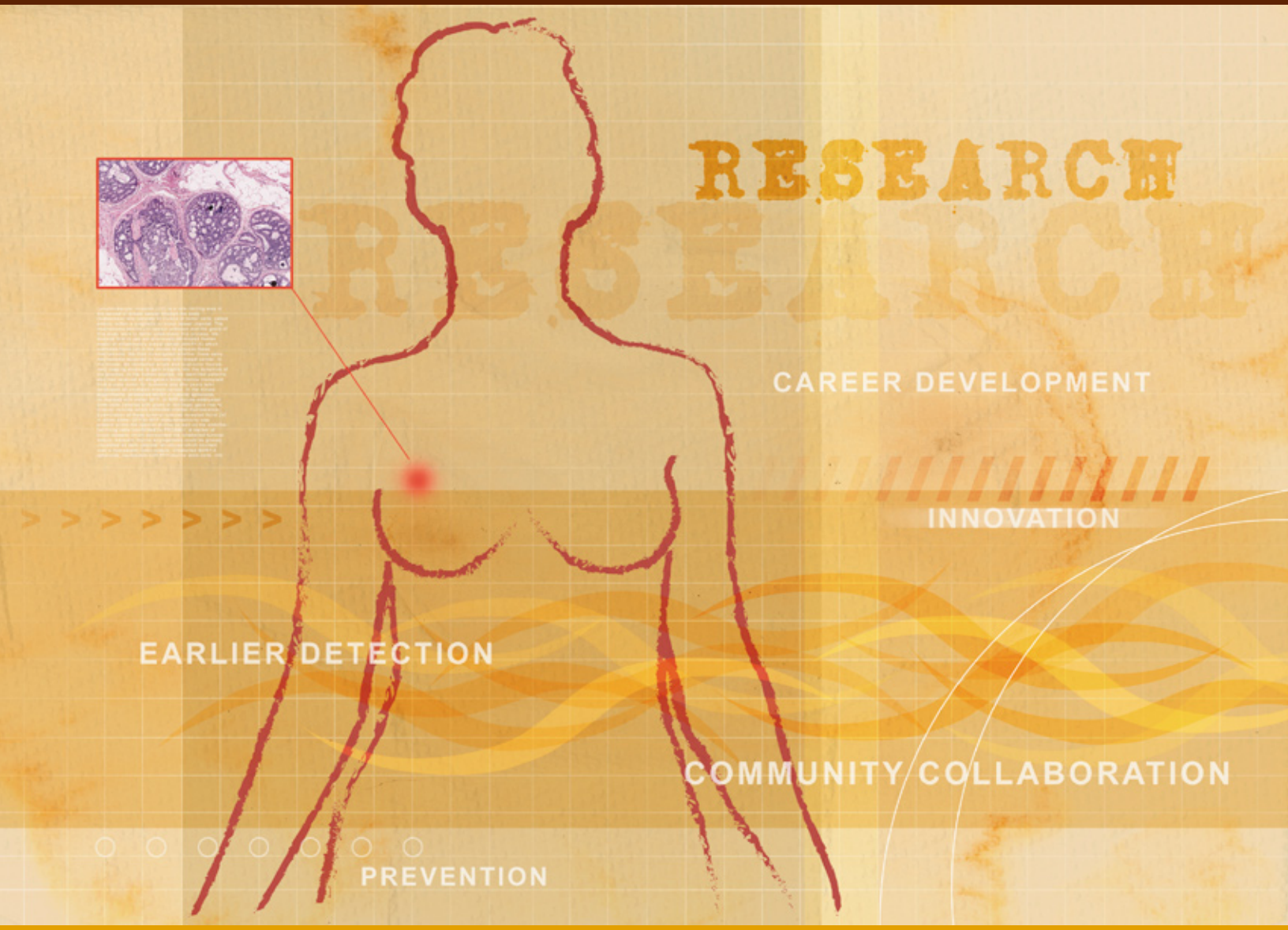
2006 Awards Compendium

Cycle 12



CALIFORNIA
Breast Cancer
Research Program

Cover inset image: *Cribriform DCIS showing microcalcifications.*

Thanks to Robert D. Cardiff, M.D., Ph.D.; image provided courtesy of the NCI Mouse Models of Human Cancers Consortium (MMHCC) Image Archive.

Table of Contents

Introduction

"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 California Breast Cancer Research Program (CBCRP) is pleased to announce the **funding of 53 new research grants** that will advance our knowledge about the causes, sociocultural aspects, biology, detection, and treatment of breast cancer. With these new awards we are **investing over $9.8 million for research projects being performed at 33 institutions across the state.**

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

- A portion of a 2¢ 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 recommends the grants 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:

- Application submission and new award data broken down by CBCRP research topics and award types
- Highlights of 2006 funding
- A portfolio summary and list of grants for our four main research priority issues
- Funded California institutions and amounts awarded
- Description of the review process and the 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.CAbreastcancer.org**

The CBCRP Application Receipt and Review Process

In January-February 2006 we received 201 grant applications in response to our Call for new research projects on breast cancer. These applications were reviewed and scored for scientific merit by our out-of-state peer reviewers.

A tally of reviewed applications by CBCRP priority issue (i.e., invited research topics) and award type is shown in the table below.

Table 1. 2006 CBCRP grant applications analyzed by award type and priority issue

Award Type	Priority Issue				
↓	Etiology & Prevention	Community Impact	Detection, Prognosis & Treatment	Biology of the Breast Cell	2006 Award Type Totals
Postdoc	2	1	8	26	37
Dissertation	2	3	6	8	19
IDEA	16	10	47	40	113
IDEA-competitive renewal	1	2	2	4	9
CRC Pilot	1	16	1	0	18
CRC Full	0	5	0	0	5
2006 Priority Totals:	22	37	64	78	201

Compared to the previous year (2005/Cycle 11) we received a nearly identical number of applications this year (202 vs. 199). For our award types, the IDEAs were increased in number by approximately 10 percent and postdoc applications decreased by about 20 percent. For our priority issues, the Community Impact category increased by about 20 percent, while the Etiology & Prevention and Biology of the Breast Cell categories were slightly decreased in number.

After the peer review, those applications in the upper two-thirds of average scientific merit were rated by our advisory council for responsiveness to stated CBCRP programmatic criteria. To select grants for funding, the council balanced the scientific merit scoring and programmatic ratings. Thus, the successful applicant responded both in terms of presenting a high quality research project *and* by meeting the interests of CBCRP stakeholders. An additional application in 2006 was submitted under our Joining Forces Conference award mechanism. It was reviewed directly and recommended for funding by our council.

Overview of CBCRP Funding in 2006

- Applications received and reviewed = 202
- Applications offered and accepting funding = 53
- Overall success rate = 26.2%
- Amount awarded in 2006 = $9,828,329

The two tables below summarize the 2006 funded grants by award type and priority issue.

