Cycle 14

2008 Awards Compendium

CALIFORNIA
Breast Cancer
Research Program

On the cover: On average, 1 in 8 California women will develop breast cancer in her lifetime.

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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 42 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 almost $8.1 million for research projects being performed at 22 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 sets program priorities and selects 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 (priority issues) and award types
- Highlights of 2008 funding
- A portfolio summary and list of grants for our four main research priority issues
- Funded California institutions and amounts awarded
- Description of the application evaluation process and the review committee membership

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.

Submissions & Review Process

We received 200 submissions in response to our 2008 *Call for Applications* for new research grants on breast cancer. They were evaluated, discussed in a study section format, and scored for scientific merit by our out-of-state peer reviewers. Joining Forces Conference Award applications were reviewed by our advisory council.

The final tally of application submissions by CBCRP priority issues (i.e., invited research topics) and award types is shown below.

Table 1. 2008 CBCRP application distribution by award type and priority issue

Award Type	Priority Issue				
↓	Etiology & Prevention	Community Impact	Detection, Prognosis & Treatment	Biology of the Breast Cell	2008 Award Type Totals
Postdoctoral Fellowship	4	3	9	32	48
Dissertation	1	4	13	14	32
IDEA	12	5	35	30	82
IDEA-competitive renewal	2	1	3	4	10
Translational	0	0	9	0	9
Conference	0	4	0	0	4
CRC Pilot	0	8	0	0	8
CRC Full	0	7	0	0	7
Priority Totals	19	32	69	80	200

Compared to the previous year (2007/Cycle 13) we received approximately 10 percent fewer applications. In terms of award types, we received 20 percent fewer IDEA and CRC submissions; however, dissertation award application volume increased. In terms of CBCRP priority issue (i.e., broad research topic), the majority of our submissions were in Biology of the Breast Cell.

After the peer review process and scoring, only the applications ranked in the upper two-thirds of average scientific merit were evaluated by our advisory council for responsiveness to CBCRP programmatic criteria. There are seven criteria for each award type. To select grants for funding, the council balanced the scientific merit and programmatic ratings. Thus, the successful applicant responded both in terms of presenting a high quality research project *and* by addressing the interests of CBCRP stakeholders.

Overview of 2008 Funding

- Applications submitted = **200**
- Applications offered and accepting funding = **42**
- Applications offered funding, but declined = **3**
- Overall success rate (42/200) = **21%**

Amount awarded in 2008 = $8,087,394

The two tables below summarize the 2008 funding distribution by award type and priority issue.

Table 2. 2008 portfolio distribution by CBCRP award type

Award Type ↓	Number of Applications	Grants Funded (success rate)	Amount Awarded	Percentage of total funding
Dissertation	32	11 (34%)	$759,909	9.4%
Postdoctoral Fellowship	48	6 (12.5%)	$745,956	9.2%
IDEA	82	11 (13%)	$2,284,111	28.2%
IDEA-Competitive Renewal	10	2 (20%)	$621,906	7.7%
Translational	9	2 (22%)	$1,553,111	19.2%
CRC Pilot Award	8	2 (25%)	$386,796	4.8%
CRC Full Award	7	4 (157%)	$1,645,686	20.3%
Joining Forces Conference	4	4 (100%)	$89,919	1.1%

Table 3. 2008 portfolio distribution by CBCRP priority issue

Priority Issue ↓	Number of Applications	Grants Funded (success rate)	Amount Awarded	Percentage of total funding
Community Impact	32	15 (47%)	$2,706,131	33.5%
Etiology & Prevention	19	7 (37%)	$1,007,913	12.5%
Biology of the Breast Cell	80	9 (11%)	$1,016,985	12.6%
Detection, Prognosis & Treatment	69	11 (16%)	$3,356,365	41.5%

