University of Southern California; Dr. Dennis Slamon of University of California, Los Angeles; Dr. Dimitrios Trichopoulos of Harvard University; and Dr. Roger Tsien of University of California, San Diego.

THE VISION FOR THE FISCAL YEAR 2005 PROGRAM

Congress again appropriated $150M to continue the BCRP in FY05. Seven award mechanisms were offered to sustain the BCRP's investment in innovation, training, and translational research. All of the award mechanisms were previously established by the BCRP and were offered to push the boundaries and advance discoveries in

Signs and Symptoms

Nearly all breast cancers can be treated successfully if detected early in development, and mammography is a valuable method for early detection of breast cancer. When breast cancer has grown to a point where physical symptoms are present, such indicators may include the following:

- New lump or mass in the breast
- Generalized swelling, distortion, or tenderness of the breast
- Skin irritation or dimpling
- Nipple pain, scaliness, ulceration, retraction, or spontaneous discharge

Breast pain is often attributable to benign conditions and is usually not the first indication of breast cancer.

–American Cancer Society, *Cancer Facts and Figures*, 2005.

breast cancer research. The two research award mechanisms are Idea Awards (designed to boldly explore revolutionary ideas in breast cancer research) and Clinical Translational Research Awards (designed to accelerate the progression of recent, highly promising findings in preclinical breast cancer research from the laboratory to the clinic). Breast Cancer Center of Excellence Awards were offered to encourage the formation of a multidisciplinary, multi-institutional research program focusing on a pivotal question in breast cancer research. The training/recruitment award mechanisms that were offered to invest in the best and the brightest include the HBCU/MI Partnership Training, Multidisciplinary Postdoctoral (mentored training program in more than one major discipline), and Predoctoral Traineeship Awards. Finally, the Era of Hope Scholar Awards were offered to recognize the talents and accomplishments of early-career, gifted scientists. A total of 1,261 proposals were received across the seven award mechanisms, as detailed in Table IV-2, and approximately 150 awards are expected.

Table IV-2. Award Mechanisms Offered and Proposals Received for the FY05 BCRP

Categories and Award Mechanisms	Number of Proposals Received
Research	
Clinical Translational Research	*10*
Idea	*820*
Research Resources	
Breast Cancer Center of Excellence	*10*
Training Recruitment	
HBCU/MI Partnership Training	*3*
Multidisciplinary Postdoctoral	*96*
Predoctoral Traineeship	*306*
Other Award Mechanisms	
Era of Hope Scholar	*16*
Total	*1,261*

SCIENTIFIC OUTCOMES AND ADVANCES

FY92 through FY04 BCRP appropriations have supported more than 4,200 awards that focus on breast cancer-specific research. The BCRP research portfolio comprises many different types of projects that encourage the investigation of innovative ideas, facilitation of translational research, and training of future leaders in breast cancer research. BCRP-supported researchers are exploring revolutionary ideas and emerging trends across all areas of laboratory, clinical, behavioral, and epidemiologic research. The projects detailed in this section highlight some of the diverse research funded by the DOD BCRP that is impacting the war against breast cancer. Additional examples of scientific outcomes, products, and technologies resulting from BCRP support can be found in Section III of this annual report.

ERA OF HOPE 2005

The Era of Hope meetings are recognized as some of the premier breast cancer research conferences in the United States. The fourth Era of Hope meeting for the DOD BCRP was held on June 8–11, 2005 in Philadelphia, Pennsylvania. With over 1,600 attendees, this meeting provided a forum for researchers in different fields and research areas to share their ideas and present promising new advances in breast cancer research. The meeting was organized around three main research topics: (1) Understanding Risk – A Different Perspective, (2) Understanding Who Needs Intervention, and (3) Understanding Treatments – Effectively Treating Primary and Metastatic Disease. Featured speakers included Frances Visco, BCRP Integration Panel Chair and President, National Breast Cancer Coalition, whose advocacy has impacted and transformed breast cancer research; Dennis Slamon, M.D., Ph.D., Chief, University of California Los Angeles Oncology Center, whose work led to the development of the breast cancer drug Herceptin®; and keynote speaker Rosabeth Kanter, Ernest L. Arbuckle Professor of Business Administration, Harvard Business School, a distinguished speaker on thinking outside-the-box and implementing change.

Over 1,200 BCRP grantees highlighted their recent scientific accomplishments in symposia and poster sessions. As in past meetings, participation of breast cancer survivors, a hallmark at all levels of the BCRP and this meeting, was tremendous with over 270 breast cancer survivors from 95 organizations attending, 48 survivors co-chairing or moderating sessions, and 10 survivors presenting. Overall, the Era of Hope 2005 meeting reflected the broad scope of the research funded by the DOD, as well as the unique aspects of the BCRP. Media coverage of the meeting was extensive and included on-site reporters and approximately 150 stories in newspapers, on the Internet, by wire, on radio, and on television. Additional information about the Era of Hope meetings and archived abstracts are available on the CDMRP website http://cdmrp.army.mil.

