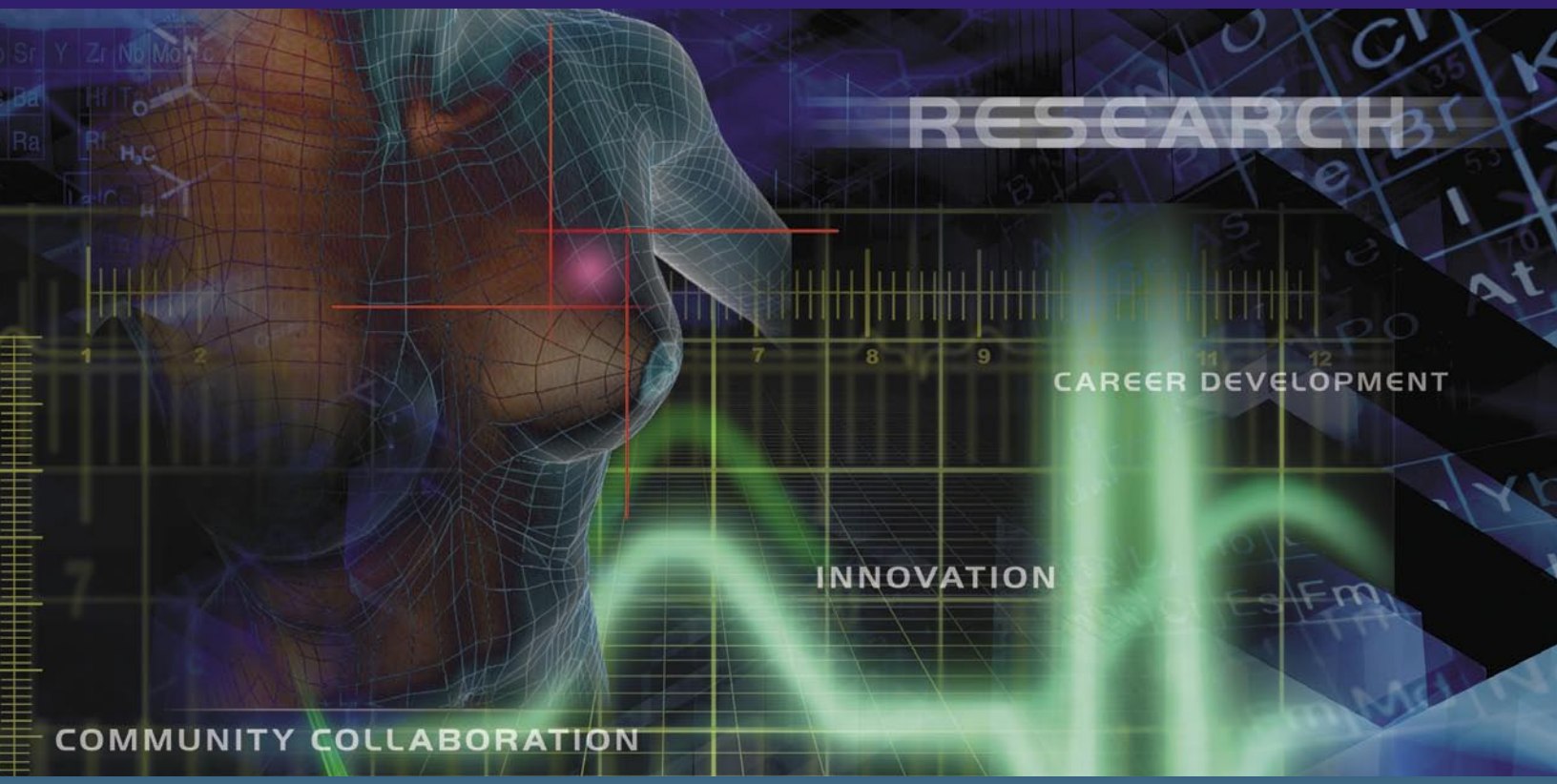
2005 Awards Compendium

Cycle 11



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CALIFORNIA
Breast Cancer
Research Program

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Introduction

The California Breast Cancer Research Program (CBCRP) presents the outcome of our Cycle 11 2005 grant application review and funding process. We are pleased to announce the **funding of 53 new research grants** that will advance our knowledge about the causes, prevention, sociocultural aspects, biology, detection, and treatment of breast cancer. With these new awards we are **investing over $7.7 million for research projects being performed at 24 institutions across the state**, including universities both public (e.g., University of California campuses) and private (e.g., Stanford University); national laboratories (e.g., Lawrence Livermore National Laboratory); research institutes (e.g., The Scripps Research Institute); medical centers (e.g., John Wayne Cancer Institute); and community organizations (e.g., Women's Cancer Resource Center).

The CBCRP supports breast cancer research in California from funds obtained through:

- A portion of a 2 cents per pack State cigarette tax
- Contributions from individuals using the State's income tax check-off option
- Donations from concerned community members dedicated to defeating breast cancer

The CBCRP is administered by the University of California, Office of the President, in Oakland. Our overall objectives, strategies, and priorities are developed with the assistance of a volunteer advisory council, which also makes recommendations on the applications to be funded. The council consists of 16 members: five are representatives of breast cancer survivor/advocacy groups; five are scientists/clinicians; two are members from nonprofit health organizations, one is a practicing breast cancer medical specialist, two are members from private industry, and one is an *ex officio* member from the DHS breast cancer early detection program, Every Woman Counts.

Below and in the sections to follow are summaries, discussions, and listings of newly funded CBCRP grants for 2005 including:

- Grant applications and new awards shown by CBCRP research topics and award types
- Highlights of 2005 funding
- A portfolio summary and list of grants for our research priority issues
- Funded California institutions
- Description of the review process and review committee membership lists

The full abstracts of these newly funded grants, as well as those from previous CBCRP funding cycles, can be found on our website: www.cbcrp.org.

The Goals of Our Research Funding

"The mission of the CBCRP is to eliminate breast cancer by leading innovation in research, communication, and collaboration in the California scientific and lay communities."

The CBCRP seeks to fund a unique grant portfolio that does not overlap with other research agencies. To establish the CBCRP's priorities and advance our mission, our advisory council identified these key criteria for the research CBCRP funds:

- **Nurture collaboration** and synergy between California scientists, clinicians, advocates, community members, and others
- **Recruit, retain, and develop high-quality California-based investigators** who focus on breast cancer research
- Foster **innovative ideas** (i.e., new drugs, new strategies and new paradigms)
- **Address the public health outcomes** of prevention, earliest detection, effective treatments, and quality of life
- **Translate research** to more effective products, technologies, or interventions and their **application/delivery to Californians**
- **Drive policy** in both the private and public sectors on breast cancer in California
- **Reduce disparities** and/or **address the needs of the underserved** in California
- **Complement, build on, and/or feed into**, but do not duplicate the research programs of other funding agencies interested in breast cancer
- Respond to feedback on breast cancer research needs and **expectations of the CBCRP as identified by scientists and the public** in California

We are constantly evaluating our granting efforts to better meet the needs of both the research and the breast cancer advocacy communities in California.

CBCRP Funding Changes for 2005

In order to maximize our impact and build on our strengths, the CBCRP and our advisory council instituted substantial changes to our research program starting in 2005. We decided to pursue two paths to support critical breast cancer research in California. The CBCRP is launching a new initiative to address the following critical research topics: (1) defining the influence of the **environment and lifestyle** on breast cancer and (2) uncovering the reasons for the **unequal burden (disparities)** of breast cancer. We are setting aside 30 percent of our research funding to support this initiative, which will take shape in the next 1-2 years. Through

the work of external experts, we will determine how CBCRP's resources can be leveraged to make the biggest leaps forward in tackling these issues.

The remaining 70 percent of our research funding continues to support traditional grants. We are focusing our core funding efforts in the areas of innovative research, career development, and community participation. The CBCRP award types now include four categories:

- **Dissertation** and **Postdoctoral Fellowship** career development awards
- **IDEAs** (innovative, developmental, exploratory awards). We offer a **competitive renewal** for the most promising projects, and junior investigators are strongly encouraged to apply under this award type
- **Community Research Collaboration (CRC)** awards
- **Joining Forces Conference Awards**

A number of previous CBCRP award types (RFA, TRC, SPRC, New Investigator, Training Program, Career Enrichment, and Mentored Scholar) were eliminated. An additional change for 2005 was to eliminate the distinction between "primary" and. "complementary" award types and priority issues (research topics). Thus, in 2005 all applications competed equally for funding.

As a result of these changes, we reduced our application volume in Cycle 11 by 10 percent (223 in 2004 vs. 201 in 2005). However, because we eliminated many of our more expensive award types (e.g., RFAs), we were able to fund a higher percentage and greater number of applications.

The CBCRP Funding Process

In January-February 2005 we received 199 grant applications in response to our Call for new research on breast cancer. These applications were reviewed and scored by our out-of-state scientific and advocate reviewers. Our review committee membership lists and the review process are described at the end of this booklet.