Comparing the 2008 vs. 2007 portfolios reveals a number of changes. Due primarily to funds returned from existing grants, we were able to award nearly $1 million more in research dollars this year. As a result, the number of grants increased from 35 in 2007 to 42 in 2008. Funding for dissertation awards, translational research, conference awards, and new IDEAs increased, while funding for community research collaborations decreased in 2008, which reflects a decrease in application volume. Our advisory council opted to award fewer IDEA–competitive renewals in favor of additional funds for translational research and new IDEAs. Although the IDEA and IDEA–competitive renewal funding mechanisms are very competitive (13% and 20% success rates, respectively), the CBCRP directs the largest proportion (36%) of our portfolio into supporting innovative breast cancer research. Since our most expensive award types, the community research collaborations and translational research, are in the Community Impact and Detection, Prognosis and Treatment CBCRP priority issues, these research areas receive the bulk of funding dollars. The CBCRP funded more grants in 2008 (7) vs. 2007 (2) under our Etiology and Prevention priority issue. Finally, CBCRP has made a strong effort to encourage research to move basic science projects down the "critical path" to practical applications, so our funding is directed less towards the Biology of the Breast Cell priority issue compared to a few years ago.

2008/Cycle 14 Funding Highlights

- Six awards are research projects to **community groups collaborating with traditional researchers** to address issues important to the community, such as rural access to support groups and risk factors impacting immigrant/underserved communities
- Nine grants aim to further our understanding of **tumor biology,** such as metastasis and factors that allow for tumor growth and progression
- Eleven projects explore novel methods to **detect breast cancer and develop novel approaches for treatment**
- Thirteen projects are for **innovative, exploratory, and high-risk/high reward research** projects to push boundaries, challenge existing paradigms, and initiate new research programs. Eleven of these grants are for new projects, and two grants are for renewal funding of past CBCRP IDEA grants showing excellent progress. Three recipients of IDEA grants are "junior" investigators—just starting independent research careers in breast cancer
- Seventeen awards provide opportunities in **career development** at the levels of graduate student and postdoctoral training. These researchers bring fresh thinking to their respective disciplines
- ☑ **Four awards are of special interest,** and are supported by revenue CBCRP receives from the voluntary **California State Income Tax Check-off**
- ➔ One new award was supported, in part, by a $30,000 grant from the **California Community Foundation**
- ✯ **Faith Fancher Research Award**
  Faith Fancher was a long-time television news anchor and personality with KTVU (Oakland) who was taken from us in October 2003 after a six-year struggle with breast cancer. In her honor, and to commemorate all that she did for breast cancer education and research, we have created this award. The recipients of the **2008 Faith Fancher Research Award** are **Natasha Riley (Vista Community Clinic), Georgia Sadler (University of California, San Diego),** and **Vanessa Malcarne (San Diego State University)** for their community collaborative project, *Breast Cancer Clinical Trials Education Program*. The overall goal of this research project is to increase participation in cancer trials by African American and Latina women. Low clinical trial participation by minorities is a problem because it: (1) limits researchers' ability to apply findings to diverse populations; (2) often means that minorities will be given medical care based on research that involved mostly white middle class communities; and (3) means that cutting- edge medical care options usually associated with clinical research will not be available to minorities. This new program will use the theme, "women united against breast cancer 'sisterhood'" in English and Spanish.

Description of CBCRP Award Types

- **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. *CRC Pilot* (18-month) and *CRC Full Research awards* (three years) are available.
- **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.
- **Translational Research:** supports projects that overcome barriers and put prior research knowledge to practical use in the patient or community setting.
- **Postdoctoral Fellowship:** for career development-oriented training under a breast cancer research mentor.
- **Dissertation:** funds the completion of dissertation research by masters or doctoral candidates.
- **Joining Forces Conference:** 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 comprised of diverse communities differing by multiple 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?

To address these issues the CBCRP solicits applications from community academic partnerships as well as individual investigators.

The CBCRP has been supporting Community Research Collaborations (CRC) for over 12 years. These partnerships are based on the established principles of community-based participatory research (CBPR) whereby academic and community investigators work together to identify the research question, develop the study design, carry out the research, analyze results, and disseminate information to scientific and lay communities.

The CBCRP offers pre-application teleconferences to provide information on CRC application requirements and tips for successful grant applications. We are encouraged that many CRC grants focus on the underlying disparities of underserved populations through innovative and understudied research areas. For example, Cycle 14 grantees are addressing needed research topics including clinical trials participation, breast education for immigrant women, survivorship for underserved groups, complimentary and alternative methods for quality of life enhancement, and interventions that link chronic illness care with mammography for at-risk women. We feel that addressing these gaps in our knowledge will lead to promising solutions for underserved communities disproportionately affected by breast cancer.