Table 2. 2006 portfolio analyzed by CBCRP award type

Award Type ↓	Number of Applications	Grants Funded (success rate)	Amount Awarded	Percentage of total funding
Dissertation	19	7 (37%)	$497,985	5.1%
Postdoctoral Fellowship	37	8 (22%)	$945,000	9.6%
IDEA*	113	22* (19%)	$5,049,387	51.4%
IDEA-Competitive Renewal	9	1 (11%)	$464,750	4.7%
CRC Pilot Award	18	8^ (44%)	$1,459,235^	14.8%
CRC Full Award	5	2 (40%)	$1,347,272	13.7%
Joining Forces Conference	1	1 (100%)	$24,700	0.3%
Award Totals:	202	53^^ (26%)	$9,828,329^^	

**For the IDEA category: we offer this award to both established and "junior" investigators (at a career level past postdoc, but less than three years as an independent investigator). We received 32 applications from junior investigators and funded six grants (19%), so junior investigators compete equally for IDEA funding.*

^ Does not include 4 CRC-planning grants

^^ Includes 4 CRC-planning grants ($40,000 total)

Table 3. 2006 portfolio analyzed by CBCRP priority issue

Priority Issue ↓	Number of Applications	Grants Funded (success rate)	Amount Awarded	Percentage of total funding
Community Impact	38	14* (37%)	$3,132,432*	31.9%
Etiology & Prevention	22	3 (14%)	$797,337	8.1%
Biology of the Breast Cell	78	15 (19%)	$2,331,263	23.7%
Detection, Prognosis & Treatment	64	17 (27%)	$3,527,297	35.9%
Priority Totals:	202	53^ (26%)	$9,828,329^	

** Does not include 4 CRC-planning grants*

^ Includes 4 CRC-planning grants ($40,000 total)

Comparing the funded grants in 2006 vs. 2005 reveals a number of significant changes. For our award types, in 2006 CBCRP awarded more grants in the CRC categories, and the dollar amount of total CRC funding increased almost four-fold. However, because the total amount awarded for all grants in 2006 was increased by over $2 million, the impact of more CRC funding was minimal on the other award types. There was a modest decrease in funding for postdoctoral fellowships and an increased dollar amount for IDEAs. In terms of priority issue funding, for 2006 there was an almost 2.5-fold increase in funding for both the Detection, Prognosis & Treatment and Community Impact categories. The Biology of the Breast Cell and Etiology & Prevention categories showed decreases in funding by 40 percent and 30 percent, respectively. In the basic science topics, there was a marked increase in the quality of "treatment-oriented" applications, which placed more competitive pressure on the "discovery-oriented" portion of our portfolio.

2006/Cycle 12 Funding Highlights

- Ten 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
- Four **planning grant awards** were awarded to teams of community groups collaborating with traditional researchers to further develop their research for re-consideration in the next funding cycle.
- Fourteen awards deal with **sociocultural/psychological issues,** including eight studies on **underserved populations and ethnic minorities**
- Fifteen grants aim to further our understanding of **tumor biology,** especially the process of metastasis and the role of stem cells
- Seventeen projects explore novel methods to **detect breast cancer and develop novel approaches for treatment**
- Twenty-two projects are for **innovative, exploratory, and high-risk/high reward research** projects to push boundaries, challenge existing paradigms, and initiate new research program
- Fifteen awards provide opportunities in **career development** at the levels of graduate student and postdoctoral training. These researchers bring fresh thinking to their respective disciplines
- ☑ **Seven 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 recipient of the 2006 Faith Fancher Research Award is **Irene Yen, Ph.D.** at the **University of California, San Francisco,** for her study, "Neighborhood Environment and Obesity in Pre-adolescent Girls." Dr. Yen is studying the impact of city planning policies and neighborhood conditions and services on girls' eating and exercise habits. Obesity is a significant risk factor for breast cancer, and childhood obesity may lead to early puberty, which is an additional breast cancer risk.

Description of CBCRP Award Types Funded in 2006

- **Community Research Collaboration (CRC):** 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. Pilot (18-month), Full Awards (three years), and Planning Grants ($10,000) are awarded
- **Innovative, Developmental, and Exploratory Award (IDEA):** for promising high-risk/high-reward research. The CBCRP incorporates the "critical path" concept that requires applicants to place their project

on a research continuum leading to practical applications. IDEAs are offered to both "junior" and established investigators

- **IDEA–competitive renewal:** 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:** supports career development-oriented training under a breast cancer research mentor
- **Dissertation award:** supports the completion of dissertation research by masters or doctoral candidates
- **Joining Forces Conference award:** supports 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 blend of diverse communities offering a unique opportunity to investigate disparities and the unequal burden of breast cancer. Critical questions to be addressed include:

- How do poverty, race/ethnicity, and social factors impact incidence and mortality for breast cancer?
- What are the sociocultural, behavioral, and psychological issues faced by women at risk or diagnosed with breast cancer?
- What services are needed to improve access to screening and care, quality of life, and reduce suffering?

The CBCRP has been supporting community-based collaborations for 10 years, and we offer pre-application workshops and technical assistance to facilitate new partnerships and successful grant applications. We are encouraged that many CRC grants focus on underserved populations to address the underlying disparities. We feel that an "evidence-based" community project has the greatest potential to lead to 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 2006:	**18***	**26%**
Funded amount:	**$3,132,432***	**32%**

***Includes 4 CRC planning grants**

Community Impact Portfolio Summary:

Several newly funded grants have a primary focus on the disparities research topic. Women with disabilities and Latinas are two groups that have not received sufficient attention for breast cancer screening. Research shows that fewer women with major physical disabilities follow the mammography guidelines, and that many fewer Latinas follow the mammography guidelines than the non-Hispanic white population. Many Latinas never get mammograms—double the numbers who are not Latina. The team of **Stephen Kaye** from the **University of California, San Francisco,** and **Elsa Quezada** at the **Central Coast Center for Independent Living** propose to adapt and expand to disabled Latinas, a health education project previously successful in motivating white and African American women with disabilities to obtain mammograms. The outreach strategy for the Latina population will build the cultural and communication supports, and work toward systems change through community education and dissemination of project findings. Next, Latinas have a lower breast cancer survival rate than non-Latina white women and their mortality rates from Type 2 diabetes are 1.5 times higher. Breast cancer and diabetes are linked in ways that may be used to reduce disparities for both

illnesses. First, obesity/overweight and inactivity—both preventable—are leading risk factors for both breast cancer and diabetes for Latinas. Second, diabetic women are less likely to receive age-appropriate mammography. **Stergios Roussos** at **California State University, Fullerton,** and **Christine Noguera** from **Golden Valley Health Centers (GVHC)** will develop an intervention for Latina women with limited English proficiency that incorporates breast cancer prevention into the evidence-based GVHC's Diabetes Program. The intervention will be tailored to Latino culture. They will assess differential change in mammography compliance for this group of women.

A failure to provide complete care is known to be the primary cause of racial/ethnic disparities in survival. This pattern is replicated in California's Central Valley, particularly among women who receive care from safety-net providers. **Mary Wallace** from the **San Joaquin Valley Health Consortium** and **John Capitman** at the **California State University, Fresno,** are funded for an 18-month pilot project in Fresno County to identify barriers in the health care process where disparities in care occur. Based on their findings they intend to design a navigation service that responds to the diversity within the community and health system. The pilot will prepare for a larger project that tests health and cost impacts of this service.

The African American community also has a high mortality rate from breast cancer, and outreach to this community faces special barriers to success. **Grace Yoo** from **California State University, San Francisco,** was awarded a Joining Forces Conference Award to support a meeting between researchers and African American breast cancer survivors in the San Francisco Bay Area to exchange ideas and facilitate future research projects. One health care modality underutilized by African American breast cancer survivors is acupuncture. Scientific studies have shown that acupuncture is useful for improving wellness in survivors by reducing symptoms and improving quality of life. **Michael Johnston** at the **University of California, Los Angeles,** and **Carolyn Tapp** from the **Women of Color Breast Cancer Survivors Support Project** are funded through a CRC planning grant to strengthen the scientific design and partnership elements of an unsuccessful application in order to resubmit a stronger application in the CBCRP's next funding cycle. Their application intends to offer educational workshops to women of color to increase awareness of the potential benefits of acupuncture for African American breast cancer survivors. Finally, **Yoshiko Umezawa,** a doctoral student at the **University of California, Los Angeles,** is funded to develop a theoretical model for the impact of the partnership between patient, family and providers on patient quality of life (QOL). She will examine the health-protective effects of the family and religious community for older Latina and African American women with breast cancer. It is hoped that study will enhance the scientific basis for developing effective, culturally sensitive interventions aimed at both breast cancer patients and their families to improve quality of life.