After the peer review, those applications having sufficient scientific merit were rated by our advisory council for responsiveness to stated CBCRP programmatic criteria. The end result is that the CBCRP's advisory council balances the scientific merit and programmatic ratings to arrive at a funding recommendation for each application. Thus, the successful applicant has responded both in terms of presenting a high quality research project and by meeting the interests of CBCRP stakeholders. An additional two applications were submitted under our Joining Forces Conference award mechanism. These were reviewed directly by our advisory council and both were funded.

Overall CBCRP Funding in 2005

Applications received and reviewed = **201**
Applications offered and accepting funding = **53**
Overall Success rate = **26.4%**
Amount awarded in 2005 = **$7,738,540**

2005 Cycle 11 Funding Highlights

- Seven awards to **community groups collaborating with traditional researchers** to address issues important to the community, such as end-of-life issues, patient decision-making, and health access.
- Eight awards focus on **etiology and prevention**, including chemoprevention, hormone receptors, and a project targeting lymphedema.
- Two grants investigate the underlying reasons behind **racial and ethnic disparities** associated with breast cancer.
- Eight awards deal with **sociocultural/psychological issues,** including studies on underserved populations and ethnic minorities.
- Twenty-four grants further our understanding of **tumor biology**, especially the process of metastasis and the role of stem cells.
- Nine projects explore novel methods to **detect breast cancer and develop novel approaches for treatment**.
- Four new awards focus on **health policy and services** including reducing disparities, new avenues of communication, and cost effectiveness issues.
- Twenty-three projects are for **innovative, exploratory, and high-risk/high reward research** projects to push boundaries, challenge existing paradigms, and initiate new research programs.
- Two awards were for **competitive renewals of previous innovative awards** in the topics of BRCA1 gene function and the detection of circulating cancer cells.
- Nineteen awards provide opportunities in **career development** at the levels of graduate and postdoctoral training. These researchers bring fresh thinking to their respective disciplines.
- ☑ **Five awards are of special interest**, because they are funded, in part, by revenue from the **California State Income Tax Check-off**.
- **Faith Fancher Research Award**
  Faith Fancher was a long-time television news anchor and personality with KTVU (Oakland) who was taken from us in October 2003 after a six-year struggle with breast cancer. In her honor, and to commemorate all that she did for breast cancer education and research, we have created this award. The recipients in 2005 are **Beverly Burns, M.S., L.Ac.,** at the **Charlotte Maxwell Complementary Clinic** in Oakland and **Shelley Adler, Ph.D.,** from the **University of California, San Francisco**, for their project, ***Underserved Women with Breast Cancer at End of Life*.**

2005 Applications and Grants by CBCRP Priority Issues

Priority Issue:	Number of Applications	Grants Funded (success rate)	Amount Awarded	Percentage of total funding
Community Impact	29	12 (41%)	$1,178,444	15.2%
Etiology & Prevention	26	8 (31%)	$1,151,051	14.9%
Biology of the Breast Cell	82	24 (29%)	$3,996,716	51.6%
Detection, Prognosis & Treatment	64	9 (14%)	$1,412,329	18.3%

2005 Applications and Grants by CBCRP Award Types

Award Type:	Number of Applications	Grants Funded (success rate)	Amount Awarded	Percentage of total funding
Dissertation	20	7 (35%)	$514,605	6.6%
Postdoctoral Fellowship	51	12 (24%)	$1,359,047	17.6%
IDEA*	104	23 (22%)	$4,436,166	57.3%
IDEA-Competitive Renewal	4	2 (50%)	$690,774	8.9%
CRC Pilot Award	18	7 (39%)	$687,948	8.9%
CRC Full Award	2	0 (0%)	$0	0%
Joining Forces Conference	2	2 (100%)	$50,000	0.6%

*For the IDEA category: we offered this award in 2005 to both established and “junior investigators” for the first time. Junior investigators are at a career level past postdoc, but less than three years as an independent investigator. We received 26 applications from junior investigators and funded 6 grants (23%), so this category was equally competitive compared to IDEAs from established investigators.

Description of Award Types Funded in 2005

- **Community Research Collaboration (CRC) award:** Brings community organizations—such as breast cancer advocacy organizations, community clinics, or organizations serving underrepresented women—together with experienced scientists to investigate breast cancer problems that are important to that community, using culturally-appropriate research methods.
- **Innovative Developmental and Exploratory Award (IDEA):** Funds promising high-risk/high-reward research to "road test" innovative concepts. In 2005 the CBCRP introduced the "critical path" concept that requires applicants to place their project on a research continuum leading to practical applications.
- **IDEA–competitive renewal:** Introduced in 2005, this award allows recently funded recipients of CBCRP IDEA grants to compete for additional funding, if the project has met key milestones and is on a critical path for success.
- **Postdoctoral Fellowship award:** For advanced training under a breast cancer research mentor. In 2005 the CBCRP limited the total postdoctoral tenure (prior training plus new CBCRP funding) to five years. We also increased the maximum award duration to three years.
- **Dissertation award:** Supports the completion of dissertation research by masters or doctoral candidates. In 2005 the CBCRP increased the award amount to $76,000 (total direct costs).
- **Joining Forces Conference award:** To support a conference, symposium, retreat, or other meeting to link breast cancer researchers, non-breast cancer investigators, and community members for the purpose of stimulating new ideas and collaborations.

The Community Impact of Breast Cancer:
The Social Context

Overview: California is a unique blend of diverse communities, and our state offers tremendous opportunities to uncover the basis for disparities and the unequal burden of breast cancer. What is the influence of poverty, race/ethnicity, and social factors on breast cancer? What are the sociocultural, behavioral, and psychological issues of those affected by breast cancer and what services are needed to reduce suffering? We encourage health policy, health services, and sociocultural, behavioral, and psychological research that address the needs of California's diverse communities.

A major focus of the CBCRP is to foster collaborative interactions between traditional researchers having the skills in grant preparation and research capacity with community groups having more direct experience with the human issues of breast cancer. The NIH in a recent program announcement (PAR-05-026) has listed many of the advantages for supporting community-based participatory research as follows, "…involving community and academic partners as research collaborators may improve the quality and impact of research by:

- More effectively focusing the research questions on health issues of greatest relevance to the communities at highest risk;
- Enhancing recruitment and retention efforts by increasing community buy-in and trust;
- Enhancing the reliability and validity of measurement instruments (particularly survey) through in-depth and honest feedback during pre-testing;
- Improving data collection through increased response rates and decreased social desirability response patterns;
- Increasing relevance of intervention approaches and thus likelihood for success;
- Targeting interventions to the identified needs of community members;
- Developing intervention strategies that incorporate community norms and values into scientifically valid approaches;
- Increasing accurate and culturally sensitive interpretation of findings;
- Facilitating more effective dissemination of research findings to impact public health and policy;
- Increasing the potential for translation of evidence-based research into sustainable community change that can be disseminated more broadly."

The CBCRP has been supporting community-based collaborations for nine years, and we offer workshops and technical assistance to facilitate new partnerships and successful grant applications. We are encouraged that many CRC grants focus on underserved and under-represented populations and disparities that underlie unequal access to care and less favorable outcomes in breast cancer treatment. We feel that an "evidence-based" community project has the greatest potential for a successful intervention.

In addition to the CRC awards, the CBCRP supports the community impact priority issue with innovative IDEA grants and career development awards.

Three of the CBCRP's research topics are represented in this section:

- ***Health Policy and Health Services:*** ***Better Serving Women's Needs***

- ***Disparities:* *Eliminating the Unequal Burden of Breast Cancer***
- ***Sociocultural, Behavioral, and Psychological Issues Relevant to Breast Cancer: The Human Side***

Funding Data:

		Proportion of Total
Community Impact grants awarded in 2005:	**12**	**23%**
Funded amount:	**$1,178,444**	**15%**

Community Impact Portfolio Summary:

In 2005 the CBCRP funded seven Community Research Collaboration (CRC) pilot awards. These support community-based participatory research that requires equal partnership between scientists and community members. These projects are intended to allow the gathering of pilot data and to prepare the research team to launch a three-year full research project. Six of these new CRC awards address racial/ethnic minority populations, and another addresses economically disadvantaged women.

Shelley Adler, Ph.D., from the **University of California, San Francisco,** and **Beverly Burns, M.S., L.Ac,** at the **Charlotte Maxwell Complementary Clinic** will examine the beliefs, values, concerns, expectations, and goals about end-of-life from the viewpoints of underserved women with breast cancer, their physicians, complementary and alternative medicine practitioners, and informal caregivers. A January 1998 Institute of Medicine report highlighted the fact that there is room for a great deal of improvement in end-of-life care.

Anna Napoles-Springer, Ph.D., M.P.H., at the **University of California, San Francisco,** and **Carmen Ortiz, Ph.D.**, of **Circulo de Vida**, San Francisco, will examine the individual, social, and cultural factors that serve to either increase or decrease access to support services among Spanish-speaking Latinas with breast cancer. The aim is to determine support program components that are most useful and the type of training that peer support counselors need to enable them to provide adequate support to Latinas with breast cancer. Based on this information, they intend to develop a culturally appropriate outreach and support intervention.