In addition to the CRC awards, the CBCRP supports the "Community Impact" priority issue with IDEA grants, career development awards, and the Joining Forces Conference Award.

The CBCRP funded fifteen new grants in 2008 to advance our Community Impact priority issue. Two CBCRP research topics are represented in this section:

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

Community Impact Portfolio Summary:

The Community Impact portfolio represents the most diverse group of projects in terms of topics and award types. The CBCRP funded six community research collaboration grants in 2008. Four of these projects deal with the issue of disparities in access to clinical trials and care.

First, the breast cancer education needs for immigrant women is an understudied area. This is critically important, because breast cancer is the leading cause of cancer death for many immigrant groups, and breast cancer incidence may increase with length of U.S. residency. In their project, *Adapting a Breast Cancer Education Program for South Asians,* **Beth Glenn** and **Roshan Bastani** with **University of California, Los Angeles,** have teamed with **Zul Surani** with the **South Asian Cancer Foundation.** They will adapt a DVD that was developed through previous CBCRP-funding for deaf women for use with South Asian women. The investigators will modify this DVD to include language, images, and cultural specificity to address breast cancer needs.

The goal is to improve breast cancer education for "at risk" women and survivors. Once developed, the team will apply for additional funding for implementation and evaluation.

Next, **Christine Noguera** at **Golden Valley Health Centers** and **Steve Roussos** with the **San Diego State University Research Foundation** will collaborate on a project for *Increasing Mammography Screening in Latinas with Diabetes.* They are continuing their previously funded CBCRP pilot work located in Merced County. The question to be addressed is: "Can age-appropriate mammography screening be increased for Latinas with diabetes through a health care systems-integrated intervention that links their diabetes care with methods to promote mammography?" The rationale for the diabetes link is to capitalize on routine diabetes care to check for and improve compliance with mammography screening recommendations for Latino women age 40 and older.

Next, clinical trials participation, especially among underserved groups, will be investigated by **Natasha Riley** with **Vista Community Clinic, Georgia Sadler** with **University of California, San Diego,** and **Vanessa Malcarne** with **San Diego State University Foundation.** They will test a *Breast Cancer Clinical Trials (BCCT) Education Program* specifically to increase African American and Hispanic American women's knowledge of, positive attitudes toward, and participation in breast cancer clinical trials. In this randomized controlled trial the team hypothesizes that a single program (BCCT) will produce statistically significant improvements in women's breast cancer clinical trials knowledge, attitudes, and research related behaviors compared to a control group. It is designed to benefit African American and Hispanic American women equally.

The Community Impact portfolio represents the most diverse group of projects in terms of topics and award types.

Finally, the CBCRP funded a "planning grant" to **Linda Navarro** from the **Turtle Health Foundation** and **Marlene von Friederichs-Fitzwater** at the **University of California, Davis,** to focus on *Breast Cancer Risk Reduction in American Indian Women.* The eventual goals are to increase mammography screening rates and address breast cancer risk issues associated with obesity. Urban and tribal health clinic partner research sites will recruit American Indian women who will receive: (1) the "Mother's Wisdom Breast Health Program" interactive, multimedia DVD; (2) a "Personal Journal" with stories of behavior change, recipes, and food and physical activity logs; and (3) an electronic pedometer.

Two newly funded community research collaboration grants focus on sociocultural, behavioral and psychological issues associated with breast cancer.

First, few studies address complimentary and alternative methods for quality of life following breast cancer treatment. **Rebecca Crane-Okada** with the **Beckman Research Institute of the City of Hope** and **Holly Kiger** with **WISE and Healthy Aging,** are determining the effects of a 12-week *Mindful Movement Program (MMP) for Breast Cancer Survivors.* This research combines movement-dance techniques and mindfulness (attention and attitude) techniques to determine their effects on the quality of life and mindfulness-associated outcomes in older breast cancer survivors. The aims of this program are to: (1) test the effects of an MMP intervention in older survivors who are 12 months out from completion of their treatment; (2) compare mindfulness qualities between the experimental and control arms; and (3) describe the experimental arm's perceptions of the MMP.