The Wealth of the Rain Forest

Deborah A. Lannigan, Ph.D., University of Virginia, Charlottesville, Virginia

During the 1960s a federal initiative was implemented to systematically collect botanicals for use in the discovery, identification, and characterization of pharmaceutical agents to treat and cure diseases. Dr. Deborah A. Lannigan and collaborators at the University of Virginia focused on this library of plant extracts to find a new treatment for breast cancer. To screen the extracts, a high-throughput enzyme-linked immunosorbent assay that uses luminescence as an indicator of substrate phosphorylation was developed. It was the Principal Investigator's (PI's) intention to look for inhibitors of the p90 ribosomal S6 kinase (RSK), a critical member of the mitogen-activated protein kinase pathway. It was shown that one extract specifically inhibited the constitutively active RSK by 90% while not inhibiting other kinases such as FAK, PKA, p70, S6K, or MSK1. The extract originated in the South American rain forest from a species of the dogbane family named *Forsteronia refracta*. The extract was fractionated and the inhibitor, a kaempferol glycoside called SL0101, was isolated. Studies demonstrated that RSK enzymatic activity did not change with the addition of the inhibitor, but alterations of the binding constant for ATP showed

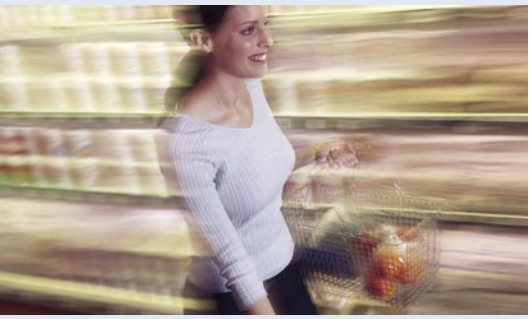
that SL0101 is a competitive inhibitor. Site-specific studies delineated the residues that are important for SL0101 binding. In growth inhibition experiments, SL0101 repressed the growth of MCF-7 cells, a human breast cell line, but not that of the normal human breast cell line, MCF-10A. Cell cycle analysis confirmed that the anti-proliferative effect is due to a G1 cell cycle block. Additional studies, including short interfering RNA (siRNA) experiments, corroborated the supposition that RSK1 and RSK2 are required for MCF-7 proliferation. Dr. Lannigan and her team extended their research to include a survey of breast cancer tissues; these analyses established that 50% of breast cancer tissues have increased levels of both isoforms of RSK compared to normal breast tissue. Taken together, these results point to a new target for breast cancer therapy and a novel agent, which may be further developed for breast cancer treatment. The inhibitor SL0101, derived from a natural resource, offers new avenues for treatment and for future drug design and development. Natural resources provide a wealth of health care treatments. This research was made possible through an FY02 BCRP Idea Award.

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

Smith JA, Poteet-Smith CE, Xu Y, et al. 2005. Identification of the first specific inhibitor of p90 ribsomal S6 kinase (RSK) reveals an unexpected role for RSK in cancer cell proliferation. *Cancer Res* 65:1027–1034.

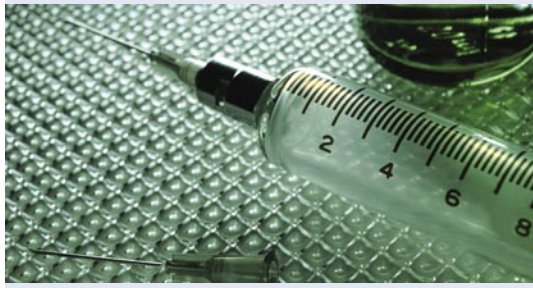
"The Era of Hope [Scholar] Award has had a tremendous impact on my research career. Its arrival just as I am starting a new position has allowed me to focus on top-notch research, instead of working on small projects to acquire preliminary data for my next grant."

Edward Brown, Ph.D., FY04 BCRP Era of Hope Scholar Award Recipient



Soy and Breast Cancer: Food for Thought

Dietary factors may be among the environmental aspects influencing the development and progression of breast cancer. It has been established that women in Asian countries consume more soybean products than women in the United States and that the incidence of breast cancer in women in Asian countries is generally lower. While this association is correlative and no causative effect has been demonstrated, an increasing body of evidence suggests that soybean product consumption may be protective, thus reducing the risk of breast cancer development. Many studies supported by the BCRP have been designed to characterize the effects of soybean protein and its byproducts on both normal breast epithelial cells and breast cancer cells. Approaches to determining whether soy exerts a positive effect on lowering the risk of breast cancer development have varied greatly and have involved human volunteers (and human tissues) and mouse and rat models of human disease. Several BCRP-funded research proposals have addressed various aspects of the relationship between a diet high in soybean protein and breast density, a risk factor for developing breast cancer. Studies have also included an evaluation of the effect of high soy intake on the aggressiveness of breast cancer cells. Other research projects have examined the effects of soy products at the molecular



level by determining changes in the expression of genes implicated in cancer susceptibility; changes in DNA methylation status of estrogen receptor genes; and changes in expression of markers for cellular activities such as differentiation, adhesion, and proliferation. Current studies are examining the interplay of a high soybean protein diet and standard therapeutic breast cancer treatment. Overall, the BCRP has funded a broad range of research exploring the association between a diet rich in soybean protein and breast cancer development and progression. Selected awards are shown in Table IV-3 and their associated abstracts can be viewed on the CDMRP website (http://cdmrp.army.mil).