Also addressing the needs of Latinas are **Rena Pasick, Ph.D.,** at the **University of California, San Francisco,** and **Maximiliana Ruiz** at the **Women's Cancer Resource Center**, Oakland. They will look at the role of lay health workers (LHW), who play an important role in linking the Latina community and the mainstream medical care system. Their study will design optimal LHW models to reduce breast cancer disparities for limited English proficiency in Latina women by identifying and evaluating best practices in breast cancer outreach, education and support.

Peggy Reynolds, Ph.D., at the **California Department of Health Services**, Oakland (award funded through **Impact Assessment, Inc.**), and **Kim Nguyen** from the **Asian Health Services** will systematically collect information on Vietnamese women working in nail salons in Alameda County. The study will examine health care access and utilization, risk behaviors such as smoking and exercise, and occupational exposures. This information will lay the groundwork for future interventions to reduce breast cancer risk among Vietnamese women.

Also studying an underserved Asian community are **Roshan Bastani, Ph.D.,** at the **University of California, Los Angeles,** and **Zul Surani** at the **South Asian Cancer Foundation**, who will conduct a needs assessment in order to determine how best to design an intervention to address the practical and psychological needs of South Asian women (Indian, Pakistani, Sri Lankan, and Bangladeshi will be surveyed). California has the largest population of any state of South Asian women, who are the third largest Asian group in the US, and little is known about their specific breast health and breast cancer service needs.

Economically disadvantaged, rural communities face significant barriers for access to quality health care. **Jeff Belkora, Ph.D.,** at the **University of California, San Francisco,** together with **Sara O'Donnell** and **Joy Hardin, Ed.D.,** from the **Cancer Resource Center of Mendocino County** and the **Humboldt Community Breast Health Project** respectively, are examining how to help patients absorb, remember, make decisions, and act upon the information and advice they get from breast specialists. While this topic applies to all patients, the focus of this research will be the Native American and Latina minorities served by these community organizations. These individuals typically face cultural and language barriers in addition to the common rural challenges of poverty, geographic isolation, and health literacy. The team will interview doctors, patients, and health agency staff to uncover what helped or hindered patient understanding, recall, and decision-making. The goal is to use this information to develop a consultation support intervention.

Kimlin Ashing-Giwa, Ph.D., at the **University of California, Los Angeles,** and **Janette Robinson-Flint** at **Black Women for Wellness** received a CRC research planning grant to develop a cooking and eating behavioral trial, grounded in cultural practices, to increase fruit and vegetable intake and reduce the dietary-related risk of breast cancer in the African American community.

Four newly funded CBCRP grants are for either innovative research (IDEA) grants or dedicated to career development. **Sonia Ancoli-Israel, Ph.D.,** at the **University of California, San Diego,** is studying how chemotherapy may disrupt the body's biological clock and whether this may increase the symptoms of sleeplessness, fatigue, and depression associated with chemotherapy. She will pilot test a bright light intervention (during chemotherapy) and evaluate the results using questionnaires and sleep recordings.

Linda Fiorentino at the **University of California, San Diego,** received dissertation funding to also look at the impact of chemotherapy on sleep. She will use cognitive behavioral therapy techniques, including group educational sessions coupled with cognitive strategies to challenge dysfunctional thoughts and attitudes about sleep and daily functioning. Homework assignments in the form of diaries to track sleep patterns and monitor thoughts associated with sleep patterns will also be used.

Leah Karliner, M.D., at the **University of California, San Francisco,** is addressing the need for physicians to evaluate and incorporate into their medical practice new approaches to care, some of which involve new technologies. The central hypothesis of this grant is that breast cancer patients' access to new tests and treatments can be improved through techniques designed to help doctors integrate them into medical practice and communicate them to patients. This will require better understanding of physicians' decision-making processes, which Dr. Karliner will explore through face-to-face interviews with physicians and a mail survey.

Allison Kurian, M.D., at **Stanford University** received a postdoctoral fellowship award to identify cost-effective strategies for the use of magnetic resonance imaging (MRI) as an addition to mammography for early breast cancer detection. She will use a computer simulation model to generate breast cancer outcomes for individual women and to present their aggregate results at the population level. This approach will be adapted to include the detection ability of MRI, the characteristics of women with dense breast tissue, and women with high inherited breast cancer risk, including the impact of risk-modifying factors. The results will be a measure of estimated mortality reduction of screening MRI, its cost-effectiveness and an optimal screening schedule according to a woman's age and breast cancer risk level.

The CBCRP funded **Laura Esserman, M.D.,** from the **University of California, San Francisco,** through a Joining Forces Conference award to address the critical need to improve health care quality. Workshops are planned to incorporate the principles of quality improvement by developing feedback processes, employing novel core data systems, and to provide a blueprint to change behavior at the point-of-care in the patient-physician-provider network. The CBCRP will support the initial meeting to get this new paradigm started.

Community Impact Grants Funded in 2005:

Health Policy and Health Services

A Blueprint for Advancing Quality in Breast Cancer
Laura J. Esserman, M.D.
University of California, San Francisco
Award type: Joining Forces Conference
$25,000

New Breast Cancer Approaches: Integration, Communication
Leah S. Karliner, M.D.
University of California, San Francisco
Award type: IDEA
$150,000

Cost-effectiveness of Breast MRI Screening by Cancer Risk
Allison K. Kurian, M.D.
Stanford University School of Medicine
Award type: Postdoctoral fellowship
Duration: 2 years
$90,000

Disparities

Breast Cancer Risk Profile of Vietnamese Nail Salon Workers
Kim D. Nguyen and Peggy Reynolds, Ph.D.
Asian Health Services and Impact Assessment, Inc.
Award type: CRC Pilot
$119,963

Consultation Recording for Rural Underserved Breast Cancer Patients
Sara O'Donnell; Jeff Belkora, Ph.D.; and Joy Hardin, Ed.D.
Mendocino Cancer Resource Center; University of California, San Francisco; and Humboldt Community Breast Health Project
Award type: CRC Pilot
$115,391

Partnership to Reduce Cancer Disparities in Spanish Speakers
Maximiliana P. Ruiz and Rena J. Pasick, Dr.P.H.
Women's Cancer Resource Center and University of California, San Francisco
Award type: CRC Pilot
$119,501

Sociocultural, Behavioral, and Psychological Issues

Effect of Bright Light on Fatigue in Breast Cancer
Sonia Ancoli-Israel, Ph.D.
University of California, San Diego
Award type: IDEA
$149,496

Underserved Women with Breast Cancer at End of Life
Beverly Burns, M.S., L.Ac, and Shelley Adler, Ph.D.
Charlotte Maxwell Complementary Clinic and University of California, San Francisco
Award type: CRC Pilot
$110,669

Treating Insomnia with CBT in Women with Breast Cancer
Lavinia Fiorentino, M.S.
University of California, San Diego
Award type: Dissertation
$76,000

Psychosocial Support Services for Latinas with Breast Cancer
Carmen Ortiz, Ph.D., and Anna M. Nápoles-Springer, Ph.D., M.P.H.
Circulo de Vida and University of California, San Francisco
Award type: CRC Pilot
$100,000

Kitchen Divas: Breast Cancer Risk Reduction for Black Women
Janette Robinson-Flint and Kimlin T. Ashing-Giwa, Ph.D.
Black Women for Wellness and University of California, Los Angeles
Award type: CRC Planning Grant
$10,000

 **South Asian Women with Breast Cancer: What are Their Needs?**
Zul Surani; Roshan Bastani, Ph.D.; and Beth Glenn, Ph.D.
South Asian Cancer Foundation and University of California, Los Angeles
Award type: CRC Pilot
$112,424

Etiology and Prevention: Finding the Underlying Causes

Overview: Although our foundation of knowledge for the basic science aspects of breast cancer has expanded greatly over the past ten years, there still remains a gap in our strategies for large-scale prevention due to uncertainties over the underlying causes of the disease and their relative importance. The *Breast Cancer and Environmental Research Act of 2005* (S.737/ H.R. 2231), which amends the existing *Public Health Service Act,* summarizes many of the key issues related to the etiology and risk for breast cancer as follows:

- "Breast cancer is the second leading cause of cancer deaths among American women.
- More women in the United States are living with breast cancer than any other cancer (excluding skin cancer). Approximately 3,000,000 women in the United States are living with breast cancer, about 2,000,000 of which have been diagnosed and an estimated 1,000,000 who do not yet know that they have the disease.
- Breast cancer is the most commonly diagnosed cancer among women in the United States and worldwide (excluding skin cancer). In 2005, it is estimated that 269,730 new cases of breast cancer will be diagnosed among women in the United States, 211,240 invasive breast cancers and 58,490 cases of ductal carcinoma in situ (DCIS).
- Approximately 40,410 women in the United States will die from the disease in 2005. Breast cancer is the leading cause of cancer death for women in the United States between the ages of 20 and 59, and the leading cause of cancer death for women worldwide.
- A woman who lives into her 80s in the United States has a 1 in 7 chance of developing invasive breast cancer in her lifetime. This risk was 1 in 11 in 1975. In 2005, a new case of breast cancer will be diagnosed every 2 minutes and a woman will die from breast cancer every 13 minutes.
- All women are at risk for breast cancer. About 90 percent of women who develop breast cancer do not have a family history of the disease."