Second, very few studies have specifically addressed Latina breast cancer survivors' knowledge, attitudes, beliefs, or experiences and needs in terms of planning for and accessing medical care for surveillance, monitoring, and management of cancer and non-cancer medical issues. **Diana Tisnado** with the **University of California, Los Angeles** and **Brian Montaño** with the **Partnered for Progress** are undertaking a CRC pilot project entitled *Latina Breast Cancer Survivors…Our Experience* to study survivorship issues for Latinas after treatment for breast cancer. The aims of the project are to: (1) explore the definitions and meanings of survivorship and activities related to survivorship, and (2) to identify the barriers to survivorship. The results will be disseminated and used to develop a series of interventions to improve the survivorship experience of Latinas.

In addition to community collaborations, the CBCRP funded three additional projects to support career development in the topics of sociocultural, behavioral, and psychological issues associated with breast cancer.

First, communication between breast cancer survivors and health care providers is a key component to long-term survival. **Sara Fernandes-Taylor** from

the **University of California, Berkeley** is completing her dissertation research to examine whether breast cancer survivors' perceived control over their health, health behaviors, and health outcomes over ten years are predicted by the quality of communication these women experience with their healthcare providers. In this context they believe that reframing cancer as a chronic condition will aid in informing patient and provider-based communication interventions.

Next, a dissertation project called *Reproductive Concerns and Depression among Younger Survivors* will be conducted by **Jessica Gorman** at the **University of California, San Diego.** She will address depression and fertility issues using data from approximately 200 younger breast cancer survivors who participated in the Women's Healthy Eating and Living (WHEL) study. WHEL is a nutritional intervention designed to test whether a diet high in fruits and vegetables can lower breast cancer recurrence. Ms. Gorman will perform a follow-up survey to ask: (1) whether survivors wanted to have children or attempted pregnancy, (2) whether they've had problems with infertility or fertility-related side effects of their treatment, (3) whether they currently have any symptoms of depression, and (4) about their current feelings toward pregnancy and their ability to have children.

Finally, **Yoshiko Umezawa** at the **University of California, Los Angeles,** is funded for a postdoctoral fellowship to study why low income women, especially ethnic minorities, that have completed breast cancer treatment have a lower health-related quality of life (HRQOL) index compared to women in the general population. This study uses an ecological approach to examine how individual cognitive factors and systemic barriers (e.g., institutional discrimination) may, directly or indirectly, predict HRQOL. In addition, Dr. Umezawa will use GIS (geographic information system) technology to evaluate the effects of community health services on quality of life outcomes.

Two newly funded grants are for innovative research projects in topics that are not yet well established, but offer "high reward", if successful.

First, to what degree do differences in the quality of detection and treatment services utilized by "vulnerable women" (i.e., educational attainment, racial/ethnic minority, household income, and rural/urban residence) lead to disparities? **Lauren Goldman** at the **University of California, San Francisco,** will analyze 1998-2004 data from the seven Breast Cancer Surveillance Consortium (BCSC) registries in California to determine whether "wait time" for scheduled diagnostic mammography varies by facility and whether the staffing and the availability of same-day readings explain differences in quality. The objective is to inform possible areas where policy interventions at the mammography facility level could decrease differences in quality impacting vulnerable women.

Second, **Irene Yen** also at the **University of California, San Francisco,** is funded for an additional two years to continue an innovative project: *Neighborhoods and Obesity in Pre-Adolescent Girls.* The goal is to understand the relationship between neighborhood conditions, such as lack of access to affordable nutritious foods, recreational opportunities, or the physical circumstances (e.g. "hazards" such as litter, graffiti, or poorly maintained sidewalks) represent key factors contributing to childhood obesity. A better understanding these relationships might lead to new strategies for prevention or reducing the risk of childhood obesity, adult obesity, and the lower the risk for breast cancer.