Other disparities-focused projects cover a range of special populations to address low screening and breast cancer information issues. Breast cancer is the second leading cause of cancer death among Native American women and they have the lowest cancer screening rates of any ethnic group in California. **Linda Navarro** from the **Turtle Health Foundation** and **Marlene von Friederichs-Fitzwater** at the **University of California, Davis,** will test the feasibility and effectiveness of a culturally-sensitive, interactive, multimedia DVD that can be used with standard DVD players and TV monitors. The goal is to increase awareness and knowledge of breast health and breast cancer risk reduction among Native American women. This unique educational/information intervention will attempt to integrate the principles of indigenous healing (nutrition, exercise/movement, spirituality, etc.) with Western medicine.

Cambodian, Laotian, Thai, and Vietnamese women have the lowest rates of breast cancer screening among all Asians and Pacific Islanders. **Mary Anne Foo** from the **Orange County Asian and Pacific Islander Community Alliance** and **Marjorie Kagawa-Singer** at the **University of California, Los Angeles,** will examine various patient navigation programs. They will consider the barriers Southeast Asian patients face and how patient navigators overcome these barriers. They plan to develop a formal curriculum that can be used to train patient navigators helping women with breast health services in other underserved communities.

Finally, the Slavic community, like other immigrant groups, brings health-related problems derived from their culture, their migration experience, and their marginal status in California. These issues often manifest as higher disease incidence, severe morbidity, barriers to health care utilization or limited access to services, an apparent higher prevalence of unhealthy behaviors, and a lower impetus for preventive health practices. The team of **Debora Paterniti** from the **University of California, Davis,** and **Roman Romaso** at the **Slavic Assistance Center** aim to better understand the breast cancer experience of Slavic women so that they may develop a program for Slavic community-based health educators who will have the skills and training materi-

als to help women in the community to understand breast health, access prevention and screening, and seek care for breast cancer.

Two CRC grants aim to increase breast cancer screening rates in special populations, and while one was funded the other received a planning grant to assist the team in strengthening their application for the upcoming funding cycle. Public medical facilities are challenged by the critical task of providing health care access to large numbers of ethnically diverse women not proficient in either English or Spanish, who speak a variety of less common languages. **Linda Engelstad** at **Alameda County Hospital Authority** and **Susan Stewart** from the **University of California, San Francisco,** plan to examine the key linguistic, cultural and institutional barriers to breast cancer screening and diagnostic services among low-income women with limited English proficiency (LEP). This team received a planning grant to strengthen their application for the upcoming funding cycle. If f fully funded in the upcoming year, they will try to develop a multilingual access program (MAP) comprised of key steps that institutions need to address in order to provide equal language-access to breast health services. Finally, **Mary Jo Clark** at the **University of San Diego** and **Bulaporn Natipagon-Shah** from the **Thai Health and Information Service** received a pilot grant to address breast cancer screening among older Thai women in Southern California. The team will study why older Thai women do not participate in breast cancer screening so strategies can be developed to encourage their participation.

Two CRC Full (three-year) awards address topics of special interest. First, there are virtually no tailored breast health and breast cancer programs for deaf and hard of hearing women, in part due to lack of the kind of research that has been critical in developing effective programs for hard of hearing women. **Heidi Kleiger** at the **Greater Los Angeles Council on Deafness** and **Barbara Berman** at the **University of California, Los Angeles,** will continue a project, first funded by the CBCRP as a pilot grant in 2001, to develop, evaluate, and distribute a tailored breast health educational program for deaf and hard of hearing women.

Rural patients are at a disadvantage in their access to adequate breast cancer services. Studies have shown that cancer patients benefit from having another trained person prompt them to have questions ready about treatment options ("consultation planning") before their appointment with an oncologist or surgeon, but these studies have not been translated into practice in the rural setting. **Sara O'Donnell** at the **Mendocino Cancer Resource Center** and **Jeff Belkora** from the **University of California, San Francisco,** are continuing CBCRP-funded work begun in 2004 to expand consultation planning to more diverse patients, including Native American, Latina, and Frontier (extremely rural) residents, and to evaluate the feasibility and effectiveness of delivering consultation planning by telephone.

Other topics funded under the Community Impact topic deal with sociocultural and health policy/health services topics. While considerable literature exists supporting the need for formal social support programs for breast cancer survivors, only a few studies have looked at the roles that informal supporters (i.e., family and friends) play in survivor quality of life. Breast cancer is the leading cancer for Samoan women, yet there exists no studies on the relative importance of informal and formal support for their long-term survival and quality of life. **Sora Park Tanjasiri** at **California State University, Fullerton,** and **Sala Mataalii** with the **Samoan National Nurses Association** will study informal and formal support in a very ethnically close community of Samoans in Southern California in order to increase the knowledge base regarding social support among survivors. This CRC Pilot project will contribute to the refinement and testing of an existing community-based social support model and measure the impact on quality of life among Samoan breast cancer survivors.

The Filipino population is second among Asians only to the Chinese in number and they suffer a disproportionate burden of breast cancer compared with most other Asian subgroups. Resources for and data regarding Filipina women with breast cancer are almost non-existent. **Nancy Burke** from the **University of California, San Francisco,** and **Edwin Jocson** at the **West Bay Pilipino Multi-Service Center** (which helped begin the first Filipina support group in California in 2004) received a CRC planning grant to examine Filipina women's beliefs and values around cancer, survivorship, and social support. Ultimately, they plan to evaluate the strengths and weaknesses of their existing Sinag Tala Breast Cancer Support Group, factors that keep women from participating in the existing group, and other barriers to design a culturally appropriate support service building upon existing community resources (social networks).

Irene Yen at the **University of California, San Francisco,** will study the association between city planning policies and neighborhood environment (e.g., food stores, fast food chains, etc.) and girls' growth and obesity patterns. Obesity is an important risk factor for postmenopausal breast cancer, and childhood obesity may

lead to early pubertal development and menarche, itself a risk factor for adult breast cancer. Also, girls who are overweight or obese are more likely to be overweight or obese women. Thus, it is important and timely to understand the social factors that influence how girls eat and exercise.

There is very little research and information available on the judgment and decision-making styles related to breast health that affect decisions by the large sub-Asian population (Chinese, Filipino, Laotian) in California to undergo screening, diagnosis and treatment. **Suzanne Lindsay** from **San Diego State University Research Foundation** and **Joel San Juan** at **Operation Samahan Health Clinic** received a planning grant to prepare a revised application, which, if funded, will investigate this issue and better understand the breast health beliefs of these women. They plan to use the findings to develop the appropriate resources that will effectively address the needs of Asian women from education to screening, diagnosis and treatment.

Finally, **Dana Petersen,** a doctoral student at the **University of California, Berkeley,** will explore why some long-term breast cancer survivors experience high levels of quality of life and functional ability while others report physical and mental concerns long after treatment. It is important to discover the reasons why some breast cancer survivors recover more fully and remain healthy while others do not so that public health researchers and practitioners can promote the well-being of all survivors.