Although there is an extensive laundry list of factors associated with increased and decreased risk for breast cancer, controversy exists over the relative importance of diet, exercise, family history, pregnancy, alcohol, hormone replacement therapy, and others. Because the vast majority of all breast cancers are sporadic and not associated with hereditary risk factors (e.g. BRCA genes), interest has shifted to looking at "the environment" to explain the elevated levels of breast cancer over the past 20-30 years. Although environment can mean many things, a topic of special focus in California is the exposure to synthetic chemicals and radiation. In addition, the focus on the environment is expected to shed light on disparities in breast cancer incidence, ethnic factors, and variations across diverse communities. Thus, researchers are looking both inside cancer cells for clues to the key genes that initiate and cause cancer to progress *and* outside of the individual to find external causative factors that might be eliminated or modified to reduce risk.

Etiology and prevention (or risk reduction) go hand-in-hand. The Breast Cancer Prevention Trial (BCPT) to study tamoxifen in high-risk women and the STAR (Study of Tamoxifen and

Raloxifene) trial have yielded promising, often controversial results, but "reduction" falls far short of prevention for most women. More complete results of the STAR trial are expected in 2006.

Although prevention research has focused on the role of estrogen and modification of lifestyle factors (diet, exercise), more work is needed on such topics as androgens, the ER-β form of the estrogen receptor, and more complex tissue interactions in the breast (stromal-epithelial) that might be influenced by aging and environmental factors.

Two of CBCRP's research topics are represented in this section:

- ***Etiology: The Role of the Environment and Lifestyle***
- ***Prevention and Risk Reduction: Ending the Danger of Breast Cancer***

Funding Data:

		Proportion of Total
Etiology and Prevention grants awarded in 2005	**8**	**15%**
Funded amount:	**$1,151,051**	**15%**

Etiology and Prevention Portfolio Summary:

Four newly funded grants focus on the etiology of breast cancer. A Joining Forces Conference award to **Susan Love, M.D.,** supported the *4th International Symposium on the Intraductal Approach to Breast Cancer*. The meetings were held on March 10-13, 2005, in Santa Barbara and hosted by the **Dr. Susan Love MD Research Foundation**, Pacific Palisades. More than 100 researchers, clinicians, and patient advocates from California and elsewhere met to discuss the current status and future of this technology. The intraductal method involves obtaining breast duct fluid via the nipple either as aspirate fluid or as a lavage. The cells and fluid can then be analyzed for pre-cancerous and cancerous proteins, genes, and cytology.

Two newly funded grants consider hormonal factors. **Yanyan Hong** at the **Beckman Research Institute of the City of Hope** received dissertation funding to characterize the three-dimensional structure of human aromatase. It is the aromatase pathway that largely determines estrogen levels in postmenopausal women, and aromatase inhibitors are especially effective in preventing recurrence in postmenopausal women. Structural information on aromatase may enable the discovery of additional compounds for the chemoprevention and treatment of breast cancer.

Wei Wang, Ph.D., at the **University of Southern California** received a postdoctoral fellowship to look at the possible role played by the androgen receptor in breast cancer. In women, this "male" hormone may have a dual role, indirectly as a source of estrogen (thus increasing risk), and directly by binding to a breast cell receptor (thus possibly protective). The overall impact on risk may depend on the genetically determined balance between the two actions. Dr. Wang will examine DNA from a large sample of African American, Hispanic, and white women.

Stanley Rockson, M.D., at **Stanford University** will investigate the development of lymphedema, a condition that involves swelling of the soft tissues of the arm or hand. This condition, a result of surgical disruption of the lymph system of the arm, occurs in as many as 25%-50% of women who undergo complete lymph node removal as part of the breast cancer

surgery. While not life-threatening, the swelling may be accompanied by numbness, discomfort, and sometimes infection, and has a profound impact on quality of life. Dr. Rockson will consider the hypothesis that insulin resistance contributes to the risk of lymphedema and that genetic variation in the ”forkhead” transcription factor (FOXC2) gene mediates part of the risk. The FOXC2 gene has been shown to be mutated in individuals with inherited lymphedema syndromes, and its protein product regulates several aspects of adipocyte (fat cell) metabolism.

Four newly funded CBCRP grants are concerned with prevention and risk reduction.

There are two forms of the estrogen receptor, ER-α and ER-β, and their presence and relative amounts may determine whether estrogen-receptor modulators (such as Tamoxifen) are effective in certain women. Surprisingly, little work has been performed on the ER-β to test this idea. **Peter Kushner, Ph.D.,** at the **University of California, San Francisco,** will test the efficacy of a new estrogen receptor modulator, diarylpropionitrile (DNP) as a chemopreventive agent for breast cancer for women of all ages. Dr. Kushner will use cell studies and a special breed of mouse (MMTV-c-neu) to test the ability of DPN to inhibit estrogen-driven breast cancer cell proliferation in culture, and prevent the occurrence of hyperplasia.

Melanie Palomares, M.D., at the **Beckman Research Institute of the City of Hope**, will study whether grape seed extract (GSE), a powerful inhibitor of aromatase activity in mice, can be taken by human subjects without adverse affects. GSE is undergoing a small Phase I clinical trial and Dr. Palomares' study is meant to examine whether there are any longer-term side effects. Blood samples will be examined by proteomics techniques to specifically see whether GSE affects testosterone-related hormones, cholesterol and blood clotting proteins, insulin resistance, and blood vessel growth.

Current chemoprevention strategies rely primarily on selective estrogen-receptor modulators (SERMs) using a single drug, and while they do have benefit for some women, it is clear that there is room for much improvement. **Jeffrey Gregg, M.D.,** at the **University of California, Davis,** will investigate whether combination chemoprevention could be more effective. Using a mouse model bred to mimic the biology, pathology, and behavior of human ductal carcinoma *in situ* (DCIS), mice will be treated with different dosages and combination of agents, and the effectiveness and toxicity of each treatment will be assessed.

Increased breast mammographic density is one of the strongest predictors of breast cancer risk, but we know little about the biological basis of this effect. **Thea Tlsty, Ph.D.,** from **University of California, San Francisco,** will investigate whether the supporting breast stromal (fibroblast cell) tissue can interact with early developing breast cancer cells to alter tumor initiation and progression. Dr. Tlsty will implant combinations of fibroblasts from dense vs. normal human breasts along with human breast tumor cells using mice as a host. The goal is to identify clinically relevant biomarkers for the early genetic and epigenetic events in carcinogenesis that reflect altered stromal-epithelial interactions. Understanding the risk factors associated with dense breast stromal tissue might lead to novel preventive strategies.

Etiology and Prevention Grants Funded in 2005:

Etiology

Structural Characterization of Aromatase
Yanyan Hong, M.S.
Beckman Research Institute of the City of Hope
Award type: Dissertation
$70,750

4th International Symposium on the Intraductal Approach to the Breast
Susan Love, M.D.
Susan Love MD Foundation
Award type: Joining Forces Conference
$25,000

☑ **Breast Cancer Lymphedema: Role of Insulin Resistance/FOXC2**
Stanley G. Rockson, M.D.
Stanford University
Award type: IDEA
$234,178

Androgen Receptor Gene and p21 Gene in Breast Cancer
Wei Wang, M.D.
University of Southern California
Award type: Postdoctoral fellowship
$134,998

Prevention and Risk Reduction

Targeted Chemoprevention in a Mouse Model for DCIS
Jeffrey P. Gregg, M.D.
University of California, Davis
Award type: IDEA
$135,726

Estrogen Receptor Beta Agonists to Prevent Breast Cancer
Peter J. Kushner, Ph.D.
University of California, San Francisco
Award type: IDEA
$150,000

Grape Seed as a Natural Breast Cancer Chemopreventive Agent
Melanie Ruth Palomares, M.D.
Beckman Research Institute of the City of Hope
Award type: IDEA
$252,236

☑ Breast Cancer Risk Associated with High Mammographic Density

Thea D. Tlsty, Ph.D.
University of California, San Francisco
Award type: IDEA
$148,163

Detection, Prognosis, and Treatment:
Delivering Clinical Solutions

Overview: We know that breast cancer mortality rates have recently begun to decline. The underlying reasons are believed to be a combination of improved screening rates, better prognostic information available to clinicians, and more varied treatment options. However, the most significant factor for improved survival appears to be the diagnosis of smaller tumors at an earlier stage. Examining 25 years of breast cancer records, lead researcher **Elena Elkin, Ph.D.** at **Memorial Sloan-Kettering Cancer Center** in New York, recently concluded that smaller tumor size accounted for over 60 percent of the improvement in survival when cancer had not spread beyond the breast, and almost 30 percent when it had spread minimally. Thus, improved detection and imaging technologies are essential to continue this beneficial trend. Although yearly X-ray mammography screening is the gold standard, many questions have emerged over its real value. We know that mammography is less effective in pre-menopausal women or post-menopausal women on hormone replacement therapy. It often fails to detect tumors in high-density breast tissue, irrespective of age and hormone use. Almost one-third of diagnosed tumors are missed in mammography screening, and false-positives lead to unnecessary biopsies, cost, and stress.