Table IV-3. Selected BCRP Awards: Soy and Breast Cancer

Principal Investigator	Institution	Fiscal Year/Award Mechanism	Proposal Title
Salil Das	Meharry Medical College	FY02 Idea Award	Is Peripheral Benzodiazepine Receptor (PBR) Gene Expression Involved in Breast Cancer Suppression by Dietary Soybean Protein?
Coral Lamatiniere	University of Alabama at Birmingham	FY02 Idea Award	Proteomic Analysis of Genistein Mammary Cancer Chemoprevention
Bill Helferich	University of Illinois	FY02 Idea Award	Interaction of Dietary Genistein, Equol and Aromatase Inhibitors on Growth of Estrogen-Dependent Human Breast Cancer (MCF-7CA) Cells in Athymic Mice
Sonia Boyapati	Vanderbilt University	FY02 Postdoctoral Traineeship Award	Soy Food Intake, Tamoxifen Use, Estrogen Receptor Polymorphism, and Breast Cancer Survival
Xiao Ou Shu	Vanderbilt University	FY01 Idea Award	A Cohort Study of Ginseng, Soy and Other Complementary Medicine Use and Breast Cancer Survival
Jeffrey A. Tice	University of California San Francisco	FY00 Idea Award	Soy and Tamoxifen for Breast Cancer Prevention in High Risk Pre-Menopausal Women
Leejane W. Lu	University of Texas Medical Branch Galveston	FY00 Clinical Translational Research Award	Soybean Diet and Breast Density
Coral Lamartiniere	University of Alabama at Birmingham	FY99 Idea Award	Genistein Programming against Breast Cancer

Single Cell Protein Profiles for Improved Diagnosis and Treatment of Breast Cancer

Norman Dovichi, Ph.D., University of Washington, Seattle, Washington

Widespread use of mammography has made it possible to discover breast tumors at their earliest stages. Nevertheless, more detailed information is still required for guiding therapy. Fine needle aspirate biopsies of breast tumors are often obtained for the detection of cancer; however, these samples typically contain a limited number of breast epithelial cells mixed in a heterogenous pool of various cell types. Dr. Dovichi, the recipient of a FY02 BCRP Exploration Award, developed a two-dimensional (2D) fingerprinting method that can

produce protein profiles from a single cell, compared to the 100,000 cells normally required for the detection of protein with 2D gel electrophoresis. The generation of single-cell proteome fingerprints from cancer biopsies will potentially be a powerful prognostic tool in the characterization of breast cancers. As cited in a publication co-authored by Dr. Dovichi, "Single cell protein fingerprinting allows study of the cell-to-cell variation in response to treatment, which can provide insight into those factors that determine the response of a particular cell to treatment" (Hu S et al., 2004). The data from an individual's 2D protein profile may greatly accelerate the discovery of relevant biomarkers representing various stages of breast cancer, which will aid in the diagnosis and treatment of the disease.

PREVENTING THE ANGIOGENIC SWITCH IN HUMAN BREAST CANCER

Judah Folkman, M.D., Children's Hospital & Harvard Medical School

The BCRP Innovator Award was designed to fund talented individuals to pursue creative, potentially breakthrough research that could accelerate the eradication of breast cancer. In his first year of funding under this award, Dr. Judah Folkman has met this expectation. He has accumulated substantial evidence for his hypothesis that microscopic tumors can be held in check by a molecular switch that controls angiogenesis. When human breast cancer cells were separated into angiogenic and nonangiogenic subpopulations and implanted into immune-deficient mice, there was a significant difference in the elapsed time before palpable tumors arose in the mice receiving nonangiogenic tumor lines. In addition, 5% to 10% of nontumorigenic subpopulations reproducibly switched to the angiogenic phenotype. Some clues about the molecular angiogenesis switch are given by analyzing the balance between the endogenous angiogenesis inhibitor thrombospondin-1 and its negative regulator c-Myc in these cell lines. Dr. Folkman and colleagues showed that two breast cancer cell lines that formed nonangiogenic, dormant tumors in mice expressed very high levels of thrombospondin-1 and very low levels of c-Myc. Conversely, two breast cancer cell lines that formed angiogenic tumors in mice expressed very low levels of thrombospondin-1 and high levels of c-Myc. Dr. Folkman's group has evidence that angiogenic breast cancer cell lines repress the expression of thrombospondin-1 in surrounding stromal fibroblasts, and breast cancer cell lines that produce nonangiogenic dormant tumors stimulate thrombospondin-1 expression in stromal fibroblasts. The biochemical changes associated with the angiogenesis switch likely happen after the switch is flipped on, but before a tumor is palpable. Dr. Folkman showed that in mice bearing different types of human cancer, specific angiogenic proteins produced by a tumor are taken up by platelets and sequestered. The peak concentration of a given angiogenic protein is in direct proportion to the time the tumor has been present. This "platelet angiogenic profile" can detect an early microscopic tumor as small as 1 cubic millimeter, offering exciting possibilities for early cancer detection. The corollary to detecting tumors at this early stage is that treatment with angiogenesis inhibitors could prevent the development of cancer from these microscopic tumors essentially indefinitely, turning cancer into a "chronic manageable disease" in Dr. Folkman's words.

For additional information about this research, please refer to the following publication:

Hu S, Michels DA, Fazal MA, et al. 2004. Capillary sieving electrophoresis/micellar electrokinetic capillary chromatography for two-dimensional protein fingerprinting of single mammalian cells. *Analytical Chem* 67:4044–4049.

