UNIVERSITY
OF
CALIFORNIA

2012 COMPENDIUM OF AWARDS

Cycle 18

CALIFORNIA
Breast Cancer
Research Program

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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 19 new research grants** that will advance our knowledge about the community impact, biology, detection, and treatment of breast cancer. With these new awards we are **investing $4,848,956 for research projects being performed at 15 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 Breast Cancer Research Council (BCRC), which sets program priorities and recommends the grants to be funded. The BCRC 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 California Department of Health Services breast cancer early detection program, "Every Woman Counts."

CBCRP research funding is organized through a number of sub-program units including:

- **Community initiatives** supports research grants that incorporate both traditional researcher and community group co-investigators to study a problem specific to a community, but with wider dissemination potential.
- **Core funding** focuses on investigator-initiated traditional grants to support smaller, innovative projects, larger translational grants, and conferences.
- **Special Research Initiative (SRI)** grants target topics related to environmental causes of breast cancer, disparities in disease incidence and survival in various populations, and novel strategies for prevention based on environmental causes and related to disparities.

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.

Overview of CBCRP award types

CBCRP funded new research projects using a variety of award types in 2012:

- **Community Research Collaboration (CRC)** awards bring community organizations—such as breast cancer advocates, community clinics, or organizations serving under-represented women—together with experienced scientists to investigate breast cancer problems that are important to that community, using culturally-appropriate research methods. CRC Pilot (18-month) and CRC Full Research awards (three years) are available.
- **Innovative Developmental and Exploratory Awards (IDEAs)** are 12-18 month grants for targeted high-risk/high-reward projects. 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 new and established investigators.
- **Translational Research** awards support projects that overcome barriers and put prior research knowledge to practical use in the patient or community setting.
- **Conference Awards** 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.

LOI and application submissions & review

IDEA and Translational Research Awards applications must pass through a letter of intent (LOI) screening process conducted by our Council to select projects that best meet our award type and programmatic criteria. We view this as a benefit to both the applicants and Program in terms of reducing the effort to prepare full applications and the CBCRP's corresponding peer review costs.

Table 1. LOI submission and approval results

Award Type	LOIs submitted	LOIs approved	Percent approved
IDEA	113	59	52%
Translational Research Award	29	7	24%

After the LOI process the full application data is shown in the table below.

Table 2. 2012 full application submissions by award type and priority issue

Award Type ↓	CBCRP Priority Issue				Award Type Totals
	Etiology & Prevention	Community Impact	Detection, Prognosis & Treatment	Biology of the Breast Cell	
Innovative, Developmental & Exploratory (IDEA)	9	2	29	14	54
Translational	0	1	6	0	7
Community Research Collaboration (CRC) Pilot and Full	1	5	0	0	6
Joining Forces Conference	1	1	0	0	2
Priority Totals	11	9	35	14	69

Overall, the number of applications was reduced by 20% compared to the previous 2011 cycle. This was due to the elimination of the IDEA Competitive Renewal award type.

Funding highlights

Table 3. 2012 grant distribution by award type

Award Type	Number of Applications	Grants Funded (Success Rate)	Amount Awarded	Percentage of Total Funding
IDEA	54	11 (20%)	$2,018,197	41.6%
Translational	7	2 (29%)	$1,543,088	31.8%
Community Research Collaboration (CRC)	6	4 (67%)	$1,237,671	25.6%
Conference	2	2 (100%)	$50,000	1.0%
Total	69	19 (28%)	$4,848,956	100%

Three awards are of special interest, and are supported by revenue received from the voluntary **California State Income Tax Check-off**. They are a Community Research Collaboration Award to **Kim Harley**, **University of California, Berkeley and Kimberly Parra, Clinica de Salud del Valle de Salinas** for "Decreasing Endocrine Disruptor Exposure in Latina Teens"; and IDEA grants to **Debasish Tripathy**, **University of Southern California** to investigate "Co-Targeting the Notch and EphB4 Receptors in Breast Cancer" and **Deanna Kroetz**, from the **University of California, San Francisco** for "Genetic Predictors of Chemotherapy Toxicity in Breast Cancer."

Faith Fancher Research Award

Faith Fancher was a long-time television news anchor and personality with KTVU (Oakland) who waged a very public battle against breast cancer. She also was the founding member of the CBCRP Executive Team, which formed in 2001 to help raise the visibility and fundraising profile of our program. Faith passed away in October 2003 after a six-year struggle with breast cancer. In Faith's honor, and to commemorate all that she did for breast cancer education and research, we have created this annual award. The selected grant reflects the values that Faith held most closely and extends the work that Faith did for all women facing breast cancer.