In terms of improved breast cancer prognosis, gene-based profiling of cancer patients is now commercially available. In addition to existing tests for BRCA1 and BRCA2 mutations, companies like Genomic Health in Redwood City have recently introduced Oncotype DX™. This test profiles the activity of 21 genes and determines risk of recurrence in early stage breast cancer as well as the potential benefit of chemotherapy in certain patients. These genetic tests are expected to emerge as an improvement over single-marker analysis, such as estrogen receptor and Her-2 oncogene. Certainly, genetic testing is beginning to open the door to individualized medicine.

In the past few years the treatment situation for breast cancer has also seen significant advances. Aromatase inhibitors are now used as a first line drug in place of tamoxifen in postmenopausal women. They seem to work well in preventing cancer recurrence and are associated with reduced side effects compared to selective estrogen-receptor modulators (SERMs). Angiogenesis inhibitors, such a Genentech's Avastin™, are showing promising results in late clinical trials for metastatic breast cancer and should be widely available in the near future.

Four research areas show promise in developing new and more effective breast cancer treatment strategies. First, we need to apply our improved understanding of the cellular, genetic basis of the disease, and translate this information to the clinic. Genetic profiling has identified major cancer subtypes, so that research efforts can be directed towards more aggressive, less differentiated, and highly metastatic subtypes that are poorly addressed in current clinical practice. This would be a big step towards individualized therapy. Emerging models of breast cancer that point towards a stem cell origin and the existence of a treatment-resistant population of breast cancer stem cells represent another significant milestone. Second, combination therapies to target multiple tumor cell growth and signaling pathways are needed to allow better management of the disease and reduce recurrence. Third, incorporation of scientific paradigms from such disciplines as cell and human aging (senescence), inflammation, and the tissue

microenvironment (e.g. stromal-epithelial interactions) promise a better conceptual framework to either envision new treatments or test existing treatments (e.g. COX-2 inhibitors) in the appropriate preventive or clinical setting. Finally, in terms of the pre-clinical aspects of drug development, more appropriate cell and animal models are needed to better duplicate the heterogeneity seen in the human disease. A promising step in this direction is the NCI's Mouse Models of Human Cancers Consortium (MMHCC). This collaborative program is designed to derive and characterize mouse models, to generate resources, and to use innovative approaches in pre-clinical trials and drug development.

Two of the CBCRP's research topics are represented in this section:

- **Imaging, Biomarkers, and Molecular Pathology:** ***Improving Detection and Diagnosis***
- **Innovative Treatment Modalities:** ***Search for a Cure***

Funding Data:

		Proportion of Total
Detection, Prognosis & Treatment grants awarded in 2005:	**9**	**17%**
Funded amount:	**$1,412,329**	**18%**

Detection, Prognosis, and Treatment Portfolio Summary:

Three new grants in 2005 address the topic of breast cancer imaging. Two of them have evolved from research funding provided by the CBCRP to **John Boone, Ph.D.,** at the **University of California, Davis**. Dr. Boone built the first dedicated breast computerized tomography (CT) scanner during the past five years. To enable this technology he overcame two barriers. First, he was able to show that the radiation dose for breast imaging could be reduced to make annual screening by CT a reality. Second, he was able to develop a special table for breast imaging that had the advantages of not exposing other parts of the body to radiation and not requiring breast compression, a major discomfort in mammography. These solutions combined to make the dedicated breast CT scanner a practical alternative to mammography. Currently, the new breast CT scanner is undergoing a Phase II clinical trial using NIH funding. In a new IDEA grant, Dr. Boone will be adding a positron emission tomography (PET) capability to his CT scanner. This will enable molecular imaging capabilities. In PET imaging a patient is injected with a radioactively labeled or tagged compound to show the chemical functioning of tissues. If the combined CT-PET scanner develops further, then this hybrid technology will allow both anatomical and physiological images of the breast.

Thomas Nelson, Ph.D., at the **University of California, San Diego,** is developing a novel three-dimensional ultrasound scanner that will use the same patient mechanical platform as Dr. Boone's CT scanner. In fact, the 3-D ultrasound technology will be compared to CT images to validate performance in a clinical setting. Traditional ultrasound imaging is currently limited by weak resolution and operator variability, so this new approach from Dr. Nelson may well provide a critical breakthrough to stimulate more acceptance of ultrasound as a detection-diagnostic tool for breast cancer.

Brian Thorndyde, Ph.D., from **Stanford University** is funded through a postdoctoral fellowship to improve PET imaging by reducing respiratory artifacts. PET scans take several minutes and

the breast image quality is degraded by body movements associated with breathing. Dr. Thorndyke is developing and testing a way to sort imaging data and use algorithms to improve resolution.

The remaining six new grants funded by the CBCRP in 2005 in this section are in the treatment topic. Two projects focus on metastasis.

Brunhilde Felding-Habermann, Ph.D., at **The Scripps Research Institute**, La Jolla, will attempt to treat brain metastasis in animal models of breast cancer by delivering single-chain fragments (scFv) of human antibodies via inhalation through the nose. The technical approach is to place the antibodies as parts of special viruses, called phage, that can be taken-up nasally, cross the blood-brain barrier, and localize to tumor cells resident in the brain. This is truly high risk-high reward research that attempts to treat the most lethal of breast cancer metastatic sites.

David Hoon, Ph.D., from the **John Wayne Cancer Institute**, Santa Monica, will be testing a potential new biomarker to predict metastasis. The ID4 gene is a member of the "inhibitor of DNA-binding" protein family, which blocks a group of DNA-binding transcription factors, called helix−loop−helix. The point of Dr. Hoon's project is to determine whether ID4 analysis on primary tumor samples can be used to separate groups of patients that require sentinel lymph node biopsy from patients who will not benefit. This might significantly improve patient prognosis and spare some patients the need for this expensive, and possibly dangerous, procedure.

The remaining treatment grants deal with the structural aspects of key tumor genes and proteins that, when understood better at the molecular level, might prove to be drug targets or improve the application of current drugs in breast cancer treatment.

Mark Moasser, M.D., is a clinician-scientist at the **University of California, San Francisco,** whose interest focuses on the ErbB family of tyrosine kinases. Although the launch of Herceptin® by Genentech in 1999 was the first molecular therapeutic for Her-2, many patients receiving it do not respond. Dr. Moasser is interested in the portion of the ErbB receptors that resides inside of the cell and represents the signaling, kinase portion. Her-3 in breast cancer cells can serve to restore function to Her-2, and is a potential culprit in allowing cancer cells to evade drug treatment such as Herceptin®. This project employs novel siRNA techniques to find the link between Her-3 and the key PI3K/Akt signaling pathway in breast cancer cells to develop a new therapeutic angle.

Sanjay Saldahna, Ph.D., also at **The Scripps Research Institute,** is funded for a postdoctoral fellowship to study a major cellular signaling protein kinase, called protein kinase A (PKA). Although PKA is found in many cells and would seem to be an unlikely target for selective cancer therapy, Dr. Saldahna is targeting a single regulatory PKA alpha subunit. This subunit, when repressed, appears to have a significant effect on breast cancer cells. The aim of Dr. Saldahna's project is to find small drug candidates that block the binding of cyclic-AMP, a ubiquitous intracellular messenger, to the PKA alpha-subunit that would repress breast cancer.

Jiewen Zhu, Ph.D., at **University of California, Irvine,** is also interested in finding candidate drugs, but works on the mechanism of DNA repair that depends on BRCA2 and an associated protein called Rad51. If the association of BRCA2 and Rad51 can be disrupted, then it is thought that cancer cells will become hypersensitive to radiation therapy. This strategy, if successful, would permit much smaller doses of DNA-damaging chemotherapy and radiotherapy. The aim is to lessen the side-effects associated with these treatments.

Although SERMS (e.g., tamoxifen) remain frontline therapies for women with estrogen receptor positive disease, they fail to help some patients. A key underlying reason is that the ER-associated gene regulatory machinery is very complex and not completely understood. **Oksana Tyurina, Ph.D.,** at **University of California, San Diego,** is studying the role of inflammatory cytokines, often present at tumor sites due to the presence of macrophages, as potential modulators of how well SERMs function. Apparently under certain conditions, proteins normally found in the nucleus can migrate to the cytoplasm to mediate a reversal of SERM actions on the estrogen receptor. If Dr. Tyurina can dissect these novel pathways, it could open the door to new approaches to make SERMs work in more patients for a longer duration.