An Antibiotic That Kills Breast Cancer Cells

Shaomeng Wang, Ph.D., University of Michigan, Ann Arbor, Michigan

More than 60% of breast tumors have inappropriate activation of a protein called Signal Transducers and Activators of Transcription 3 (Stat3). This Stat3 activation is not observed in normal breast epithelial cells. It is believed that activation of Stat3 confers a growth advantage for cancer cells as well as resistance to conventional chemotherapeutic agents. Therefore, Stat3 is an attractive tumor-specific molecular target for new therapeutic agents. The goal of Dr. Shaomeng Wang of the University of Michigan was to discover small molecule inhibitors of Stat3 that were effective at killing breast cancer cells while having potentially low toxicity to normal breast cells. With funding from a FY02 BCRP Concept Award, Dr. Wang's laboratory and colleagues from the Ohio State University identified a promising compound. They analyzed the protein structures and binding sites of more than 429,000 compounds by virtual database screening. The goal was to find a compound that would be expected to bind to Stat3 in a region that would prevent Stat3 proteins from binding to each other, or homodimerizing. Homodimerization is required for activation of Stat3 proteins. One hundred compounds were selected and tested in cell-based assays. From these 100 compounds, the STA-21 compound was selected as the strongest inhibitor of Stat3 activity. STA-21 is a natural product and a member of the angucycline class of antibiotics. STA-21 inhibited the growth and survival of breast cancer cell lines that have constitutively activated Stat3; however, it had no effect on the growth of other breast cancer cells. Studies of STA-21 mechanisms of action showed that STA-21 blocked the ability of Stat3 proteins to homodimerize, move to the nucleus, and bind to DNA. The next steps are to test the efficacy of STA-21 in animal models of human cancer and to make the STA-21 compound more potent. STA-21, a promising candidate for drug development, represents a new class of anticancer drugs for treating human breast tumors that contain activated Stat3.

This research was published in the following journal article:

Song H, Wang R, Wang S, and Lin J. 2005. A low molecular-weight compound discovered through virtual database screening inhibits Stat3 function in breast cancer cells. *Proc Nat Acad Sci USA* 102:4700–4705.

MMP-3-Induced Epithelial–Mesenchymal Transition and Genomic Instability

Mina Bissell, Ph.D.,[2] California, Hong Liu,[3] and Celeste M. Nelson, Ph.D.,[4] Lawrence Berkeley National Laboratory, Berkeley, California

In recent years, many cancer researchers have focused on identifying and studying oncogenes, but compelling evidence indicates that the microenvironment of epithelial cells plays a critical role in the responses of normal and malignant cells to stimuli (including therapeutic agents), and when the extracellular context is altered, regulatory pathways signal differently. The proteolytic enzymes known as matrix metalloproteinases (MMPs) are major contributors to these microenvironmental signals because they degrade structural components of the extracellular matrix, making tumor invasion and metastasis possible. Dr. Mina Bissell, an FY01 Innovator Award recipient, and her colleagues have shown that stromelysin-1/MMP-3, a stromal enzyme that is upregulated in many breast tumors, can cause epithelial–mesenchymal transition (EMT). EMT causes epithelial cells to break away from neighboring cells, become mobile, and break through such barriers as the walls of lymph and blood vessels, thus facilitating metastasis. In the current study, Bissell and colleagues explored the molecular pathways through which MMP-3 exerts this effect. They found that the Rho guanosine-triphosphatase proteins (GTPases), which control the proteins that define the cytoskeleton, play a key role in the link between MMP-3 and EMT. When normal cells were treated with MMP-3, the cells expressed Rac1b, an unusual form of Rho GTPase previously found in breast and colon cancers. Rac1b dramatically altered the cytoskeleton, allowing epithelial cells to separate and move away from neighboring cells. The changes that Rac1b induced in the cytoskeleton increased the formation of reactive oxygen species (ROS), which are highly reactive, oxygen-containing molecules. The increased ROS had a direct impact on genomic DNA by activating key genes that control the EMT. The duplicated and missing DNA regions that resulted from the increased ROS are key characteristics of cancer development. The researchers have developed a method to block the formation of Rac1b. When they used RNA interference (RNAi) to reduce the levels of Rac1, they prevented MMP-3 from exerting its effect on the EMT. This technique offers a possibility for intervening in the tumor development pathway identified in this study. The study also suggests other potential therapeutic targets, including stopping the cytoskeleton alterations, ROS effects, and the process through which ROS activates genes that induce EMT and facilitate metastasis.

[2] *Supported by FY01 Innovator Award.*

[3] *Supported by FY02 Predoctoral Traineeship Award.*

[4] *Supported by BC03 Postdoctoral Award.*

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

Radisky DC, Levy DD, Littlepage LE, et al. 2005. Rac1b and reactive oxygen species mediate MMP-3-induced EMT and genomic instability. *Nature* 436(7047):123–127.

THE STAMP OUT BREAST CANCER ACT

Public Law 105-41, which resulted from the work of breast cancer advocates, led to the issuance of a first-class semipostal stamp, the U.S. Postal Service Breast Cancer Research Semipostal (BCRS).