The recipients of the **2012 Faith Fancher Research Award** are **Annette Maxwell (University of California, Los Angeles**) **and Sandra Young** (**Mixteco/Indigena Community Organizing Project)** for their community collaborative project, ***Building Mixtec Community Capacity to Address Breast Health***. The focus of the project is to lay the groundwork for future breast health-related collaborative activities in the Ventura County Mixtec community. With approximately 20,000 farm workers in the immediate area and some 82,000-125,000 statewide, Mixtec represent one of the largest indigenous groups of farm workers. This study will address questions related to the prevalence of the breast cancer burden, issues related to screening, contributing factors to normative beliefs, and identify of evidence-based practices from other marginalized communities that could be adapted for this population.

Community Initiatives: new grants

Overview: California is comprised of diverse communities differing by characteristics such as ethnicity, culture, language, sexual identity, immigration history, and socioeconomic status. This diversity offers the unique opportunity to investigate disparities and the unequal burden of breast cancer among underserved groups. 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 for or diagnosed with breast cancer?
- What services are needed to improve access to care in order to improve quality of life and reduce suffering?

The CBCRP has been supporting Community Research Collaborations (CRC) for 16years. These partnerships are based on the established principles of community-based participatory research (CBPR). The CRC grants enable academic and community investigators working together to identify a research question, develop the study design, conduct the research, analyze results, and disseminate new information to the scientific and lay communities.

In addition, the CBCRP provides Conference Awards to link breast cancer researchers, non-breast cancer investigators, and community members for the purpose of stimulating new ideas and collaborations.

Community Initiatives Portfolio

The CBCRP funded six new community initiatives grants for a total of $1,237,671 that focus on underserved women in either specific ethnic groups or from rural areas of California.

Two **Conference Awards** were funded in 2012.

Dr. Kimlin Ashing-Giwa from **City of Hope National Medical Center** organized "The Global Chinese Breast Cancer Alliance Conference (GCBCA)" that took place in Los Angeles on April 25-27, 2012. The structure of this 3-day conference included diverse breast cancer experts as keynote speakers; in addition there were four plenary sessions with topics such as: "Hereditary Breast Cancer in Chinese" and "Breast Cancer in the Chinese American Community: Challenges and Outlooks", eight breakout sessions including "Research Professional Forum" for researchers, "Medical Professional Forum" for clinicians, and "Introduction of Research Studies" targeting to community organizations and advocates who are interested in participatory research. Also there were eight workshops, topics include: "Integration of Research Studies and Community Work", "Infrastructure and Capacity Building" and "Grant Writing and Creating a Fundraising Project" facilitate capacity building, training, leadership, communication and supportive care practice among volunteers and advocate leaders. Over 250 participants including researchers (20%), clinicians (30%), public health workers/cancer educators (10%), advocates (30%), and survivors (10%) from California and around the world attended.

Dr. Christina Gonzalez with Latinas Contra Cancer was funded for the "3rd Biannual National Latino Cancer Summit" held July 23-25 UCSF Mission Bay in San Francisco. This meeting will focus on the impact of the environment on Latinos and cancer; including not only bench science, but the social determinants that put Latinos in their environment at risk for cancer. The Summit provides opportunity for researchers, health care providers, leaders of Community Based organizations as well as community health educators, (i.e., "promotores"), to meet, network and find ways to collaborate. Whether it's a community of farm workers exposed to pesticides, school children lacking access to physical activity, social stressors of the working poor or policies that by their nature create at risk neighborhoods, the mix of cultural, social, economic and toxic hazards, all seemingly contribute to increased risk in the Latino community.

The CBCRP funded **four Community Research Collaborations awards** in 2012 that focused on the Latina or Mixtec populations in California.

Synthetic chemicals (e.g., parabens and phenols) are used extensively in cosmetics, shampoos, and other personal care products as fragrances, preservatives, or stabilizers. Many of these chemicals are "endocrine disruptors", which means meaning that they mimic or block the effects of hormones, including estrogen, which is a key factor in the development of breast cancer. **Kim Harley** from the **University of California, Berkeley** is partnering with **Kimberly Parra** at the **Clinica de Salud del Valle de Salinas** to examine the exposure of synthetic chemicals used in cosmetic, shampoos and other personal care products among Latina teenagers and to evaluate the impact of changing cosmetic and personal care products to low-chemical brands. Using eight research assistants from the Youth-based Community Council (YCC), they will recruit 100 teenage girls from the Salinas Valley to participate in an interview about their personal care product use and provide a urine sample for later analysis of exposure to ED chemicals. There has been very little research done in chemical exposures in teens. It has been well-established that the age of puberty is decreasing, and this is believed to contribute to an increased risk for breast cancer later in life.