Community Impact Grants Funded in 2006:

☑ **Telephone-Based Decision Support for Rural Patients**
Jeffrey Belkora, Ph.D. (co-PI)
University of California, San Francisco
Sara O'Donnell (co-PI)
Mendocino Cancer Resource Center
Award type: CRC Full
$310,914 (UCSF)
$361,358 (MCRC)

Breast Cancer Education for Deaf and Hard-of-Hearing Women
Barbara Berman, Ph.D. (co-PI)
University of California, Los Angeles
Heidi Kleiger (co-PI)
Greater Los Angeles Council on Deafness, Inc.
Award type: CRC Full
$310,000 (UCLA)
$375,000 (GLACD)

Filipina Breast Cancer Support: What Model is Meaningful?
Nancy Burke, Ph.D. (co-PI)
University of California, San Francisco
Edwin Jocson (co-PI)
West Bay Pilipino Multi-Service Center
Award type: CRC Planning Grant
$5,000 (UCSF)
$5,000 (WBPMC)

Fresno Breast Cancer Navigator Pilot Program
John Capitman, Ph.D. (co-PI)
California State University, Fresno
Mary Wallace (co-PI)
San Joaquin Valley Health Consortium
Award type: CRC Pilot
$50,400 (CSU)
$138,500 (SJVHC)

Factors Influencing Breast Cancer Screening Among Older Thai
Mary Jo Clark, Ph.D., R.N. (co-PI)
University of San Diego
Bulaporn Natipagon-Shah (co-PI)
Thai Health and Information Service
Award type: CRC Pilot
$86,973 (USD)
$88,427 (THIS)

Multilingual Access to Breast Cancer Early Detection
Linda Engelstad, M.D. (co-PI)
Alameda County Hospital Authority
Susan Stewart, Ph.D. (co-PI)
University of California, San Francisco
Award type: CRC Planning Grant
$5,000 (UCSF)
$5,000 (ACHA)

Introducing Acupuncture to Black Survivors for Wellness
Michael Johnston, Ph.D. (co-PI)
University of California, Los Angeles
Carolyn Tapp (co-PI)
Women of Color Breast Cancer Survivors Support Project
Award type: CRC Planning Grant
$5,000 (UCLA)
$5,000 (WCBCSSP)

☑ **Southeast Asian Breast Health Navigation**
Marjorie Kagawa-Singer, Ph.D., R.N. (co-PI)
University of California, Los Angeles
Mary Anne Foo, M.P.H. (co-PI)
Orange County Asian & Pacific Islander Community Alliance
Award type: CRC Pilot
$187,500 (OCAPICA)

Increasing Mammography among Latinas with Disabilities
H. Stephen Kaye, Ph.D. (co-PI)
University of California, San Francisco
Elsa Quezada (co-PI)
Central Coast Center for Independent Living
Award type: CRC Pilot
$50,000 (UCSF)
$125,000 (CCCIL)

Breast Health Literacy and Health Care Decision Making
Suzanne Lindsay, Ph.D., M.S.W., M.P.H. (co-PI)
San Diego State University
Joel San Juan, M.S. (co-PI)
Operation Samahan Health Clinic
Award type: CRC Planning Grant
$5,000 (SDSU)
$5,000 (OSHC)

Informal and Formal Support and Needs among Samoan Survivors
Sala Mataalii (co-PI)
Samoan National Nurses Association
Sora Park Tanjasiri, Dr.P.H. (co-PI)
California State University, Fullerton
Award type: CRC Pilot
$125,039 (SNNA)
$69,686 (CSUF)

☑ **Addressing Cultural and Tribal Issues in Breast Cancer**
Linda Navarro (co-PI)
Turtle Health Foundation
Marlene von Friederichs-Fitzwater, Ph.D. (co-PI)
University of California, Davis
Award type: CRC Pilot
$88,625 (THF)
$79,100 (UCD)

Mammography Screening for Latinas with Diabetes
Christine Noguera, M.S. (co-PI)
Golden Valley Health Centers
Stergios Roussos, Ph.D., M.P.H. (co-PI)
California State University, Fullerton
Award type: CRC Pilot
$110,332 (GVHC)
$92,294 (CSUF)

The Breast Cancer Experience of Slavic Women
Debora Paterniti, Ph.D. (co-PI)
University of California, Davis
Roman Romaso (co-PI)
Slavic Assistance Center
Award type: CRC Pilot
$73,609 (UCD)
$93,750 (SAC)

Social Capital, Social Support and Long-Term Quality of Life
Dana Petersen
University of California, Berkeley
Award type: Dissertation
$67,540

Social Support and QOL in Older Minority Women with Breast Cancer
Yoshiko Umezawa
University of California, Los Angeles
Award type: Dissertation
$70,838

 **Neighborhood Environment and Obesity in Pre-Adolescent Girls**
Irene Yen, Ph.D.
University of California, San Francisco
Award type: IDEA
$162,847

Dialogue with Breast Cancer Survivors
Grace Yoo, Ph.D.
California State University, San Francisco
Award type: Joining Forces Conference
$24,700

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 decade, 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. There is an extensive list of factors associated with increased and decreased risk for breast cancer. However, the relative importance of diet, exercise, family history, pregnancy, alcohol, hormone replacement therapy, and other factors remains controversial. The CBCRP's newly launched Special Research Initiatives seeks to increase knowledge of and create solutions to the environmental causes of breast cancer.

Two of the 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

Unfortunately, no grants in the Prevention topic were funded in 2006.

Funding Data:

		Proportion of Total
Etiology grants awarded in 2006:	**3**	**6%**
Funded amount:	**$797,337**	**8%**

***Includes 4 CRC planning grants**

Etiology Portfolio Summary:

Why do some breast cancers spread to other organs while others don't? Is there a "hereditary component" associated with metastasis? Recently, a new genetic modifier of metastatic efficiency has been identified in mice, and this suggests that comparable metastasis-modifiers might be present in humans. **Alice Whittemore** at **Stanford University** will look at information collected about breast cancer in families in which there are two or more women with breast cancer. If it turns out that metastasis potential is a heritable trait, then it would set the stage to identify specific genes.

The lifetime risk of developing breast cancer in individuals with a BRCA mutation may be as high as 85 percent, but this risk may vary among ethnic groups having different patterns of genetic mutations. The aims of the IDEA project awarded to **Jeffrey Weitzel,** at the **Beckman Research Institute of the City of Hope,** are to gather data on the frequency of BRCA mutations that are common among Hispanics in order to develop a more efficient way of providing genetic cancer risk assessment to this group of women.

Xenoestrogen (XE) is a term applied to chemicals, whether they are pesticides or compounds found in plastics (bisphenol A), that elicit estrogen-like effects. Previous studies involving the role of XE's in the etiology of breast cancer has used human breast tumor cell lines, which are far removed from the true biology of the normal breast epithelium. **Shanaz Dairkee** from the **California Pacific Medical Center Research Institute** is funded to examine the effects of the XE bisphenol A (BPA) on normal breast epithelial cells in co-culture with fibroblasts isolated from adjacent connective breast tissue. Dr. Dairkee will analyze aberrant expression profiles of estrogen- and progesterone-responsive genes, as well as other genes, which initiate defective growth regulation.