ANALYZING DIFFERENCES IN BREAST CANCER INCIDENCE AND OUTCOMES AMONG AFRICAN AMERICAN AND CAUCASIAN WOMEN: HBCU/MI PARTNERSHIP TRAINING AWARD

Agnes Day, Ph.D., Howard University Cancer Center

Last year, we described the HBCU/MI Partnership Training Award mechanism. Through this award mechanism, HBCU/MI faculty investigators work alongside established breast cancer researchers to ultimately increase the number of investigators at HBCU/MI studying breast cancer research. This year, we focus on one of these awards, granted in FY00 to Dr. Agnes Day of Howard University Cancer Center (HUCC) in collaboration with the Walter Reed Army Institute of Research (WRAIR). This extremely productive partnership has produced four new collaborative research projects between investigators at HUCC and WRAIR. In addition, this HBCU/MI Partnership Training program offers workshops for faculty and students at HUCC on such hands-on topics as imaging in animals, rodent-handling techniques, proteomics, and grantsmanship. It also supports several graduate students and postdoctoral fellows who have presented talks and posters at national or international cancer meetings, received travel awards to participate in numerous conferences, and served as co-authors on published manuscripts. HUCC has developed new cancer-related courses on integrative oncology and basic oncology for non-biology majors and has enhanced its current molecular biology course through the addition of new lectures and laboratories. The training and research experiences offered by the partnership have led to the submission of several additional grant applications, as well as several publications in peer reviewed journals and presentations at conferences. In addition, the PI has received significant training and experience, as well as mentorship, through this award. As a result, scientific progress is being made toward understanding the differences in breast cancer incidence and mortality rates between African American and Caucasian women. Research funded through this award has identified differences in expression of 12 matrix metalloproteinases (MMPs) between African American and Caucasian breast cancer cell lines. MMPs are enzymes involved in normal cellular development and wound healing but are also implicated in carcinogenesis. This altered expression pattern of MMPs may be a contributing factor to the differences in breast cancer mortality rates between African American and Caucasian women. Thus, the research experience offered by the partnership is yielding progress toward understanding the differences in breast cancer incidence and mortality rates between African American and Caucasian women, while the training component of this award is increasing the number and quality of HBCU/MI investigators involved in breast cancer research.

Net revenues from the BCRS are used to support breast cancer research at both the DOD BCRP and the National Institutes of Health (NIH), with the BCRP receiving 30% of the funds raised from the sale of this stamp.

Since the introduction of the BCRS in 1998, the BCRP has received 14 installments totaling $13.2M. These monies have been used to fully fund 26 BCRP Idea Award proposals submitted to the BCRP and partially fund one other proposal, for a total of 27 awards. BCRP Idea Awards are intended to encourage innovative approaches to breast cancer research and are a well-recognized backbone of the BCRP's portfolio of awards. As with all BCRP awards, the submissions funded through the BCRS are reviewed according to the two-tier review system originally recommended by the IOM. Table IV-4 details BCRP-supported research funded through the BCRS.

Table IV-4. BCRP Research Funded by the BCRS

Fiscal Year	Principal Investigator	Institution	Proposal Title	Research Area
FY99	Daly	Garvan Institute	Identification of Novel Prognostic Indicators for Breast Cancer through Analysis of the EMS1/Cortactin Signaling Pathway	Cell Biology
	Deuel	Scripps Institute	Novel Angiogenic Domains: Use in Identifying Unique Transforming and Tumor Promoting Pathways in Human Breast Cancer	Molecular Biology
	Heyer	University of California, Davis	In Vitro Recombination Activities of the Breast Cancer Predisposition Protein Brca2	Molecular Biology
	Musgrove	Garvan Institute	Role of Cyclin D1 and p27 in Steroidal Control of Cell Cycle Progression in the Mammary Gland In Vivo	Cell Biology
	Shah	University of Arkansas	Role of a Novel Matrix-Degrading Metalloproteinase in Breast Cancer Invasion	Cell Biology
	Wang	Texas A&M University	Scanning Microwave-Induced-Acoustic Tomography	Imaging
	White	University of Texas Southwestern Medical Center	Isolation of Factors That Disrupt Critical Protein/Protein Interactions within the Telomerase Holoenzyme for Use in Breast Cancer Therapeutics	Molecular Biology
	Wreschner	Tel Aviv University	Analysis of the Secreted Novel Breast-Cancer-Associated MUC1/Zs Cytokine	Cell Biology
FY00	Adamson	Burnham Institute	Cripto: A Target for Breast Cancer Treatment	Cell Biology
	Akporiaye	University of Arizona	Tumor-Mediated Suppression of Dendritic Cell Vaccines	Immunology
	Penn	University of Toronto	Exploiting the Novel Repressed Transactivator Assay to Identify Protein Interactors and Peptide Inhibitors of the Myc Oncoprotein	Molecular Biology

Table IV-4. BCRP Research Funded by the BCRS (cont.)