Health literacy among minority populations was identified in Healthy People 2020, the nation's (DHHS) health initiative, as a key objective to: "Increase the proportion of persons who report their health care provider always gave them easy-to-understand instructions about what to do to take care of their illness or health condition…" (HC/HIT–1.1). **Sheila Casteneda** at the **San Diego State University Research Foundation** will collaborate with **Ilana Brongiel** from **Centro de Salud de la Comunidad de San Ysidro, Inc.** to conduct qualitative research, including key informant interviews with 15 women and focus groups with 80 women to incorporate breast cancer risks, screening and prevention into a culturally acceptable program for Latinas. Then, the next phase involves conducting a pilot feasibility study with 15 women to examine breast cancer health literacy intervention produced in the formative research phase. The feasibility testing will allow them to evaluate intervention fidelity (e.g., demonstrating intervention was conducted as planned), and explore recruitment and retention issues, participant satisfaction, and health educator perception's on areas for improvement in each session.

mHealth is a term used for the practice of medicine and public health, supported by mobile devices. mHhealth, and specifically e-messing strategies, are turning out to be a source of tremendous patient empowerment. Since Latina women are more likely to be diagnosed with an advanced stage of breast cancer and are 20% more likely to die of breast cancer than non-Hispanic white women, mHealth approaches for communication are an emerging strategy underutilized in the population. **Ingrid Oakley-Girvan** with the **Cancer Prevention Institute of California** will team with **Claudia Del Rio** at **Tiburcio Vasquez Health Center, Inc.** to develop and test e-messaging for Latinas with an abnormal mammogram. They call their approach Automated Breast follow-up Communications (ABC), and their aims is to develop and study content for acceptability, cultural competence, and effectiveness. In this 18-month, pilot project they will they will conduct focus groups with 6-8 Latina breast cancer patients and interview with 10 primary care providers at Tiburcio Vasquez Health Center, a federally qualified health center that provides services for Latinas at four Bay Area clinics. Ultimately 30 women will be randomized to either receiving e-messages about an abnormal mammogram or standard follow-up care.

The Mixtec (i.e., indigenous Mesoamerican peoples inhabiting the Mexican states of Oaxaca, Guerrero and Puebla) represent one of the largest groups of California farm workers. Many members of the community speak only their own non-written language which further increases the group's exclusion in terms of access to services. In addition to linguistic and socioeconomic factors that contribute to health disparities, many Mixtec also hold culturally normative beliefs that can be challenging for addressing breast health. **Annette Maxwell** from the **University of California, Los Angeles** will team with **Sandra Young** with the **Mixteco/Indigena Community Organizing Project** to train Mixteco and Spanish-speaking promotores to conduct a needs assessment with 1,000 Mixtec households. The promotores also will conduct the focus groups and informant interviews to identify potential barriers to and facilitators of screening, particularly in terms of cultural norms. From the needs assessment and the focus groups the collaborators plan on developing an intervention to be supported by future funding.

Community Initiatives Grants Listing

Increasing California's Capacity to Partner in Global Breast Cancer Research
Award Type: Conference
Ashing-Giwa, Kimlin, Ph.D.
City of Hope National Medical Center
$25,000

Latina Breast Cancer Health Literacy Pilot Project
Award Type: CRC-Full
Castaneda, Sheila, Ph.D. (co-PI)
San Diego State University Research Foundation
$98,462
Brongiel, Ilana, MPH (co-PI)
Centro de Salud de la Comunidad de San Ysidro, Inc.
$113,026

3rd Biannual National Latino Cancer Summit
Award Type: Conference
Gonzalez, Christina, Ph.D., M.D.
Latinas Contra Cancer
$25,000


Decreasing Endocrine Disruptor Exposure in Latina Teens
Award Type: CRC-Full
Harley, Kim, Ph.D. (co-PI)
University of California, Berkeley
$389,094
Parra, Kimberly (co-PIs)
Clinica de Salud del Valle de Salinas
$257,337


Building Mixtec Community Capacity to Address Breast Health
Award Type: CRC-Pilot
Maxwell, Annette, Dr. PH. (co-PI)
University of California, Los Angeles
$75,000
Young, Sandra (co-PI)
Mixteco/Indigena Community Organizing Project
$93,750

E-messaging for Abnormal Mammogram Follow-up in Latinas
Award Type: CRC-Pilot
Oakley-Girvan, Ingrid, Ph.D. (co-PI)
Cancer Prevention Institute of California
$123,985
Del Rio, Claudia (co-PI)
Tiburcio Vasquez Health Center, Inc.
$87,017

Core funding: new grants

Overview: Since first awarding grants in 1995, the CBCRP has attracted new researchers to breast cancer and provided current breast cancer researchers with the resources to tackle the evolving landscape of the disease. Thus, the core funding unit at CBCRP supports investigator-initiated research across a wide range of breast cancer topics. Funded projects must either correspond to the IDEA (innovative, developmental, exploratory award) level of research, or the research must be focused on translational, practical endpoints.