Detection, Prognosis, and Treatment Grants Funded in 2005:

Imaging, Biomarkers, and Molecular Pathology

Molecular Imaging of Breast Cancer Using Breast PET/CT
John M. Boone, Ph.D.
University of California, Davis
Award type: IDEA
$100,000

☑ **Early Breast Cancer Detection Using 3-D Ultrasound Tomography**
Thomas R. Nelson, Ph.D.
University of California, San Diego
Award type: IDEA
$149,879

Removing Respiratory Artifacts in Nuclide Breast Imaging
Brian Thorndyke, Ph.D.
Stanford University
Award type: Postdoctoral fellowship
$90,000

Innovative Treatment Modalities

☑ **Inhibition of Brain Metastases in Breast Cancer**
Brunhilde Felding-Habermann, Ph.D.
The Scripps Research Institute
Award type: IDEA
$278,850

ID4: A Prognostic Factor of Breast Cancer Metastasis
David S. Hoon, Ph.D.
John Wayne Cancer Institute
Award type: IDEA
$283,200

HER3 Infidelity and Resistance to Tyrosine Kinase Inhibitors
Mark M. Moasser, M.D.
University of California, San Francisco
Award type: IDEA
$150,000

cAMP Antagonists of Protein Kinase as Breast Cancer Drugs
Sanjay Adrian Saldanha, Ph.D.
The Scripps Research Institute
Award type: Postdoctoral fellowship
$90,000

An Approach to Antiestrogen Resistance in Breast Cancer
Oksana V. Tyurina, Ph.D.
University of California, San Diego
Award type: Postdoctoral fellowship
$135,000

Inhibition of the BRCA2-RAD51 Interaction in Breast Cancer
Jiewen Zhu, Ph.D.
University of California, Irvine
Award type: Postdoctoral fellowship
$135,400

Biology of the Breast Cell:
The Basic Science of the Disease

Overview: To understand the origin of breast cancers, more research is needed on the pre-cancerous causative events in the normal breast. We need to understand the cancer-related genetic and physiological changes associated with breast development, aging, pregnancy, and consider the influence of lifestyle and environmental factors. Breast cancer is a complex disease, and the underlying genetics of the variability seen in the clinic need clarification at the basic science level. Basic scientists need to use more relevant cell and pre-clinical animal models of breast cancer. It is hoped that new genetic and molecular "cancer signatures" of cancer sub-types and stages of progression may provide useful biomarkers for better diagnosis and prognosis, so treatments can be individualized and women spared the use of ineffective drugs. More research on the underlying cellular signaling pathways for growth control, cell death, DNA repair, and cell migration/metastasis are needed to develop into new targets for therapy and prevention.

Some recent advances in basic science have altered our conceptual view of breast cancer and promise to have a significant impact over the next few years. First, researchers at the **University of Michigan**, including **Dr. Michael Clarke** and **Dr. Max Wicha**, demonstrated the existence of breast cancer stem cells. According to this paradigm of breast cancer origin and progression, a small population of pluripotent stem cells acquire mutations that lead to tumor formation, tumor spread to distant organs, and resistance to most current therapies. Only a small fraction (1-2 percent) of cells in a tumor mass retain stem cell properties, and these are the tumor component that must be targeted in any effective therapy. Over the past twenty years, we have seen the limit of cancer therapies that merely shrink tumors, but allow the cancer stem cell population to persist and lead to recurrence.

Second, cancer epigenetics research is gaining strength with diffusion of the technology and informatics spawned from the Human Genome Project. Epigenetic changes alter gene functions without modifying the genetic code and are essential to normal development. In terms of cancer, sometimes the epigenetic changes will disable tumor suppressor genes and DNA repair mechanisms. Studies have suggested that epigenetic effects may be as common in some tumor cells as actual genetic mutations. At least a dozen drugs that target epigenetic mechanisms, such as methylation, are in clinical trials and more are in development. One of these drugs is now used to treat a rare bone marrow disorder, called myelodysplastic syndrome.

Third, the use of RNA-interference (RNAi) technologies is becoming widespread. Discovered in plants, and then in nematode worms in 1998, RNAi is an elegant, endogenous mechanism of "gene silencing" with potential therapeutic utility. In the basic research setting, siRNA (small interfering RNA) is commonly being used to dissect signaling pathways and knock out the expression of single genes. Although promising in cell-based studies, it remains unclear if this approach can make the leap into the anti-cancer therapeutic arena.

A critical area where basic science could benefit from a new organizational approach is through the discipline of systems biology. Thus, the traditional way of doing science in single labs or small research groups might give way to a team-based, integrative style. Systems biology is the study of living organisms in terms of their underlying network structure rather than by dissecting

their individual molecular components (i.e., reductionist logic). A system can be anything from a gene regulatory network to a cell, a tissue, or an entire organism. Because systems biology requires the consideration of all interacting components simultaneously, high-throughput, computational technologies are essential. Perhaps the most articulate proponent is **Leroy Hood, M.D., Ph.D.,** from **The Institute for Systems Biology**, Seattle. As the complexity and heterogeneity of breast cancer becomes more obvious, then progress will demand that researchers adapt to new paradigms to effectively tackle the disease. The NIH has adopted this approach by incorporating "Research Teams of the Future" as a part of the new NIH Roadmap plan. Director **Dr. Elias Zerhouni** has written, "The scale and complexity of today's biomedical research problems increasingly demand that scientists move beyond the confines of their own discipline and explore new organizational models for team science."

Two of the CBCRP's research topics are presented in this section.

- ***Biology of the Normal Breast:* *The Starting Point***
- ***Pathogenesis:* *Understanding the Disease***

Biology of the Breast Cell Funding Data:

		Proportion of CBCRP's Total
Grants awarded in 2005:	**24**	**45%**
Funded amount:	**$3,996,716**	**52%**

Biology of the Breast Cell Portfolio Summary:

Breast cancer begins with early pre-cancerous changes in individual cells, which could be breast stem cells or their immediate progenitors. As cancer progresses, the molecular events that regulate chromosomal surveillance, DNA repair, cell division and differentiation, movement, apoptosis (programmed cell death), and epithelial-stromal interactions become defective. However, the window of opportunity for prevention, early detection, and treatment is extensive, since the period from initiation to clinical diagnosis can span a decade or more.

Stem cells are the focus of three newly funded grants. **Alexander Borowsky, M.D.,** from the **University of California, Davis,** will use pre-cancerous breast tissues from a genetically defined mouse cancer model to identify gene patterns important for progression and to find evidence for an early breast cancer stem cell in these tissues. Once isolated, Dr. Borowsky will be able to test his underlying hypothesis that the "multiple gene hits" commit a stem cell to begin the journey to cancer, and, once committed, cancer progression does not depend on additional genetic mutations.

Steven Artandi, Ph.D., at **Stanford University** will be studying the role of telomerase in the context of breast stem cells in mice. Telomerase maintains the ends of chromosomes and is "turned on" in 90 percent of human breast cancers, including DCIS. Dr. Artandi has postulated a novel function for telomerase in the proliferation of breast stem cells, and this function is thought to be critical for cancer initiation as well.

Stefanie Jeffrey, M.D., also from **Stanford University,** will attempt to isolate stem cells from the most aggressive type of breast cancer, estrogen receptor- and progesterone receptor-negative tumors that are either Her-2 positive or negative. Patients with these tumors have a similar genetic profile, and their tumors and metastatic sites are very resistant to current

therapies. If the tumor-generating stem cell population can be isolated from these patients, then more information can be obtained on how to eradicate them. It is thought that current therapies often fail the patient because, although tumors will usually shrink, the stem cell population persists and becomes the source of disease recurrence.

Four newly funded grants examine breast cancer in the context of early disease progression. **Albert Davalos, Ph.D.,** at **Lawrence Berkeley National Laboratory** is studying human mammary epithelial cells (HMECs) to examine the contribution of the microenvironment in regulating how cells respond to DNA damage. Dr. Davalos will focus on extracellular matrix (ECM)-driven signaling to see how breast cells that lack critical repair proteins, mainly BRCA1 and NBS1, are able to respond to DNA damage. If successful, this model system has the potential to identify novel markers for early detection and targeted therapies.

Andrew Ewald, Ph.D., from the **University of California, San Francisco,** will study invasiveness of breast cells, and how matrix metalloproteinase-2 and fibroblast growth factor receptor-2 influence cell movements. The invasive process is essential to forming the primary ductal network in breast development and might be a mechanism of epithelial invasion when aging makes our tissues more permissive to the cancer phenotype.

Transforming growth factor-beta (TGF-β) has inhibitory effects in normal breast cells, but it can promote invasion and metastasis later in cancer progression. **Xiaoman Xu** from the **University of California, Irvine,** was funded though a dissertation award to determine whether a gene-regulatory transcription factor, called LMO-4, is a modulator of TGFβ. This study will use genetically modified mice. Given that TGFβ has such diverse effects, this project could provide biomarkers to predict the response to therapy in patients.

Zhengquan Yu, Ph.D., also at the **University of California, Irvine,** will also study LMO-4 in the context of signaling through the Her-2 oncogene pathway. LMO-4 levels are increased in about 50 percent of breast cancers, and it may serve to increase cell proliferation and influence cell growth and death pathways.