Fiscal Year	Principal Investigator	Institution	Proposal Title	Research Area
FY01	Cai	Vanderbilt University	Genetic Polymorphisms, Mitochondrial DNA Damage, and Breast Cancer Risk	Epidemiology/ Genetics
	Carraway	University of California, Davis	Identification of a Functional Human Homolog of Drosophila *Kek1*, an Inhibitor of Breast Tumor Cell Growth	Cell Biology
	Chaudhary	University of Texas Southwestern Medical Center	The Role of Ectodysplasin A (EDA) and Its Receptors in the Pathogenesis of Breast Cancer	Cell Biology
	Geahlen	Purdue University	Characterization of Syk in Breast Carcinoma Cells	Cell Biology
	Rosner	St. Luke's-Roosevelt Hospital Center	Autocrine and Paracrine Control of Breast Cancer Growth by Sex Hormone-Binding Globulin	Cell Biology
FY02	Dou	University of South Florida	Synthetic Beta-Lactam Antibiotics as a Selective Breast Cancer Cell Apoptosis Inducer: Significance in Breast Cancer Prevention and Treatment	Therapy
	Godwin	Fox Chase Cancer Center	The Nuclear Death Domain Protein p84N5; a Candidate Breast Cancer Susceptibility Gene	Genetics
	Perkins	Yale University	Rapid Genomic Approach to Cancer Gene Discovery in Breast Cancer	Genetics
FY03	Chung	Yale University	Quantitative In Situ Assessment of the Somatostatin Receptor in Breast Cancer to Assess Response to Targeted Therapy with 111-in-Pentetreotide	Diagnostics
	Kaaks	International Agency for Research on Cancer	Fatty Acid Synthesis Gene Variants and Breast Cancer Risk; a Study within the European Prospective Investigation into Cancer and Nutrition (EPIC)	Epidemiology/ Genetics
	Yaswen	Lawrence Berkeley National Laboratory	Functional Analysis of BORIS, a Novel DNA-Binding Protein	Molecular Biology
	Ziv	University of California, San Francisco	Admixture and Breast Cancer Risk among Latinas	Epidemiology/ Genetics
FY04	Bissell	Lawrence Berkeley National Laboratory	Use of HA-Metal Nanoparticles to Identify and Characterize Tumorigenic Progenitor Cell Subsets in Breast Tumors	Cell Biology
	Clarke	Northern California Cancer Center	The Hygiene Hypothesis and Breast Cancer: A Novel Application of an Etiologic Theory for Allergies, Asthma, and Other Immune Disorders	Epidemiology/ Genetics
	Giorgio	Vanderbilt University	Surface Functionalized Nanoparticles and Nanocrystals for Proximity-Modulated, Early Neoplasia Detection, Imaging, and Treatment of Breast Cancer	Diagnosis
	Lemmon	University of Pennsylvania	Harnessing Novel Secreted Inhibitors of EGF Receptor Signaling for Breast Cancer Treatment	Therapy

Several exciting research accomplishments have resulted from the research supported by the BCRS. Of the 27 grants awarded, most are studying the basic biology of mammary cells and how breast cancer develops from normal breast cells. Investigators have discovered new pathways and new proteins involved in regulating breast cell growth; this includes proteins that inhibit tumor cell growth.

- Dr. Kermit Carraway of the University of California, Davis found a new molecule (a human form of Kek1) that inhibits the activity of epidermal growth factor, a molecule that encourages cell growth. This molecule has potential as a therapeutic agent.
- Dr. Michael White of the University of Texas Southwestern Medical Center found that molecules such as siRNA that inhibit telomerase activity (one specific component of DNA replication) can keep breast cancer cells from proliferating. Dr. White and his team are evaluating the usefulness of the siRNA compounds as therapeutics in a mouse model system.
- Dr. Mark Lemmon of the University of Pennsylvania is developing a new class of breast cancer therapeutics that neutralize breast cancer growth signals/growth factors rather than the cellular receptors that respond to these growth factors.

For a tumor to grow and spread, it must acquire the ability to gain a new blood supply (a process called angiogenesis) and to evade the immune system. Several of the BCRS-funded awards seek to develop new drugs to stop these tumor processes.

- Dr. Roger Daly of the Garvan Institute is investigating a protein called cortactin that seems to be involved in the growth and spread of cancer cells. He has applied for patents on work involving protein complexes comprising cortactin and their uses.
- Dr. Robert Geahlen of Purdue University is examining Syk, another cellular protein that keeps breast cancer calls adhering to one another and may prevent them from spreading.
- Dr. Emmanuel Akporiaye of the University of Arizona found that tumor growth in mice is inhibited when immunotherapy is enhanced by neutralizing transforming growth factor-beta, a molecule that inhibits the dendritic cell, one of the important immunologic cells.

Another approach to the study of breast cancer is to examine the risk that individuals or groups of people (populations) have of developing the disease. Several award recipients funded through the BCRS are performing population-based studies to better define the causes of and risk factors for developing breast cancer.

- A project headed by Dr. Andrew Godwin of Fox Chase Cancer Center aims to examine the role of a different gene referred to as TREX84 (p84N5) that may be associated with breast cancer susceptibility. Expression of this gene has been shown to correlate with the aggressiveness of a tumor. Thus, TREX84 may be valuable as a prognostic marker for breast cancer, and molecules that interfere with the expression of this gene may have therapeutic potential.
- Dr. Rudolf Kaaks of the International Agency for Research on Cancer is examining the links between dietary fat and breast cancer risk. In this project, Dr. Kaaks is studying the variation in key genes that control fat metabolism and the risk of developing breast cancer.
- Dr. Elad Ziv of the University of California, San Francisco is investigating whether breast cancer susceptibility among Latinas is related to differences in ancestral admixture and/or differences in hormonal, lifestyle, or other nongenetic factors.