Grants funded in 2012 are listed below under the following CBCRP funding priority areas:
1. Etiology and Prevention including; environmental and biological factors interact to increase the risk of developing breast cancer; and xenoestrogens, exercise, studies of genetic variation, and methods to modify known breast cancer genes and risk factors.
2. Detection, Prognosis and Treatment including; imaging, early detection, biomarkers, emerging treatment strategies, and novel therapy targets and approaches.
3. Biology of the Breast Cell including; tumor biology and biology of the normal breast associated with breast cancer.

Core Funding Portfolio

The CBCRP funded 13 new "core funding" grants that are presented under the three broad research areas described below.

Etiology and prevention (2 grants):

Genetic testing women for BRCA gene mutations is expensive and only a few women are positive as gene defect carriers. Currently, clinicians use statistical models that rely primarily on age at diagnosis and family history of breast and ovarian cancer, which is often imprecise, to determine a person's eligibility for genetic BRCA testing. **Ann Hamilton** from the **University of Southern California** will determine whether information from tumor pathology alone can act as a surrogate for BRCA genetic testing. This is based on previous observations by Dr. John Hopper's group in Australia that tumors from BRCA1 mutation positive women have a more aggressive tumor phenotype. Dr. Hamilton's study will use archived tissue blocks from the Los Angeles Residual Tumor Repository of women diagnosed with invasive cancer in Los Angeles over the past 10 years. These tissue blocks will be linked to information in the Los Angeles Cancer Registry to select cases according to age at diagnosis and race/ethnicity. A study pathologist will review and record information on nine tumor morphological characteristics. BRCA1 sequencing will be performed to determine the correlation between predictive pathology and DNA mutation status.

Folic acid intake has gone up dramatically in the US and Canada due to government mandates that foods be fortified to reduce developmental defects in newborns (neural tube defects). Especially at risk for excess folic acid intake are pregnant women, who are prescribed maternal vitamins containing between 400-800 ug/day, in addition to that already consumed in their fortified diet. Folic acid is a synthetic form of folate, and is thought to potentially to cause an unnatural shift toward DNA synthesis (i.e., promoting cell proliferation) when in excess. **Joshua Miller** at the **University of California, Davis** will analyze this relationship between excess folic acid intake, mammary development abnormalities, and risk for breast cancer in mouse models. Adult female mice will be fed diets containing different concentrations of folic acid through birth and weaning. Dr. Miller's group will examine folic acid-dependent changes in mammary ductal and neoplastic morphology; gene expression changes associated with proliferation, remodeling/apoptosis, and hormone receptors; and genome-level and gene-specific DNA methylation.

Detection, prognosis & treatment (7 grants):

Two newly funded grants are translational projects.

An estimated 54,000 women were diagnosed with ductal carcinoma in situ (DCIS) in 2011, but only 15% will develop invasive breast cancer in the next 10 years. Thus, ~85% of women diagnosed with DCIS will not have an invasive tumor, but often undergo unnecessary treatment such as radiation and/or hormone therapy. **Thea Tlsty** at the **University of California, San Francisco** was funded to assess epigenetic DCIS markers associated with progression to malignancy. Many genes are "silenced" during the development of cancer not due to gene mutations, but rather to epigenetic modifications. These include DNA hypermethylation, mostly in promoter CpG island regions, and histone modifications (e.g. acetylation). Dr. Tlsty's team will use a unique DCIS patient database at UCSF to focus on 16 pre-screened epigenetic biomarkers using the following criteria: i) genes representing various hallmarks of cancer; ii) genes exhibiting a very distinct methylation states between normal breast cells and DCIS lesion cells; and iii) genes with a correlation between expression level and DCIS grade and if possible disease outcome. Their goal is to develop a rapid, inexpensive prognostic clinical test within three years that will incorporate epigenetic markers and provide individual risk information for as many women as possible diagnosed with DCIS.

Perhaps the most critical issue facing breast cancer survivors is the risk of recurrence. Recent advances now allow researchers to analyze the gene signatures from archived tumor samples, often preserved in paraffin blocks, so that tumor genetic variability can be correlated with long term survival and recurrence risk. **Laura Esserman** also at the **University of California, San Francisco** will work with colleagues at the Karolinska Institute in Stockholm and The Buck Institute for Research on Aging in Novato to generate a validated set of clinical and molecular predictors to determine the overall likelihood and timing of breast cancer recurrence from women enrolled in two trials (>20 years clinical follow-up) conducted in Sweden. Dr. Esserman's team will evaluate the entire range of emerging breast cancer gene "signatures", because of the very recent advances in technology that enable the generation of high quality RNA from paraffin samples and the ability to produce 44K (44,000 gene target) expression microarrays. This capability became available in December of 2011, and this project allows them to take advantage of these recent findings and important technical advances and combine them with a unique patient resource to improve long-term breast cancer prognosis.

Two newly funded projects focus on novel detection/imaging technologies.