Cancer-causing oncogenes and cancer-preventing tumor suppressor genes are the focus of a number of newly funded grants. **Peter Kaiser, Ph.D.,** from the **University of California, Irvine,** is funded to continue his studies on the BRCA1 protein's function to selectively promote the degradation of other cellular proteins. Proteins that are essential to critical processes, such as the cell cycle pathway, are frequently marked for destruction by the attachment of ubiquitin. Dr. Kaiser will compare BRCA positive and negative cells for differences in their cellular ubiquitination patterns. In addition to giving new insight into how this critical breast cancer hereditary gene works, it could provide new disease biomarkers and strategies to prevent cancer.

The other major breast cancer hereditary gene, BRCA2, is the focus of another newly funded innovative grant to **Henning Stahlberg, Ph.D.,** at the **University of California, Davis.** BRCA2 functions in DNA repair and is associated with a protein called Rad51. The aims of Dr. Stahlberg's project are to clone and express cancer-associated BRCA2 mutants, investigate the structure of these mutants, and study the interaction of normal or mutant forms of BRCA2 with Rad51.

Sheryl Krig, Ph.D., also from the **University of California, Davis,** received a postdoctoral fellowship to study the ZNF217 oncogene, which contributes to the early progression of breast cancer by promoting cell "immortality." Dr. Krig will analyze whether ZNF217 suppresses Apaf-1 (apoptotic protease activating factor-1), which is essential for caspase activation that triggers apoptosis (cell death).

Myb oncogenes were initially described in *Drosophila* (fruit flies), and they have a role in leukemia and lymphoma. **Joseph Lipsick, M.D., Ph.D.,** at **Stanford University** will extend his studies on B-Myb into human breast cancer. Although B-Myb is included as one of the 21 genes in the Oncotype DX™ test to predict recurrence in tamoxifen-treated, node-negative breast cancer patients, its effects on chromosomal number (ploidy) in cancer progression are not well described.

Marc Milstein at the **University of California, Los Angeles,** will investigate RIN1, which regulates the Ras oncogene. Ras was one of the earliest oncogene families discovered. The Ras proteins deliver signals from cell surface receptors, such as growth factor receptors and G-protein coupled receptors, to ultimately regulate such functions as DNA synthesis and cytoskeletal organization. Mr. Milstein's dissertation project aims are to determine whether RIN1 can act as a tumor suppressor by influencing Ras, and whether the loss of RIN1 function plays a role in breast cancer.

P53 is a well-studied tumor suppressor that, while not lost or mutated as frequently in breast cancer as some other cancers, still is a subject of detailed investigation. **Lan Truong,** also from the **University of California, Irvine,** will conduct her dissertation research on the binding of p53 to a pre-mRNA splicing factor, called SAP145. Ms. Lan is interested in how the binding of Cyclin E to this complex could have an effect on the pre-mRNA splicing. The breast cancer endpoints include the cell growth and death pathways.

Breast cancer cells, even at the early DCIS stages, show profound changes in chromosomal structure that include gene deletions, duplications, and rearrangements. It remains a mystery how the genetic sequence, which is so closely monitored and repaired in normal cells, can be so profoundly altered in cancer cells and still allow proliferation. **Ewa Lis** at **The Scripps Research Institute** will identify and study basic mechanisms of mutagenesis-promoting genes in yeast, then study the corresponding genes in human breast cancer cells. Model organisms, such as yeast, have been valuable tools to study evolutionarily conserved processes, such as DNA repair and the cell cycle. In addition to facilitating cancer progression, it is thought that mutagenesis-promoting genes might be a major cause of drug resistance.

Women have two X chromosomes, but it was long believed that one of them was inactivated early in life and remained so permanently. Now it's thought that the "inactive X" might be re-activated in cancer, and this is the topic of the fellowship award to **Angela Andersen, Ph.D.,** from the **University of California, San Francisco.** The activation of the X chromosome and the regulatory protein, called *Xist*, will be studied in a variety of mouse breast cells, stem cells, early tumor hyperplastic outgrowths, and transformed cells. The X chromosome contains at least 70 cancer-related genes, so the re-activation of these genes could be the equivalent to gene duplication in other chromosomes.

Continuing along with the theme of epigenetic changes, **Judd Rice, Ph.D.,** from the **University of Southern California,** will study the patterns of a specific histone modification in a series of breast cancer cell lines with the goal of identifying markers associated with breast cancer

progression. Dr. Rice will perform chromatin immunoprecipitation (ChIP) analysis to determine different degrees of methylation for histone 4/lysine20 on cell lines derived from normal breast epithelium, primary lesions, and metastatic sites. Histones are proteins that package chromosomal DNA. Although histone methylation patterns in cancer are not fully understood, one hypothesis is that they may play a role in silencing key tumor suppressor genes and open the door to cancer progression even in the absence of other genetic changes.

The final major topic of newly funded CBCRP tumor biology grants is metastasis and angiogenesis. Although angiogenesis research appeared to promise a real breakthrough in cancer treatment five to ten years ago, actual translation to the clinical setting has been painfully slow. Genentech's introduction of Avastin in 2004 to treat colorectal cancer is the first of an anticipated new generation of molecularly-targeted therapeutics aimed at angiogenesis. Three newly funded grants focus on angiogenesis from unique perspectives.

Barbara Susini, Ph.D., at the **University of California, San Diego,** will study the role of lymphatic vessel growth (lymphangiogensis) and the altered integrin (i.e., cell surface adhesion receptor) profiles within tumor lymph-specific endothelial cells. It might seem strange that one of the body's major organs, the lymphatic system is so poorly understood. Lymphatic vessels collect fluid that has leaked into tissues from the bloodstream and return it to the blood through lymph nodes where key cells of the immune system are located. We know that tumor cells can pass through the lymphatic system, because lymph node biopsy has been a mainstay of tumor prognosis for decades. However, the mechanism of lymphatic vessel entry into tumors is an unexplored topic.

Konstantin Stoletov, Ph.D., from **The Scripps Research Institute** will use a unique animal model system, the zebrafish, to study angiogenesis. These fish are transparent, so it is easy to see organ and tissue morphology, especially in development. They have been widely used in genetics research, and the zebrafish genome has been entirely sequenced. Dr. Stoletov has shown that human breast cancer cells will grow progressively and induce angiogenesis in zebrafish, and he will focus on the RhoC gene. RhoC, whose full name is RhoC-GTPase, is a protein involved in changing the internal skeleton of a cell to allow a cell to polarize or move. It has been associated with inflammatory breast cancer, and might be a key factor in angiogenesis.

We need to know more about breast cancers that have spread to various organs, so that new treatments can target metastatic disease. **Florence Hofman, Ph.D.,** at the **University of Southern California** is focusing on breast cancer metastasis to the brain, which occurs in 10-15 percent of patients, by seeking ways to kill the tumor-associated brain blood vessel cells. Dr. Hofman will determine whether survivin, a trigger for apoptosis (cell death), can be targeted by RNA-interference molecules that are delivered by lentiviral vectors. While not directly killing tumor cells, this approach would make the tumor vulnerable to other chemotherapeutic agents by disrupting the brain-blood barrier selectively at tumor sites.

In any diagnosis of cancer, the patient and clinician want to know whether metastasis is likely to have occurred. Most tumors constantly shed small numbers of cells into the blood, so these circulating tumor cells (CTCs) are a promising source of biomarkers for metastasis and prognosis. **Kristen Kulp, Ph.D.,** at **Lawrence Livermore National Laboratory** is developing a new technology to detect CTCs through the statistical analysis of molecule-specific images derived from individual cells. This technology is based on "time of flight secondary ion mass spectrometry" (ToF-SIMS). Dr. Kulp achieved proof of principle in her previous CBCRP funding,

so a two-year renewal grant will continue these studies in both animal and human settings. The initial phase of this study is to validate that known metastatic vs. non-metastatic cells derived from culture can be isolated and distinguished when spiked into blood or grown as tumors in animal models.

Richard Neve, Ph.D., from **Lawrence Berkeley National Laboratory** will study ephrins and their receptors, which are important regulators of tissue morphogenesis. He plans to develop a new model system to co-culture various breast cell lines with normal and cancer-associated fibroblasts. Then, Dr. Neve will use RNA-interference to knock down EphA2 or EphA1 and determine whether this affects tumor formation and metastasis.

Also utilizing a novel model system is **Robert Abraham, Ph.D.,** at **The Burnham Institute**, who will grow tumor spheroids in a three-dimensional culture system. These conditions are thought to better duplicate the tumor setting compared to using tumor cells grown on plastic dishes. Dr. Abraham will use the new cell culture system to test inhibitors of the mTOR signaling pathway. The anti-fungal drug, rapamycin, has a mammalian target, called mTOR. The mTOR pathway is critical to signaling through the PI3K/Akt apoptosis pathways, so inhibiting mTOR may be useful in sensitizing tumor cells to existing therapeutics.