Etiology Grants Funded in 2006:

☑ **A Novel Biological Framework for the Role of Xenoestrogens**
Shanaz Dairkee, Ph.D.
California Pacific Medical Center Research Institute
Award type: IDEA
$279,242

Hereditary Breast Cancer and Novel Hispanic BRCA Mutations
Jeffrey Weitzel, M.D.
Beckman Research Institute of the City of Hope
Award type: IDEA
$253,500

☑ **Breast Cancer Metastasis: a Heritable Trait?**
Alice Whittemore, Ph.D.
Stanford University
Award type: IDEA
$264,595

Detection, Prognosis, and Treatment: Delivering Clinical Solutions

Overview:

The detection, prognosis, and treatment topics funded by the CBCRP continue to change as novel technologies and approaches come under investigation. CT (computerized tomography) scanning is emerging with new instruments being designed that are dedicated to breast imaging. A new type of mammography, called digital tomosynthesis, is in clinical trials. This technology takes multiple X-ray images of each breast from many angles. The result is a three-dimensional image, so that suspected breast lesions are not as easily obscured as is often the case with 2-dimensional mammograms. Ultrasound and PET technologies are moving into the surgical realm to allow a more accurate excision of tumors. For better disease prognosis, there are a number of gene expression profiling tests both in commercial use and in clinical testing. Oncotype DX, a 21-gene test, marketed by Genomic Health, Inc. in Redwood City, is designed to predict the probability of breast cancer recurrence and response to tamoxifen. In Europe, researchers are studying two main "panels" of genes for patient classification. One is a 70-gene panel, and another is a 76-gene panel. Interestingly, there are only three genes in common for both panels! A commercial test (not yet approved by the FDA) based on the 70-gene panel is already available in the United States under the name Mammaprint®. The expected benefits of genetic testing performed on tumor samples are to allow individualized therapy to spare women the unnecessary side-effects of treatments with no potential benefit—a common outcome with most non-targeted chemotherapeutics. Cancer therapeutic development continues to evolve with a focus on (i) the validation of novel cell targets and an improved understanding of the disease at the genetic and molecular levels, and (ii) an enhanced ability to match patient subgroups with individual drugs or drug combinations to assess efficacy earlier in pre-clinical testing. Alternative therapies and drugs, especially those derived from plants, continue to attract research interest.

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 2006:	**17**	**32%**
Funded amount:	**$3,527,297**	**36%**

Detection, Prognosis, and Treatment Portfolio Summary:

Three new grants in 2006 address the topic of improving breast cancer imaging. **Craig Levin** from **Stanford University** will test a novel photon detection technology, using a crystal containing cadmium, zinc, and telluride (CZT), to increase the sensitivity and resolution of PET imaging. He will build four of the CZT units, attach them to a commercially available chip that will transfer the signal from the CZT unit to a computer, and test the performance of this system. Dr. Levin's device is specifically designed to image the breast, so its performance can be optimized for this purpose, in contrast to standard PET scanners that are designed for whole body imaging.

It is appreciated that each type of breast imaging modality has its limitations, so there is increased interest in combining different imaging technologies within a single instrument to overcome these barriers. **Gultekin Gulsen** at the **University of California, Irvine,** will attempt to combine a near-infrared optical detection system, called diffuse optical tomography (DOT), with magnetic resonance imaging (MRI) and "spatially resolved" MR spectroscopy (MRS). The combined measurements are anticipated to provide information about tumor oxygenation, tumor blood flow, and tumor metabolism to reduce the "false positive" rate when using MRI or mammography as single modalities. Notably, the MR spectroscopy measurements can detect choline (needed for structural integrity/signaling roles for cell membranes and as a metabolic donor for methyl groups), a biomarker for malignancy. Using a similar approach to combine modalities, **Hyeon-Man Baek,** also at the **University of California, Irvine,** is funded for a postdoctoral fellowship to combine MRI and single voxel (volume pixel) spectroscopy (MRS). The expected benefit will be to increase the specificity of MRI for breast cancer detection.

Two newly funded grants focus on adapting imaging technologies for use in breast surgery. Breast ultrasound is becoming a standard tool for the breast surgeon, both in the clinic and the OR. Unfortunately, the standard 2-D ultrasound technique is challenging to learn and interpret, because only a single tissue plane is being visualized. **Michael Bax** from **Stanford University** is funded for a dissertation project to develop a three-dimensional ultrasound system to better detect the presence of residual tumor tissue at the time of surgical breast tumor resection. Next, **Armando Giuliano** at the **John Wayne Cancer Institute** will adapt PET technology by utilizing a radiation-sensitive probe to detect a tumor-homing radiopharmaceutical. This would enable the surgeon to survey the tumor bed following excision to identify areas of residual disease. Surgeons usually report repeat operation rates of 20-30 percent, which is due in large part to their inability to establish the tumor margin status during surgery. If either the ultrasound or PET methods is able to reduce this percentage, the clinical impact would be very significant.

Three newly funded treatment-oriented grants focus on taking compounds derived from natural sources though the very early pre-clinical testing phases by using cell models of breast cancer. First, **Gary Firestone** at **University of California, Berkeley,** will study an anti-malaria compound, called Artemisinin, which is derived from a Chinese plant commonly known as sweet wormwood. Although relatively non-toxic and inexpensive, the mechanism of action for this compound is poorly understood for treating either malaria or cancer. The funded project will test whether Artemisinin-activated signaling pathways block estrogen receptor-α mediated responsiveness and estrogen-dependent growth of breast cancer cells. Next, sulforaphane is an anti-cancer compound found in broccoli. Based on her previous work, **Olga Azarenko** from **University of California, Santa Barbara,** will test whether sulforaphane blocks cell cycle progression of breast cancer cells by suppressing the mitotic spindle apparatus necessary for chromosomal separation into daughter cells. Additionally, sulforaphane may work synergistically when combined with existing powerful anti-mitotic drugs (e.g., docetaxel) to reduce the toxicity associated with this type of treatment. Finally, **Sean McAllister** at the **California Pacific Medical Center Research Institute** will focus on the inhibition of breast cancer cell metastasis by cannabidiol, which is a non-psychotropic cannabinoid constituent of the marijuana plant, Cannabis sativa. Dr. McAllister will study whether cannabidiol will inhibit breast cancer cell aggressiveness via activation of a novel cannabinoid receptor subtype. The drug's effect is believed to be mediated by down-regulation of a protein, called Id-1, a gene-regulatory transcription factor associated with breast cancer cell invasion.

Three newly funded IDEA grants focus on improving, adapting, and showing "proof of principle" for existing therapies for the treatment of breast cancer. First, **Howard Chang** at **Stanford University** has proposed that breast cancer cells resemble certain normal cells during wound healing. It is this 'wound signature' that not only contributes to tumor progression, but is also required for tumor cell survival. Dr Chang will study cell models in more detail to determine whether the 'wound signature' profile will predict sensitivity to an FDA-approved drug, called Bortezomib (marketed as Velcade™ by Millennium Pharmaceuticals), a new anti-myeloma therapy. Bortezomib works by inhibiting an intracellular organelle, called the proteosome that is responsible for degrading proteins (the cell's garbage disposal). Although Bortezomib has not shown remarkable clinical activity as an anti-cancer agent, it may fare much better when used against a subset of cancers having the 'wound signature' profile. Next, **Michael Press** from the **University of Southern California** is funded to determine whether topoisomerase II-alpha (TOP2A) and Her-2 gene co-amplification is associated with improved response to Herceptin® plus adriamycin (doxorubicin) chemotherapy. About 40 percent of patients have co-amplification of these two genes that are in close proximity on chromosome 17. The results

of Dr. Press' analysis of recent clinical trial data should allow better "tailoring" combination chemotherapy, because when the two genes are not co-amplified, then adriamycin is not needed and this will reduce cardiotoxicity side-effects. Finally, **David Feldman,** also at **Stanford University,** will examine the efficacy of the active form of vitamin D, called calcitriol, in the treatment of breast cancer. Calcitriol inhibits prostaglandin (PG) synthesis and acts in breast cancer cells by multiple mechanisms. However, in previous studies it has shown only modest therapeutic activity. Dr. Feldman will test calcitriol in combination with non-steroidal anti-inflammatory drugs (NSAIDs) and aromatase inhibitors using cell and animal models to see whether these relatively non-toxic drugs have synergistic effects in combination.