Standard X-ray mammography relies on qualitative, shape-based information to identify cancer. This includes the presence of a suspect lesion, the shape of the lesion, and the presence of calcifications. Unfortunately, many benign breast abnormalities look qualitatively similar to tumors. The result is that only about 1 in 4 biopsies actually find cancer. **John Shepherd** also at the **University of California, San Francisco** is funded to explore a method to estimate quantitative compositional information of breast tissue using data obtainable from an X-ray mammography system. Dr. Shepherd's group developed this technique from previous studies of bone and muscle. They employ a novel dual-energy imaging technique, "3-component breast imaging" to quantify the lipid, protein and water thicknesses of breast lesions of various types including invasive ductal carcinoma, DCIS, fibroadenoma, and benign breast tissue. This technology will be used to augment standard mammogram interpretation by a radiologist to estimate the composition of suspicious breast lesions. It does not require contrast agents and is expected to be applicable even to dense breasts where sensitivity and specificity are low. A new law (#1538) has passed the California State Senate is currently under consideration by the Assembly to that would require notification to women whose breast tissue is dense.

Molecular-level assessment of breast cancer is crucial for developing a detailed understanding of the how the disease originates and spreads. Current clinical and research tools lack the ability to perform such analyses at a sub-millimeter level within a living human being, thus are unable to monitor and

quantify cellular/functional events underlying the disease. **Abhijit Chaudhari** from the **University of California, Davis** is funded to build and validate a "virtual pathology machine", which consists of a 3D positron emission tomography (PET) molecular imaging system. For human breast scanning this device may resolve molecular activity in lesions at a sub-millimeter level capable of performing detailed measurements of glucose utilization, hypoxia, angiogenesis or other key processes. Pending additional development, such an imaging system could find application for the "real-time monitoring" of a tumor's response to neoadjuvant chemotherapy.

Four new grants focus on novel chemotherapy toxicity, drug resistance, resistance mechanisms to oncogene therapy, and a novel approach to treat breast cancer brain metastasis.

Some breast cancer patients develop severe drug toxicities secondary to chemotherapy, often requiring dose reductions that may result in suboptimal disease therapy and an associated increased risk of recurrence. There is significant variability among breast cancer patients in the onset and severity of most chemotherapy-related adverse events, suggesting that genetic factors may modify risk for adverse events. **Deanna Kroetz** from the **University of California, San Francisco** will study a patient's large-scale genetic variability that impacts risk for sensory neuropathy in response to two of the most common chemotherapeutic agents. Dr. Kroetz's team will use DNA samples obtained from women with primary breast cancer who were enrolled on a large Phase III clinical trial testing whether single agent paclitaxel is as efficacious as adriamycin/cyclophosphamide. Toxicity data was collected during this treatment trial, and genotyping data is available for >500,000 "markers" across the human genome. Statistical methods will be used determine whether any of these genetic markers predict the risk of developing toxicity, especially sensory neuropathy To date, pharmacogenetic studies of drug toxicity in breast cancer treatment have looked at single genes that are thought to be important since they control the level of drug within the body.

Resistance to standard therapies virtually always develops in advanced breast cancer due to residual drug-resistant disease. There is increasing evidence that cancer stem cells and the tumor microenvironment play an important role. The EphB4 receptor promotes angiogenesis and cell survival, and the Notch receptor is known to mediate the maintenance of stem cells. Thus, **Debashish Tripathy** at the **University of Southern California** will test whether simultaneously targeting the stem-cell features of the tumor as well as the tumor microenvironment to enhances tumor regression. They will use a soluble human EphB4 fusion protein and a humanized anti-Dll-1/Dll-4 (ligands for the Notch receptor) monoclonal antibody to enhance tumor regression. These agents will be tested in both human breast cancer cell lines and in human tumors grown in mice--representing the estrogen and Her2 receptor breast cancer subtypes. Biomarkers of the tumor cells and animal tumors will be monitored to assess the success of this approach.

Many human cancers are driven by the uncontrolled signaling functions of activated oncogenes. This has led to the paradigm that these cancers can be effectively treated through the development of drugs that inactivate their "driving" oncogenes. Unfortunately, the full potential of promising oncogene-targeting drugs, such as Herceptin, are not fully realized in clinical use, since tumor cells in many patients acquire the ability to "restore" critical signaling pathways even when a major oncogene is inhibited. **Mark Moasser** also at the **University of California, San Francisco** will investigate how mTor as the the key adaptational link to HER3 functions in treatment-resistance for HER2-amplified breast cancers. mTOR integrates the input from various cellular pathways, including insulin and growth factors. It also senses cellular nutrient and energy levels and becomes deregulated in certain cancers. Dr. Moasser's group will "map" the adaptational network downstream of HER3 in mammary epithelial cells, using a small molecule pharmacologic library approach with up to 15 compounds inhibiting various nodes in the HER3-Akt-mTor signaling network. The novel concept that an evolutionarily conversed signaling/adaptational cellular network could be targeted in breast cancer is a paradigm shift from therapeutics directed at "driving" oncogenes or mutated normal genes.