The CBCRP funded four Joining Forces Conference Awards in 2008 that address a variety of topics. **Kimlin Ashing-Giwa** with the **Center of Community Alliance for Research and Education at the City of Hope Medical Center** received funding for *Increasing the Voice of African Americans in Research.* The aim is to bring together advocates and the scientific community in Southern California with a common interest in addressing breast cancer needs of African Americans in Los Angeles, Riverside, and San Bernardino Counties. The conference will facilitate new collaborations; provide advocate organizations and researchers a forum in which to network; and offer some exposure to preliminary training from organizations that can provide both researchers and advocate organizations with essential tools and resources.

Breast cancer is the leading cause of cancer death for many immigrant groups, and breast cancer incidence may increase with length of U.S. residency.

Linda Okahara with **Asian Health Services** will organize a meeting entitled *Nail Salon Workers: Chemical Exposures in the Workplace* to discuss state-of-the-science on chemical exposures for cosmetology workers (hairdressers, nail salon workers and beauticians). The overall goals are to: (1) create a mechanism for cross dialogue on research directed at the potential link between chemical compound exposure and breast cancer risks, and (2) develop a research agenda for examining this relationship as well as for improving health and safety in this understudied worker population.

Jeffrey Weitzel at **Beckman Research Institute of the City of Hope** is hosting a series of *Community Breast Cancer Screening & Prevention Conferences.* The purpose is improving access to genetic screening by underserved populations. The goal is to encourage a cycle of active feedback and constructive dialog between patients/families and physicians, patient advocates and community stakeholders, and to foster breast cancer research initiatives.

Patricia Ganz with the **University of California, Los Angeles,** received CBCRP support for the *APOS 5th Annual Conference.* The focus of this American Psychosocial Oncology Society (APOS) conference is to disseminate the results of the Institute of Medicine report—*Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs.* Released in October 2007, the report mandates changes in the delivery of quality cancer care to include psychosocial services (e.g., treatment decision-making, symptom management, and quality of life).

Community Impact Grants Funded in 2008:

Increasing the Voice of African American Women in Research
Kimlin Ashing-Giwa, Ph.D.
Beckman Research Institute of the City of Hope
Award Type: Joining Forces Conference
$25,000

Mindful Movement Program for Breast Cancer Survivors
Rebecca Crane-Okada, Ph.D. (co-PI)
Beckman Research Institute of the City of Hope
Holly Kiger, M.N. (co-PI)
WISE and Healthy Aging
Award Type: CRC-Pilot
$124,625 (COH) / $93,750 (WHA)

Provider Communication and Health in Breast Cancer Survivors
Sara Fernandes-Taylor
University of California, Berkeley
Award Type: Dissertation
$67,872

APOS 5th Annual Conference
Patricia Ganz, M.D.
University of California, Los Angeles
Award Type: Joining Forces Conference
$15,000

Adapting a Breast Cancer Education Program for South Asians
Beth Glenn, Ph.D. & Roshan Bastani, Ph.D. (co-PIs)
University of California, Los Angeles
Zul Surani (co-PI)
South Asian Cancer Foundation
Award Type: CRC-Full
$149,999 (UCLA)

Quality of Mammography Facilities Serving Vulnerable Women
Lauren Goldman, M.D.
University of California, San Francisco
Award Type: IDEA
$150,000

☑ **Reproductive Concerns and Depression among Younger Survivors**
Jessica Gorman
University of California, San Diego
Award Type: Dissertation
$35,492

Breast Cancer Risk Reduction in American Indian Women
Linda Navarro (co-PI)
Turtle Health Foundation
Marlene von Friederichs-Fitzwater, Ph.D. (co-PI)
University of California, Davis
Award Type: CRC-Planning grant
$10,000

Increasing Mammography Screening in Latinas with Diabetes
Christine Noguera, M.S. (co-PI)
Golden Valley Health Centers
Steve Roussos, Ph.D. (co-PI)
San Diego State Research Foundation
Award Type: CRC-Full
$493,666 (GVHC)/ $252,803 (SDSUF)

Nail Salon Workers: Chemical Exposures in the Workplace
Linda Okahara
Asian Health Services
Award Type: Joining Forces Conference
$25,000

Community Impact Grants Funded in 2008:

Latina Breast Cancer Survivors…Our Experience
Diana Tisnado, Ph.D. (co-PI)
University of California, Los Angeles
Brian Montaño, M.P.H. (co-PI)
Partnered for Progress
Award Type: CRC-Pilot
$168,421 (PFP)