Three grants aim to develop novel therapies for breast cancer that still require refinement in the drug design, improved tumor delivery properties, and validation of the mechanism of action. **Xiao-kun Zhang** from the **Burnham Institute for Medical Research** is funded to target apoptosis (programmed cell death) pathways using a novel paradigm. They have previously identified a nuclear receptor, designated Nur77 that can move to the mitochondria where it binds Bcl-2. This interaction serves to alter the structure of the Bcl-2 molecule, such that is loses its anti-apoptotic effects and becomes pro-apoptotic with the potential to kill cancer cells. In this project, Dr. Zhang will optimize the design of a minimal 9 amino acid peptide derived from Nur77, develop a cell-penetrating delivery system, and determine whether the combination of the Nur77 peptide with taxanes result in a synergistic death effect on breast cancer cells. Next, **Stephen Swenson** at the **University of Southern California** received IDEA funding to explore the potential of inhibiting breast cancer cell surface adhesion receptors, called integrins. He will (i) use peptides based on integrin-inhibitory snake venom proteins, (ii) produce them recombinantly (in bacteria) as compounds called rADDs, (iii) test them for the dual properties of inhibiting tumor growth and angiogenesis, and (iv) modify them to become useful as PET imaging agents. Each rADD is expected to be very selective for an individual tumor receptor, and the production of small peptides in a recombinant system may overcome the immunogenicity problems that would be encountered with the native snake venoms. Finally, Heat shock proteins (HSP) are so-named because they become increased when the cells are exposed to elevated temperatures. They play important roles as "chaperones" for protein-protein interactions, such as establishing the proper protein conformation (shape) and preventing protein aggregation. Tumor cells contain elevated amounts of HSPs and they are believed to, in part, account for both an endogenous resistance to chemotherapy and acquired drug resistance. **Chung-Wai Shiau,** also from the **Burnham Institute for Medical Research,** is funded to screen a large "library" of 200,000 compounds for binding to HSP70. Potential HSP70-inhibiting drug candidates will be analyzed and lead compounds refined for further testing.

In the "real world" of cancer detection and therapy, many tumors have already metastasized to difficult-to-treat areas, such as the brain, or they have acquired a blood supply for future growth and spread. How can advanced cancers be treated, and can the body's own defense mechanisms and biological processes be employed to assist these efforts? **Albert Deisseroth** at the **Sidney Kimmel Cancer Center** is combining three novel elements in his immunotherapy strategy: (i) the induction of an immune response specifically against the tumor blood vessels feeding the breast cancer tissue, (ii) the combination of a vaccine against the blood vessels of the tumor tissue with a vaccine against the Her-2 over-expressing cells, and (iii) the combination of the two vaccine approaches with conventional adjuvant chemotherapy. Annexin A1 is the target vascular (endothelial cell) antigen in this study, and it is expressed selectively in the breast tumor vasculature, while being absent from normal tissue vessels. Next, **Brunhilde Felding-Habermann** from the **Scripps Research Institute** is funded through two separate grants. First, she in continuing work begun in 2005 to directly target brain metastasis using a novel approach employing single-chain fragments of human antibodies. These antibodies are specific for the activated form of the adhesion receptor integrin $\alpha v \beta 3$. The therapeutic effect would be a blockage of the attachment of metastatic breast cancer cells to blood vessel walls, preventing their escape into distant organs. The antibody fragments are 'displayed' on viral particles, called phage, and they can be delivered via either an intra-nasal or IV/IP route to the brain. Although facing tremendous hurdles, this project exemplifies the IDEA funding mechanism by promising a high reward, if successful. Equally challenging is Dr. Felding-Habermann's second grant that aims to use neural stem cells as the brain tumor-homing vehicle (magic bullets) for the delivery of therapeutics. It is well known that stem cells migrate in the body and will localize to regions of tissue damage and regeneration. Whether the stem cell approach can effectively target tumor metastatic sites or can be used as a delivery vehicle for anti-tumor agents awaits testing using animal

models.

Detection, Prognosis, and Treatment Grants Funded in 2006:

Sulforaphane: Its Potential for Treatment of Breast Cancer
Olga Azarenko
University of California, Santa Barbara
Award type: Dissertation
$65,415

In Vivo MRS for Cancer Diagnosis and Treatment Monitoring
Hyeon-Man Baek, Ph.D.
University of California, Irvine
Award type: Postdoctoral fellowship
$100,000

Real-Time 3D Ultrasound Image-Guidance for Breast Surgery
Michael Bax
Stanford University
Award type: Dissertation
$66,641

A Targeted Therapy for Wound-like Breast Cancers
Howard Chang, M.D., Ph.D.
Stanford University
Award type: IDEA
$232,934

Vascular Targeting Therapy for Breast Cancer
Albert Deisseroth, M.D., Ph.D.
Sidney Kimmel Cancer Center
Award type: IDEA
$289,500

Neural Stem Cell Therapy for Breast Cancer Brain Metastases
Brunhilde Felding-Habermann, Ph.D.
Scripps Research Institute
Award type: IDEA
$302,085

Inhibition of Brain Metastases in Breast Cancer
Brunhilde Felding-Habermann, Ph.D.
Scripps Research Institute
Award type: IDEA-competitive renewal
$464,750

Breast Tumor Inhibition by Vitamin D in a Mouse Model
David Feldman, M.D.
Stanford University
Award type: IDEA
$234,388

Artemisinin Disrupts Estrogen Receptor-Alpha and Cell Growth
Gary Firestone, Ph.D.
University of California, Berkeley
Award type: IDEA
$100,000

Intraoperative Assessment of Surgical Lumpectomy Margins
Armando Giuliano, M.D.
John Wayne Cancer Institute
Award type: IDEA
$283,200

Combined Imaging Modalities for Breast Cancer
Gultekin Gulsen, Ph.D.
University of California, Irvine
Award type: IDEA
$149,382

New Technology to Enhance PET Imaging of Breast Cancer
Craig Levin, Ph.D.
Stanford University
Award type: IDEA
$155,502

Inhibition of Breast Cancer Aggressiveness by Cannabidiol
Sean McAllister, Ph.D.
California Pacific Medical Center Research Institute
Award type: IDEA
$183,000

Topoisomerase-IIa as a Predictor of Anthracycline Response
Michael Press, M.D., Ph.D.
University of Southern California
Award type: IDEA
$244,500

Chemical Inhibitors of Hsp70 for Breast Cancer
Chung-Wai Shiau, Ph.D.
Burnham Institute for Medical Research
Award type: Postdoctoral fellowship
$135,000

rADDs: Novel Disintegrins Targeting Breast Cancer
Stephen Swenson, Ph.D.
University of Southern California
Award type: IDEA
$244,500

Nur77-derived Peptides as a Novel Breast Cancer Therapy
Xiao-kun Zhang, Ph.D.
Burnham Institute for Medical Research
Award type: IDEA
$286,500

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. In breast development, cell populations must co-ordinate migration, proliferation, and apoptosis (cell death) over space and time. In cancer progression these same processes become dysregulated, initially at the genetic level that leads to the physiological changes associated with malignancy. To better mimic breast and tumor architecture, 3-D cell culture models provide a means to explore potential underlying mechanisms and show how extracellular and breast/tumor stromal factors contribute to tumor progression. An emerging paradigm identifies "stem cells" as the key to the origin of tumors. Stem cell populations reside in body organs to provide the "raw material" for tissue regeneration, repair, and for the cyclic proliferation responses to hormones and pregnancy in the breast. If this theory proves correct, then only a small fraction (1-2 percent) of cells in a tumor mass retain stem cell properties, and these "cancer stem cells" must be selectively targeted to achieve an effective eradication of the disease.