Breast cancer metastases to the brain severely impact the quality of life and are difficult to treat, showing frequent failure to respond to conventional chemotherapy or to immunotherapy, because of the protected site conferred by the blood-brain barrier. Surgical removal of individual brain metastases and/or radiation therapy of widespread lesions can temporarily help, but not halt disease progression. **Brunhilde Felding-Habermann** at the **Scripps Research Institute** will expose experimental mice bearing human breast cancer brain lesions to reduced levels of oxygen (host hypoxia equivalent to high mountain altitude) and test whether this approach substantially inhibits brain metastatic growth without impacting overall animal health. Importantly, the lowered levels of atmospheric oxygen opens a time window of reduced brain metastatic growth and increased tumor cell vulnerability to drug or radiation treatment. The drugs being tests are lapatinib, a tyrosine kinase inhibitor of EGFR1 and Her2; and SAHA, a histone deacetylase (HDAC) inhibitor. Dr. Felding-Habermann's team will test hypoxia on treatment with ER/PR+/Her2-, ER/PR-/Her2 +, and triple negative breast cancer brain metastases to obtain a good indication of which sub-type might best benefit from their approach.

Biology of the breast cell (3 grants):

Dormant breast cancer stem or stem-like cells may underlie the reason why 40% of women diagnosed and treated eventually develop a recurrence after years of disease-free survival. **Alexander Borowsky** from the **University of California, Davis** will identify the average "age" or "birthdate" of distinct cell populations in primary breast cancer samples using 14-C bomb-pulse dating. Between 1955-1963, nuclear bomb tests raised 14-C levels on earth, and consequently in living tissues. Since the test ban treaty in 1963, 14-C levels in tissue have decreased exponentially. Living tissues acquire both 14-C and 12-C at a ratio matching what is present when new DNA is synthesized. Since DNA is a relatively stable molecule in non-dividing cells, the ratio of 14-C/12-C in a tissue sample or cell population can be "age-matched." Dr. Borowsky will isolate mammary stem cells and cancer stem cells from amplifying or differentiated cell populations, respectively, from primary human breast samples. Following amplification and isolation of mammary vs. cancer stem cell populations and transplantation into mice, the 14-C/12-C ratio will be determined using Accelerator Mass Spectrometry at the facility at Lawrence Livermore National Laboratory. This research would test the generally accepted, but unproven theory that breast cancer stem cells are long-lived and this may lead to new therapeutics that selectively target and "activate" dormant stem cells.

While pregnancy has an overall protective effect against breast cancer, there exists a paradoxical increased risk of aggressive, metastatic breast cancer during the first few years following pregnancy. The mechanism of pregnancy-associated breast cancer is poorly understood, but may involve both cell intrinsic effects, such as changes in gene expression, or cell extrinsic events, such as alterations in the breast microenvironment following breast ductal involution. **Jay Desgrosellier** from the **University of California, San Diego** will to test the hypothesis that pregnancy-associated mammary stem cells promote metastatic progression in breast cancer. The increase in mammary stem cell population during pregnancy, their relation to cancer stem cells, and role of the cell surface adhesion, integrin alphaVbeta3 receptor will be studied in mouse models. A comparison of mammary stem cells from virgin vs. parous (i.e., having given birth one or more times) mice will establish the role of pregnancy.

The BRCA1 protein plays a key role in promoting homologous recombination (HR), which is a cellular process that is critical for maintaining genetic information via DNA repair pathways. Accordingly, mutations in BRCA1 can cause inefficient HR, leading to accumulative loss and mutations in genetic information, which underlies cancer progression. Using thermostat metaphor, the BRCA1 protein is important to "turn up the heat" on the normally functioning HR process, and there is a compensatory cell mechanism (called the 53BP1/RNF168-signaling pathway) to "cool down" HR. **Jeremy Stark** at the **City of Hope National Medical Center** is funded to study is to identify specific molecular targets to rescue homologous recombination (HR) in BRCA1-deficient

cells. This involves the characterization of two inhibitors of 53BP1 and RNF168, through protein domain and structural analysis. The long-term impact is the potential of developing prophylactic therapeutics to reduce the cancer risk of BRCA1 mutation carriers by restoring a cell's endogenous capacity for HR-dependent DNA repair.