BCRS revenue has also supported research into breast cancer detection. Dr. Lihong Wang of Texas A&M University developed new imaging techniques to detect breast cancer early without the use of ionizing radiation, which is used in mammography. He has applied for patents on this technology, and clinical testing of this imaging method has begun.

Finally, part of the BCRS funds disseminated in FY04 will support two new projects using nanotechnology. The ultimate goal of both projects is to use nanoparticles for early detection of breast cancer. Dr. Mina Bissell of the Lawrence Berkeley National Laboratory is developing nanoparticles to specifically identify and isolate breast cancer stem cells (tumor-initiating progenitor cells). Dr. Todd Giorgio of Vanderbilt University is developing nanoparticles that can be used for both early detection and treatment of breast cancer.

In summary, although BCRP funds from the Stamp Out Breast Cancer Act have been in investigators' hands for only a short time, there have been many exciting research accomplishments. Discoveries in the basic biology of cancer cell development, tumor formation, the role of the immune system, and advances in early detection techniques hold significant promise for understanding this disease, identifying new drugs and treatments, and assisting the body's natural defenses to fight the spread of disease. These discoveries have resulted in numerous published papers and several patent applications. The BCRP will continue to carefully invest the dollars generated by the BCRS to find and fund the best science from the nation's most innovative, qualified scientists and clinicians.

"Consumer involvement in all facets of the Breast Cancer Research Program has proven crucial to ensuring not only that the best and most innovative science gets funded but that the science will really make a difference to those of us living with the disease. The fact [that] the funded researchers must report to the public on the results of their research every 2 to 3 years is also key to ensuring we learn both what works and what doesn't, thereby ensuring hard won funds aren't wasted."

Karin Noss, FY03–04 BCRP Consumer Programmatic Reviewer

"I believe that the Era of Hope grant has given me a tremendous opportunity to make a giant leap. The organized activities associated with the Era of Hope grant will allow me to meet other investigators who are not from the same discipline and who I likely would not cross paths with, but who have complementary interests. This will allow me to further expand my vision and include an even larger pool of diverse collaborators. The flexibility of the budgeting has injected a new dynamic into this research — we are able to react to new discoveries and information based on scientific value rather than being tied to a budget that was based on a snapshot of the previous state-of-the-art."

Karen Burg, Ph.D., FY04 BCRP Era of Hope Scholar Award Recipient

BCRP RESEARCH IN THE NEWS

March 11, 2005 - ANN ARBOR, MICHIGAN

Written by Nicole Fawcett, University of Michigan Health System, News Releases

U-M Researchers Identify a Small Molecule That Inhibits Protein Involved in Cancer

Researchers have discovered a small molecule that could be the first step in developing a new drug that may one day be able to treat multiple types of cancer.

The study, published this week in the advanced online edition of the *Proceedings of the National Academy of Sciences*, identifies a small molecule that inhibits in cell cultures a protein involved in multiple types of cancer. The protein, called Stat3, is constantly activated in some but not all tumors and has been identified in breast cancer, prostate cancer, ovarian cancer, and head and neck cancer. It contributes to new cancer cells growing and prevents cancer cells from dying. It's associated with poorer prognosis for patients since traditional chemotherapy treatments cannot shut down this protein.

That's what makes it such an attractive target for new drug development, researchers say. In this new study, researchers at the University of Michigan Comprehensive Cancer Center discovered a molecule called STA-21 that blocked Stat3 activity in human breast cancer cells, stopping cancer cells from growing and allowing them to die.

"We now can use this compound as a starting point to develop a new class of anti-cancer drugs to target cancer cells with constantly activated Stat3. One of the promises of molecular target drugs like this is they will work in many types of tumors where Stat3 protein is constantly activated. While our work looked specifically at breast cancer cells, there's a potential general application for other types of cancers with constantly activated Stat3," said study author Shaomeng Wang, Ph.D., associate professor of hematology/oncology at the U-M Medical School, assistant professor of medicinal chemistry at the U-M College of Pharmacy, and co-director of the Molecular Therapeutics Program at the U-M Comprehensive Cancer Center.

Wang and his colleagues screened 3-D models of more than 400,000 small organic molecules using a computer program to search out structures most likely to bind to the Stat3 protein. This novel virtual screening strategy allowed the researchers to examine a large number of small molecules quickly and inexpensively. They identified 200 small molecules that appeared to match, and zeroed in on one, STA-21.

When STA-21 was used in cultured breast cancer cells containing activated Stat3, the cancer cells began to die off. Cells from breast cancers without a constantly active Stat3 signal and non-cancerous cell lines were unaffected by STA-21.

The research was a close collaboration between Wang's lab and Jiayuh Lin, Ph.D., formerly of the U-M Comprehensive Cancer Center and now an associate professor at the Ohio State University and member of the Ohio State University Comprehensive Cancer Center.

Targeted molecular medicine is an exciting research approach to develop safer and more effective new anti-cancer drugs than conventional chemotherapeutic agents. Researchers hope targeting proteins specifically linked to cancer cells will lead to better, less toxic treatments that are tailored to each patient's particular cancer based upon its molecular signature.