Tumor biology, which the CBCRP refers to as pathogenesis, typically involves basic science cell-based studies. In the past, researchers approached tumor biology from the "reductionist level" (i.e., studying individual genes and proteins as representing root cause of the disease). However, over the past decade researchers have realized that the underlying mechanistic driving forces of tumor biology operate though complex, concurrent genetic changes in numerous molecular pathways. Still, it remains the metastatic process that presents the greatest hurdle in our efforts to contain and destroy cancer as it too often presents itself at the time of diagnosis. Breast cancer can spread to almost any region of the body, although metastases are most common to the bone, lung and liver. Understanding the gene and physiological regulatory mechanisms for this cancer cell "diaspora" is crucial for the design of therapeutic strategies. Other important basic science topics represented in CBCRP's portfolio include: (1) cell proliferation control mechanisms through the estrogen receptor and growth factor receptors (e.g., Her-2), (2) alterations in DNA repair process that permit genetic damage to accumulate in cancer cells, (3) cell cycle changes that permit division under conditions where normal cells would undergo programmed cell death (apoptosis), and (4) novel biomarkers to distinguish pre-cancerous and cancerous cells from normal breast epithelium and their validation as potential new detection and therapy targets.

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 Total
Grants awarded in 2006:	**15**	**28%**
Funded amount:	**$2,331,263**	**24%**

Biology of the Breast Cell Portfolio Summary:

Two newly funded grants focus on the CBCRP's Biology of the Normal Breast topic. A key hurdle to move this field forward is the discovery and validation of protein and gene biomarkers from mammary stem cells in order to further study them both in breast development and deregulation in cancer. **Robert Oshima** from the **Burnham Institute for Medical Research** is funded to evaluate a new biomarker gene that is expressed in sev-

eral other types of adult stem cells and to determine if it is also preferentially expressed in mammary epithelial stem cells. The marker is called maternal embryonic leucine-zipper kinase (MELK). He will test whether MELK-expressing stem cells can serve to reconstitute the mammary grand when transplanted into mice. Since MELK has already been identified as a potential therapy target in humans, these studies in mice may provide insights into key regulatory elements in breast cancer stem cells. **Bob Liu** from **University of California, San Francisco,** is funded for a postdoctoral fellowship to study the earliest stages of tumor development. He plans to study a variant population of human mammary epithelial cells (vHMEC). The hypothesis to be tested is that a key tumor suppressor gene is "silenced" through the epigenetic (i.e., reversible, heritable changes in gene function that occur without a change in the sequence of nuclear DNA) process of hypermethylation. This would tip the balance towards genetic instability in these cells providing the groundwork for the genetic abnormalities seen in breast cancer.

Three newly funded grants explore breast cancer stem cells. A key distinction between stem cells and other dividing cells is that stem cell division is "asymmetric." One of the daughter cells retains pluripotent stem cell functions and the other daughter cell becomes committed to a differentiation pathway, eventually producing the mature cells of that particular lineage. **Claudia Petritsch** from the **University of California, San Francisco,** will test whether breast cancer stem cells divide more "symmetrically", thus producing a less differentiated population of cells that would be better able to accumulate genetic changes that drive tumor progression. She is bringing knowledge gained from insect (Drosophila) stem bell biology to bear on breast cancer. Next, **Yohei Shimono** from **Stanford University** will study stem cell-specific micro-RNAs, a family of short, non-coding RNAs that are known to be differentially present in various tissues. These micro-RNAs regulate various groups of genes, so they are thought to be a driving force for the global changes during the cell differentiation process. The aim of Dr. Shimono's study is to identify differences between normal and breast cancer stem cells that might be the basis for future anti-cancer therapies. Finally, reliable gene and protein markers are not well established for breast cancer stem cells. **Alexey Terskikh** at the **Burnham Institute for Medical Research** is funded for a project complementary to that described above for Dr. Oshima. He will test whether the MELK gene is a functional marker of breast cancer stem cells using cell transfer studies in mice. The novel therapeutic angle for this research, if successful, is that blocking MELK (or any other critical cancer-associated stem cell component) might selectively induce tumor stem cells to differentiate making them more susceptible to anti-cancer drugs.

Five CBCRP grants focus on tumor metastasis. First, **Barbara Mueller** from the **La Jolla Institute for Molecular Medicine** plans to identify metastasis genes using a completely untested approach. It is appreciated that tumors are very heterogeneous, because they contain a variety of cells in various stages of differentiation. But, only a small fraction of cells is thought to be metastasis-competent, and these are the cells that must be identified for effective therapy and prevention of relapse. Dr. Mueller has devised an approach called "reaching back in time." Basically, tumors are labeled with a complex "library of peptides" that is displayed on viral particles. The peptides are taken up by pre-metastatic tumor cells, and the peptides persist in the cells due to viral replication (a genetic "tag"). After some of the cells have metastasized, the viral-contained peptides are recovered to provide a "signature" that may distinguish the key biomarkers of pre-metastatic cells. Next, **Sherry Niessen** at the **Scripps Research Institute** will continue work on a previously funded CBCRP project to her mentor Benjamin Cravatt. She will complete her dissertation work to identify novel breast cancer proteases by proteomic profiling and mass spectroscopy, then testing the functionality of the proteases using breast cancer cell migration assays and mouse models of human breast cancer (xenografts). **Barbara Blouw** from the **Burnham Institute for Medical Research** will study podosomes, which are membrane protrusions of aggressive cells that function to degrade the extracellular matrix and facilitate invasion and metastasis. Dr. Blouw will focus on a Src oncogene substrate, called Tks5, as the key regulatory element in podosome function. Next, a critical "switch" in cancer progression is called the epithelial-mesenchymal transition (EMT). This is a program of development for cells characterized by loss of cell adhesion, repression of cell-cell interactions, and increased cell mobility. Initiation of metastasis involves invasion, which has many similarities to EMT. **Jing Yang** at the **University of California, San Diego,** will determine whether transient expression of a gene-regulatory transcription factor, called Twist, will promote reversible EMT. Transitory EMT is a novel paradigm for tumor metastasis. Finally, **Adam Adler** will use dissertation funding to complete his doctoral work at **Stanford University.** One theory of cancer holds that disease progression is analogous to a "wound that will not heal." Mr. Adler will study a panel of 512 "wound signature" genes and determine whether any of them are associated with breast cancer metastasis. The project is based on the notion that a well-known

oncogene, called Myc, becomes associated with a novel protein, called CSN5. This interaction may serve to increase Myc's transcriptional (gene regulatory) activity as a key factor leading to metastasis.