Core Funding Grants Listing

Establishing Cell Lifespans in Cancer and Normal Breast
Award Type: IDEA
Borowsky, Alexander, M.D.
University of California, Davis
$275,333

Sub-millimeter PET for Improving Outcomes in Breast Cancer
Award Type: IDEA
Chaudhari, Abhijit, Ph.D.
University of California, Davis
$149,574

Examining Metastatic Potential in Mammary Stem Cells
Award Type: IDEA
Desgrosellier, Jay, Ph.D.
University of California, San Diego
$150,000

Predicting Breast Cancer Recurrence to Improve Care
Award Type: Translational
Esserman, Laura, M.D.
University of California, San Francisco
$793,127

Host Hypoxia to Treat Breast Cancer Brain Metastasis
Award Type: IDEA
Felding-Habermann, Brunhilde, Ph.D.
Scripps Research Institute
$284,250

Predicting BRCA1 Mutation Status from Tumor Pathology
Award Type: IDEA
Hamilton, Ann, Ph.D.
University of Southern California
$246,000

 **Genetic Predictors of Chemotherapy Toxicity in Breast Cancer**
Award Type: IDEA
Kroetz, Deanna, Ph.D.
University of California, San Francisco
$100,000

Maternal Folic Acid Intake, Mammary Development, and Cancer
Award Type: IDEA
Miller, Joshua, Ph.D.
University of California, Davis
$149,944

Understanding HER3 and mTor Signaling in Breast Cancer
Award Type: IDEA
Moasser, Mark, M.D.
University of California, San Francisco
$100,000

Compositional Mammography for Breast Cancer Detection
Award Type: IDEA
Shepherd, John, Ph.D.

University of California, San Francisco
$150,000

Rescuing HR DNA Repair in BRCA1-Mutation Carriers
Award Type: IDEA
Stark, Jeremy, Ph.D.
City of Hope National Medical Center
$168,000

Using Epigenetic Changes to Stratify DCIS Biopsies
Award Type: Translational
Tlsty, Thea, Ph.D.
University of California, San Francisco
$750,000

 **Co-Targeting the Notch and EphB4 Receptors in Breast Cancer**
Award Type: IDEA
Tripathy, Debasish, M.D.
University of Southern California
$245,096

2012 CBCRP funding by institution

The following **15 California research institutions and community organizations were awarded new CBCRP funding in the 2011-2012 grant cycle.** Community collaborative (CRC) grants are split between institutions.

Institution (city)	# Awards	Amount
Cancer Prevention Institute of California (Fremont)	1	$123,985
City of Hope National Medical Center (Duarte)	2	$193,000
Clinica de Salud del Valle de Salinas	1	$257,337
Latinas Contra Cancer (San Jose)	1	$25,000
Mixteco/Indigena Community Organizing Project (Oxnard)	1	$93,750
San Diego State University Research Foundation	1	$98,462
San Ysidro Health Center, Inc.	1	$113,026
The Scripps Research Institute (La Jolla)	1	$284,250
Tiburcio Vasquez Health Center, Inc. (Union City)	1	$87,017
University of California, Berkeley	1	$389,094
University of California, Davis	3	$574,851
University of California, Los Angeles	1	$75,000
University of California, San Diego	1	$150,000
University of California, San Francisco	5	$1,893,088
University of Southern California (Los Angeles)	2	$491,096

2012 CBCRP application evaluation process & review committee rosters

The CBCRP thanks the participants in our 2012 review committees for their service and dedication to our Program!

In the first phase of the funding process, grant applications were peer reviewed and scored for scientific merit by 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. Scientific Reviewers have broad expertise in topics associated with individual applications. Breast cancer Advocate Reviewers are women active in breast cancer advocacy organizations, and many of them are also living with the disease. Advocates bring their personal knowledge and commitment to the review process. Each committee also includes a California Advocate Observer, who does not review or vote, but represents California's advocacy community. The observer gains insight into our process and provides feedback to the Program. When additional expertise is needed, an Ad Hoc Member is brought in to the review a particular application not covered by the other committee scientist reviewers.

The CBCRP uses a scientific **merit scoring system** that rates individual components (e.g., approach, innovativeness, impact). This allows our expert reviewers and Council to better differentiate applications that might otherwise appear identical. Depending on the award type, we use four or five scientific merit components in the peer review process.

We **triage** some applications that score in the lower range of a committee's portfolio using the preliminary scores of the assigned reviewers. Applications in the upper range of a committee's portfolio all receive full committee discussion, as do any of the lower scoring applications nominated to full review by one reviewer.

Applications that were not triaged were rated by the CBCRP's Council for **programmatic responsiveness**. The following criteria were used:

- Responsiveness to the CBCRP's priority issues and award type (or initiative)
- Strength of individual scientific merit component scores (e.g., innovation for IDEA applications)
- Underfunded topic
- Quality of the lay abstract
- Inclusion of advocates in the funded research
- Addressing the needs of the underserved
- Critical path/translation (IDEA and Translational Research Award), or dissemination and translational 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.