"Stat3 is a very important protein involved in key processes in a number of different cancers. Up to 60 percent of human breast cancers may contain activated Stat3, and it may play an important role in both the growth and survival of these cells. The development of a specific inhibitor of Stat3 may therefore provide a novel therapeutic approach for breast cancer," said Max Wicha, M.D., director of the U-M Comprehensive Cancer Center.

Researchers say their next step is to test STA-21 in animal models of human cancer to determine how effective STA-21 is in inhibition of tumor growth and to examine if STA-21 has any toxicity to animals. Wang also plans to work with the STA-21 compound to make it more potent and active so it becomes an even more attractive candidate for drug development.

In addition to Wang and Lin, study authors are Hui Song, a research associate in Lin's laboratory, and Renxiao Wang, a research investigator in Wang's laboratory, both at U-M.

Funding for the study was provided by the U.S. Department of Defense Breast Cancer Research Program and from the National Institutes of Health. The National Cancer Institute provided the chemical sample of STA-21.

Reference: *Proceedings of the National Academy of Sciences*, DOI 10.1073/pnas.0409894102

Wednesday, July 20, 2005 - Mayo Clinic, Rochester, Minnesota, News

Benign Breast Disease an Important Breast Cancer Risk Factor

A study led by Mayo Clinic Cancer Center adds evidence to a growing body of knowledge that shows women with benign breast disease have a higher risk for breast cancer, and that certain types of breast disease may predict the near-term development of breast cancer. The findings are published in the July 21 issue of *The New England Journal of Medicine*.

"Our findings indicate a link between select types of benign breast lesions and the later development of breast cancer," says Lynn

"As for the EOH [Era of Hope] award, it has been a tremendous help for me and my laboratory. The award enables us to explore a new area: integrating structure, function, and chemistry for the discovery and design of multidrug resistance [MDR] reversal agents. MDR, as you already know, is a big problem in breast cancer as well as other cancers too. Although conceptually simple on paper, the integration of these components is a challenge to do logistically, scientifically, and financially. The EOH award bridges this gap nicely.

I believe that we will discover a new class of inhibitor compounds that could reverse MDR in breast cancer. I bet that I will look back and see that the seed of this project started from this award."

Geoffrey Chang, Ph.D., FY04 BCRP Era of Hope Scholar Award Recipient

Hartmann, M.D., Mayo Clinic oncologist and lead investigator of the study. "Women who have a breast biopsy that is benign must discuss the possibility of additional risks with their doctors."

Benign breast disease refers to any lumps or mammographically detected abnormalities that have been biopsied and found to not contain cancerous cells. Each year in the United States it is estimated that more than 1 million women have a breast biopsy with benign findings, and Dr. Hartmann encourages clinicians to look more closely at the type of lesions they find. The Mayo team is evaluating various possible risk factors for a later breast cancer, including age at benign biopsy, family history of breast cancer and the pathologic findings of the benign lesion. "Our goal is to do a better job of risk prediction for women with various types of benign breast conditions," says Dr. Hartmann.

Dr. Hartmann and her co-investigators were heartened to find convincing evidence that women with the most common, non-proliferative forms of benign findings had no increased risk of developing breast cancer — as long as they did not have a strong family history of breast cancer. However, for proliferative and atypical types, the opposite was true, and these lesions pointed to an increased risk of a future breast cancer, even when the family history of breast cancer was negative. Dr. Hartmann and her colleagues say continued studies of this kind are necessary to help understand the process of breast cancer development.

The study population of 9,087 women was drawn from the Mayo Clinic Surgical and Pathology Indices, identifying women ages 18 to 85, who had a biopsy of a benign breast lesion during a 25-year period from Jan. 1, 1967, through Dec. 31, 1991. Family histories were obtained at time of follow-up and from Mayo medical record questionnaires.

All benign breast samples were evaluated by a breast pathologist unaware of initial diagnoses or patient outcomes and assigned to one of three categories of benign breast lesions — nonproliferative, proliferative and atypical. This information was used to link the risk of subsequent development of breast cancer to specific types of lesions.

In addition to Dr. Hartmann, members of the Mayo Clinic research team included Marlene Frost, Ph.D., Wilma Lingle, Ph.D., Amy Degnim, M.D., Karthik Ghosh, M.D., Robert Vierkant, Shaun Maloney, V. Shane Pankratz, Ph.D., David Hillman, Vera Suman, Ph.D., Jo Johnson, Celine Vachon, Ph.D., L. Joseph Melton III, M.D., and Daniel Visscher, M.D. They were joined by Thomas Sellers, Ph.D., H. Lee Moffitt Cancer Center and Research Institute, Tampa, Fla.; Cassann Blake, M.D., Wayne State University, Detroit; and Thea Tlsty, Ph.D., University of California, San Francisco.

The Department of Defense BCRP and National Cancer Institute funded this study with additional support from the Susan G. Komen Breast Cancer Foundation, the Breast Cancer Research Foundation and the Andersen Foundation.

BOTTOM LINE

Since 1992, the BCRP has provided opportunities to accelerate discovery and eradication of breast cancer. To date, the program has been responsible for managing $1.83B in congressional appropriations, which has resulted in 4,293 awards for FY92 through FY04. The program continues to offer award opportunities that benefit the current needs of the patient and research communities while not duplicating efforts of other agencies. Research highlights, award data, and abstracts of funded BCRP proposals can be viewed on the CDMRP website (http://cdmrp.army.mil).