Two newly funded grants focus on estrogen receptors from novel perspectives. First, **Eliot Bourk** at the **University of California, San Diego,** will test the hypothesis that exposure to inflammatory mediators (e.g., cytokine IL-β1 and TGF-β) for prolonged periods will affect ER-responsive genes. The connection between inflammation and cancer, as well as other diseases, is compelling. Inflammation is the body's first defense against infection, but when it persists at low levels this can lead to heart attacks, cancer, Alzheimer's and a host of other diseases as featured in the February 23, 2004, issue of Time magazine. Next, **Anastasia Kralli** from the **Scripps Research Institute** will study the role of the three Estrogen-Related Receptors (ERRs). Although the ERRs share significant protein sequence homology with ERs, they are not activated by natural estrogens. More information on ERRs may be important in the development of drugs that can be effective in ER-negative tumors. Dr. Kralli's specific focus is whether a "co-activator" of ERRα, called PGC-1α, can convert ERRα from a dormant factor to a potent regulator of gene expression.

The remaining basic science projects funded by the CBCRP in 2006 span a range of topics. First, **Jennifer Scorah** from the **Scripps Research Institute** will investigate how the cell cycle checkpoint protein, Chk1, is regulated differently during the normal cell cycle versus following DNA damage. Accurate cell cycle checkpoint control is vital for preventing genomic instability and cancer. However, the precise mechanisms involved in regulation of cell cycle checkpoints remain largely unknown. Next, cytochrome P450 proteins in humans are drug metabolizing enzymes and enzymes that are used to make cholesterol, steroids and other important lipids (e.g., prostacyclins). Aromatase is a key P450 enzyme in breast cancer, although >60 P450 forms are known, with hundreds of genetic variations possible. **Aaron Wright,** also from the **Scripps Research Institute,** will use proteomic approaches to profile the active P450s from normal breast epithelial versus breast cancer cells. If successful, this approach, called activity-based protein profiling (ABPP) developed in the lab of **Benjamin Cravatt** at Scripps, might be used to generate new P450 inhibitors or to predict the therapeutic response in patients prior to drug treatment. Finally, **Chen Yang** from the **Burnham Institute for Medical Research** will study changes in the metabolism in cancer cells specifically linked to fatty acid synthesis. The underlying hypothesis is that breast cancer cells have an altered flux through the acetyl-coA network. One of the major sources of input into acetyl-coA is via glycolysis (oxidation of glucose), which is known to be increased in tumors. Previous efforts in this topic have been conducted on a piecemeal basis, but Dr. Yang will conduct a more integrated, global analyses. He hopes to show a link between acetyl-coA metabolism and fatty acid synthetase.

Biology of the Breast Cell Grants Funded in 2006:

MYC and CSN5 in the Breast Cancer "Wound Signature" Profile
Adam Adler
Stanford University
Award Type: Dissertation
$76,000

The Role of Podosomes in Breast Cancer Metastasis
Barbara Blouw, Ph.D.
Burnham Institute for Medical Research
Award Type: Postdoctoral fellowship
$135,000

Inflammation Alters Transcription by ER in Breast Cancer
Eliot Bourk
University of California, San Diego
Award Type: Dissertation
$75,551

The Role of Estrogen-Related Receptors in Breast Cancer
Anastasia Kralli, Ph.D.
Scripps Research Institute
Award Type: IDEA
$278,850

Isolation of Cancer Precursors from Normal Human Breasts
Bob Liu, Ph.D.
University of California, San Francisco
Award Type: Postdoctoral fellowship
$135,000

☑ **Identification of Metastasis Competent Breast Cancer Cells**
Barbara Mueller, Ph.D.
La Jolla Institute for Molecular Medicine
Award Type: IDEA
$327,372

The Role of Serine and Metallo-Hydrolases in Breast Cancer
Sherry Niessen
Scripps Research Institute
Award Type: Dissertation
$76,000

A New Marker for Mammary Epithelial Stem Cells?
Robert Oshima, Ph.D.
Burnham Institute for Medical Research
Award Type: IDEA
$191,000

Role of Cell Division Asymmetry in Breast Cancer Stem Cells
Claudia Petritsch, Ph.D.
University of California, San Francisco
Award Type: IDEA
$149,990

☑ **The Role Chk1 in Breast Cancer DNA Damage Repair**
Jennifer Scorah, Ph.D.
Scripps Research Institute
Award Type: Postdoctoral fellowship
$90,000

Analysis of MicroRNA Expression in Breast Cancer Stem Cells
Yohei Shimono, M.D., Ph.D.
Stanford University
Award Type: Postdoctoral fellowship
$135,000

A Candidate Marker of Mammary Tumor Initiating Cells
Alexey Terskikh, Ph.D.
Burnham Institute for Medical Research
Award Type: IDEA
$286,500

Profiling Drug Metabolism (P450) Proteins in Breast Cancer
Aaron Wright, Ph.D.
Scripps Research Institute
Award Type: Postdoctoral fellowship
$135,000

Modeling, Targeting Acetyl-CoA Metabolism in Breast Cancer
Chen Yang, Ph.D.
Burnham Institute for Medical Research
Award Type: Postdoctoral fellowship
$90,000

Twist Activation in Breast Cancer Metastasis
Jing Yang, Ph.D.
University of California, San Diego
Award Type: IDEA
$150,000

2006 CBCRP Funding by Institution

The following 33 California research institutions and community organizations were awarded new CBCRP funding in 2006. Some grants were structured as separate awards that are split between institutions.

Institution	# Awards	Amount
Alameda County Hospital Authority	1	$5,000
Beckman Research Institute of the City of Hope, Duarte	1	$253,500
Burnham Institute for Medical Research, La Jolla	6	$1,124,000
California Pacific Medical Center Research Institute, San Francisco	2	$462,242
California State University, Fresno	1	$50,400
California State University, Fullerton	2	$161,980
Central Coast Center for Independent Living, Salinas	1	$125,000
Golden Valley Health Centers	1	$110,332
Greater Los Angeles Council on Deafness, Inc.	1	$375,000
John Wayne Cancer Institute, Santa Monica	1	$283,200
La Jolla Institute for Molecular Medicine	1	$327,372
Mendocino Cancer Resource Center, Mendocino	1	$361,358
Operation Samahan Health Clinic, National City	1	$5,000
Orange County Asian & Pacific Islander Community Alliance, Garden Grove	1	$187,500
Samoan National Nurses Association, Carson	1	$125,039
San Diego State University Research Foundation	1	$5,000
San Joaquin Valley Health Consortium	1	$138,500
Scripps Research Institute, La Jolla	6	$1,346,685
Sidney Kimmel Cancer Center	1	$289,500
Slavic Assistance Center	1	$93,750
Stanford University	7	$1,165,060
Thai Health and Information Service, Hollywood	1	$88,427
Turtle Health Foundation, Folsom	1	$88,625
University of California, Berkeley	2	$167,540
University of California, Davis	2	$152,709
University of California, Irvine	2	$249,382
University of California, Los Angeles	4	$385,838
University of California, San Diego	2	$225,551
University of California, San Francisco	7	$823,751
University of California, Santa Barbara	1	$65,415
University of San Diego	1	$86,973
University of Southern California	2	$489,000
West Bay Pilipino Multi-Service Center, San Francisco	1	$5,000
Women of Color Breast Cancer Survivors Support Project, Inglewood	1	$5,000

2006 CBCRP Application Evaluation & Review Committees

The CBCRP wishes to thank the participants in our 2006 review committees for their service and dedication to our Program.

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 nine 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
- 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
- Addressing the needs of the underserved
- Critical path/translation (IDEA), career plan/mentoring (dissertation, postoc), or dissemination and translation potential (CRC)

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

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