Brian Eliceiri, Ph.D., from the **La Jolla Institute for Molecular Medicine,** will test the novel hypothesis that estrogen promotes metastasis of breast cancer through actions on host tissues rather than on the cancer cells. He will use a breast cancer cell line that does not respond to estrogen and measure metastasis in mice that have their systemic estrogen levels modulated. Changes in the tumor vascular permeability and the extracellular matrix will be the focus of these studies.

Kyle Chiang from **The Scripps Research Institute** is funded for a dissertation project to continue research funded by the CBCRP previously to his mentor, **Benjamin Cravatt, Ph.D.** Mr. Chiang's project will focus on a protease, called KIAA1363, and he will test its relevance to breast cancer metastasis in biochemical, cell and animal models. This protease appears to be increased in aggressive cancer, so the discovery of KIAA1363's substrate and inhibitors would be major steps towards pre-clinical studies.

Biology of the Breast Cell Grants Funded in 2005:

Breast Cancer Studies in a 3-D Cell Culture System
Robert T. Abraham, Ph.D.
The Burnham Institute
Award Type: IDEA
$191,000

Reactivation of the Inactive X Chromosome and Breast Cancer
Angela Andersen, Ph.D.
University of California, San Francisco
Award Type: Postdoctoral fellowship
$90,000

Role of Telomerase in Mammary Stem Cell Function
Steven Artandi, Ph.D.
Stanford University
Award Type: IDEA
$236,519

Defining Mammary Cancer Origins in a Mouse Model of DCIS
Alexander Borowsky, M.D.
University of California, Davis
Award Type: IDEA
$150,000

Integrated Proteomic and Metabolic Analysis of Breast Cancer
Kyle P. Chiang
The Scripps Research Institute
Award Type: Dissertation
$76,000

The Role of the ECM in Breast Cancer DNA Damage Repair
Albert R. Davalos, Ph.D.
Lawrence Berkeley National Laboratory
Award Type: IDEA
$252,791

Novel Approach to Analyze Estrogen Action in Breast Cancer
Brian P. Eliceiri, Ph.D.
La Jolla Institute for Molecular Medicine
Award Type: IDEA
$310,950

Regulation of Mammary Epithelial Invasion by MMPs and FGFs
Andrew J. Ewald, Ph.D.
University of California, San Francisco
Award Type: Postdoctoral fellowship
$135,000

Survivin: Target for Breast Cancer Brain Metastases
Florence M. Hofman, Ph.D.
University of Southern California
Award Type: IDEA
$243,733

Stem Cells of Molecularly Diverse ER Negative Breast Cancers
Stephanie Jeffrey, M.D.
Stanford University
Award Type: IDEA
$234,165

Identification of BRCA1 Ubiquitylation Targets
Peter Kaiser, Ph.D.
University of California, Irvine
Award Type: IDEA, competitive renewal
$200,000

Apaf-1 is a Transcriptional Target for the ZNF217 Oncogene
Sheryl R. Krig, Ph.D.
University of California, Davis
Award Type: Postdoctoral fellowship
$53,649

Identifying Metastatic Breast Cells from Peripheral Blood
Kristen S. Kulp, Ph.D.
Lawrence Livermore National Laboratory
Award Type: IDEA, competitive renewal
$490,774

The Role of B-Myb in Human Breast Cancer Progression
Joseph Lipsick, M.D., Ph.D.
Stanford University
Award Type: IDEA
$156,106

Defining Mutagenesis Pathways in Breast Cancer Evolution
Ewa Lis
Scripps Research Institute
Award Type: Dissertation
$67,520

Evaluating the Role of RIN1 in Breast Cancer
Marc Milstein
University of California, Los Angeles
Award Type: Dissertation
$72,335

A Novel Epithelial-Stromal Model of Metastatic Breast Cancer
Richard M. Neve, Ph.D.
Lawrence Berkeley National Laboratory
Award Type: IDEA
$216,674

Histone Methylation as a Marker of Breast Cancer Progression
Judd C. Rice, Ph.D.
University of Southern California
Award Type: IDEA
$162,500

Structural Analysis of Cancer-Relevant BCRA2 Mutations
Henning Stahlberg, Ph.D.
University of California, Davis
Award Type: IDEA
$100,000

Imaging RhoC-induced Breast Cancer Invasion and Angiogenesis
Konstantin V. Stoletov, Ph.D.
The Scripps Research Institute
Award Type: Postdoctoral fellowship
$135,000

Role of Integrins in Lymphangiogenesis During Breast Cancer
Barbara Susini, Ph.D.
University of California, San Diego
Award Type: Postdoctoral fellowship
$135,000

A Role for p53 and Splicing Factor SAP145 in Breast Cancer
Lan N. Truong
University of California, Irvine
Award Type: Dissertation
$76,000

Modulation of TGF-beta Signaling in Mammary Epithelial Cells
Xiaoman Xu
University of California, Irvine
Award Type: Dissertation
$76,000

The Role of LMO4 in Breast Cancer
Zhengquan Yu, Ph.D.
University of California, Irvine
Award Type: Postdoctoral fellowship
$135,000

2005 CBCRP Funding by Institution

The following 24 California research institutions and community organizations were awarded new CBCRP funding in 2005. Some grants were structured as separate awards that are split between institutions.

Institution	# Awards	Amount
Asian Health Services, Oakland	1	$67,322
Beckman Research Institute of the City of Hope, Duarte	2	$322,986
Black Women for Wellness, Los Angeles	1	$10,000
Burnham Institute, La Jolla	1	$191,000
Charlotte Maxwell Complementary Clinic, Oakland	1	$53,346
Circulo de Vida, San Francisco	1	$20,000
Humboldt Community Breast Health Project, Arcata	1	$41,290
Impact Assessment, Inc., Oakland	1	$52,641
John Wayne Cancer Institute, Santa Monica	1	$283,200
La Jolla Institute for Molecular Medicine, San Diego	1	$310,950
Lawrence Berkeley National Laboratory	2	$469,465
Lawrence Livermore National Laboratory, Livermore	1	$490,774
Mendocino Cancer Resource Center, Mendocino	1	$35,664
Scripps Research Institute, La Jolla	5	$647,370
South Asian Cancer Foundation, Los Angeles	1	$62,118
Stanford University	6	$1,040,968
Susan Love MD Foundation, Pacific Palisades	1	$25,000
University of California, Davis	5	$539,375
University of California, Irvine	5	$622,400
University of California, Los Angeles	3	$122,641
University of California, San Diego	5	$645,375
University of California, San Francisco	11	$1,045,922
University of Southern California, Los Angeles	3	$541,231
Women's Cancer Resource Center, Oakland	1	$97,502

2005 CBCRP Application Evaluation & Review Committees

In the first phase of the funding process, grant applications were reviewed and scored for scientific merit in five peer review committees using a model that follows established practice at the National Institutes of Health (NIH). Each committee is composed of scientists and advocates from outside California. The committee chair leads the review process and is a senior researcher in breast cancer areas associated with the committee's central topics (e.g., etiology and prevention). Committee members have broad expertise in topics associated with individual applications. Breast cancer advocate reviewers are women and men active in breast cancer issues and many of whom are also living with the disease. Advocates bring their personal knowledge and commitment to the review process. Often they have specialized training in grant review, such as the NBCC's Project LEAD. Each committee also includes a California Advocate observer, who is not assigned applications for review and does not vote, but represents the California advocacy community. The observer gains insight into the research evaluation process and provides feedback to the Program on this process. Ad Hoc members participate by teleconference and bring their specialized expertise to the review of individual applications.

The majority of research funding agencies rate proposals with a single scientific merit score. For the past eight years the CBCRP has been using a merit scoring system that separates scientific merit into individual components (e.g., approach, innovativeness, impact). This allows our expert reviewers and the Program to better differentiate applications that might otherwise appear identical. For example, we can now pick the most innovative applications, or those that might have the most impact on breast cancer. Depending on the award type, we use four or five scientific merit components in the peer review process.

After the completion of all review committees, the CBCRP ranks the application pool by **average scientific merit**. The lowest one-third (approximately) of applications, ranked by average scientific merit, are excluded from further consideration for funding.

Next, applications having **sufficient scientific merit** are rated by the CBCRP's advisory council for programmatic relevance. The following criteria are used:

- Responsiveness to the CBCRP's priority issues and award types
- Career plan/mentoring, critical path/translation, or dissemination and translation potential
- Strength of individual scientific merit component scores (e.g., innovation for IDEA applications)
- CBCRP balance or an underfunded topic
- Quality of the lay abstract
- Inclusion of advocates and sensitivity to advocacy issues/concerns

This two-tiered process ensures **both** scientific excellence and relevance of the research to CBCRP's mission and goals.

The CBCRP wishes to thank the participants in our 2005 review committees for their service and dedication to our Program.

CRC Concept Paper & CRC-Sociocultural Review Committees

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The mission of the CBCRP is to eliminate breast cancer by leading innovation in research, communication, and collaboration in the California scientific and lay communities.

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