Community Impact Review Committee

►Chair:

Carolyn Gotay, Ph.D.
Prof. & Can. Cancer Soc. Chair in Cancer Primary Prev.
School of Population and Public Health
University of British Columbia
Vancouver, BC Canada

►Scientific Reviewers:

Sherrie L. Flynt Wallington, Ph.D.
Asst. Prof. of Oncology; Prog. Dir., Health Disparities
Lombardi Comprehensive Cancer Center
Washington, DC

Anna G. Hoover
Deputy Director
Nat'l Coord. Cntr. for the Public Health PBRN Prog.
University of Kentucky College of Public Health
Lexington, KY

Kathryn M. Kash, Ph.D.
Associate Professor
Thomas Jefferson University
Philadelphia, PA

►Advocate Reviewer:

Susan Pelletier
Vermont Breast Cancer Coalition
Stockbridge, VT

►California Advocate Observer:

JoAnn Loulan
Breast Cancer Action
Portola Valley, CA

►Ad-Hoc Reviewer:

Rachel Ceballos, Ph.D.
Assistant Professor
University of Washington, School of Public Health
Department of Health Services
Seattle, WA

Etiology, Prevention & Biology Review Committee

►Co-Chairs:

Kirsten Moysich, Ph.D.
Prof. of Oncology, Prog Chair, Cancer Pathology & Prev.
Department of Cancer Prevention and Control
Roswell Park Cancer Institute
Buffalo, NY

Harikrishna Nakshatri, Ph.D.
Marian J. Morrison Professor in Breast Cancer Research
Walther Oncology Center
Indiana University School of Medicine
Indianapolis, IN

►Scientific Reviewers:

Alexander J. Bishop, D.Phil.
Assistant Professor
Greehey Children's Cancer Research Institute
University of Texas Health Science Center, San Antonio
San Antonio, TX

Charles V. Clevenger, M.D., Ph.D.
Professor of Pathology
Northwestern University
Department of Pathology
Chicago, IL

Suzanne E. Fenton, Ph.D
Reproductive Endocrinologist
National Toxicology Program, Cellular & Molecular Pathology
Research Triangle Park, NC

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Molecular and Cellular Oncogenesis Program
The Wistar Institute
Philadelphia, PA

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Department of Epidemiology and Biostatistics
State University of New York at Albany
Rensselaer, NY

Joyce A. Schroeder, Ph.D.
Associate Professor
University of Arizona
Department of Molecular & Cellular Biology
Tucson, AZ

Bryan E. Welm, Ph.D.
Assistant Professor of Oncological Sciences
University of Utah
Huntsman Cancer Institute
Salt Lake City, UT

►Advocate Reviewers:

Theresa Martyka
Y-ME National Breast Cancer Organization
Chicago Ridge, IL

Madeleine R. Tress, Ph.D.
SHARE
New York, NY

Carrie Wells
Survivors' Retreat
Baltimore, MD

►California Advocate Observer:

Hannah Klein Connolly
UCSF Spore Core
Burlingame, CA

Treatment & Detection Review Committee

►Chair:

Fredika M. Robertson, Ph.D.
Professor
M.D. Anderson Cancer Center
Department of Experimental Therapeutics
Houston, TX

►Scientific Reviewers:

Joanna E. Burdette, Ph.D.
Assistant Professor
Medicinal Chemistry and Pharmacognosy
University of Illinois at Chicago
Chicago, IL

Eldon R. Jupe, Ph.D.
Vice President, Research
InterGenetics, Incorporated
Oklahoma City, OK

Julie E. Lang, M.D.
Assistant Professor of Surgery
Arizona Health Sciences Center
Tucson, AZ

William Redmond, Ph.D.
Scientist
Robert W. Franz Cancer Research Center
Providence Portland Medical Center
Portland, OR

Edward R. Sauter, M.D., Ph.D.
Director, Cancer Treatment and Prevention Center
University of Texas HSC at Tyler
Tyler, TX

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University of Colorado School of Medicine
Denver, CO

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Professor and Director
The University of Texas Health Science Center
The Brown Foundation Institute of Molecular Medicine
Houston, TX

Ratna K. Vadlamudi, Ph.D.
Professor
UTHSCSA Department of Obstetrics & Gynecology
Division of Reproductive Research
San Antonio, TX

Martin C. Woodle, Ph.D.
President & CSO
Aparna Biosciences Corp.
Bethesda, MD

►Advocate Reviewers:

David Baker
National Breast Cancer Coalition
Bellaire, TX

Valerie Fraser
Michigan Breast Cancer Coalition
Huntington Woods, MI

Nancy Key
Susan G. Komen for the Cure
Camano Island, WA

Debra L. Madden
National Breast Cancer Coalition
Newtown, CT

►California Advocate Observer

Sharima Rasanayagam, Ph.D.
The Breast Cancer Fund
San Francisco, CA