Breast Cancer Clinical Trials Education Program
Georgia Sadler, Ph.D. M.B.A. (co-PI)
University of California, San Diego
Natasha Riley, M.A. (co-PI)
Vista Community Clinic
Vanessa Malcarne, Ph.D. (co-PI)
San Diego State, Research Foundation
Award Type: CRC-Full
$158,140 (UCSD) / $372,421 (VCC)/ $208,657 (SDSU)

An Ecological Study of Quality of Life in Low-Income Women
Yoshiko Umezawa, Ph.D.
University of California, Los Angeles
Award Type: Postdoctoral fellowship
$115,960

Community Breast Cancer Screening & Prevention Conferences
Jeffrey Weitzel, M.D.
Beckman Research Institute of the City of Hope
Award Type: Joining Forces Conference
$24,919

Neighborhoods and Obesity in Pre-Adolescent Girls: Part II
Irene Yen, Ph.D.
University of California, San Francisco
Award Type: IDEA–competitive renewal
$214,406

Etiology and Prevention: Finding the Underlying Causes

Overview:

Although our foundation of knowledge for the basic science aspects of breast cancer (tumor biology) 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 lifestyle factors associated with increased and decreased risk for breast cancer. However, the role of diet, exercise, family history, pregnancy, alcohol, hormone replacement therapy, and other factors remains controversial.

The CBCRP's **Special Research Initiatives** (SRI) seeks to increase knowledge of and create solutions to eliminate the environmental factors that cause breast cancer. This program was launched in April 2008, and we are in the process of soliciting Requests for Proposals (RFPs) and Requests for Qualifications (RFQs) across seven separate topics (e.g., Making Chemicals Testing Relevant to Breast Cancer and Toward a New Paradigm of Breast Cancer Causation and Prevention). The goals for the SRI are to foster coordinated, statewide efforts to explore innovative ideas and new theories; leverage California's unique and diverse geographic, population, and research resources; and undertake critical studies that significantly move these fields forward. More information about the SRI is available on our website, www.CABreastCancer.org/sri/.

In addition, the CBCRP continues to support the Etiology and Prevention priority issue though our established "core funding" program. CBCRP funding increased significantly in 2008 for the Etiology and Prevention topic with seven new grants this year compared to two in 2007.

Etiology Portfolio Summary:

Five grants investigate aspects of hormones in breast cancer, environmental or other external factors modulating hormone activity, and hormone therapy.

It is known that an increase in circulating estrogens in postmenopausal women increases a woman's risk of breast cancer. **Kristine Monroe** from the **University of Southern California** received IDEA funding to examine whether grapefruit consumption (whole grapefruit, fresh juice, bottled juice, frozen concentrate and grapefruit soda) will serve to increase endogenous estrogen levels. Dr. Monroe will recruit between 60 and 75 postmenopausal women for a 6-week feeding study. Grapefruit products are known to interfere with numerous medications, but the link to estrogen levels and breast cancer is not yet proven.

Up to 10 million single-nucleotide polymorphisms (SNPs) exist in the human genome and new technologies are emerging to determine their association with specific diseases. **Eunjung Lee,** also from the **University of Southern California,** will perform a case-control study within the California Teachers Study (CTS) cohort to associate genes, environmental exposures, and the risk for breast cancer. She proposes to examine 442 SNPs representing 30 candidate genes involved in estrogen and progesterone metabolism, transport and signaling. It is recognized that multiple genes are involved in these functions. An innovative aspect of this research is the examination of gene-environment interactions, where hormone replacement therapy (HRT) is the "environmental" exposure.

Reina Haque at the **Kaiser Foundation Research Institute** will investigate whether concomitant tamoxifen and antidepressant medication use increases the risk of recurrence and new primary tumors in women with early stage estrogen positive breast cancer. SSRIs (selective norepinephrine re-uptake inhibitors) antidepressants (e.g., Prozac and Paxil) are powerful inhibitors of cytochrome P450 (CYP) 2D6, a group of enzymes important in the metabolism of many drugs, including tamoxifen. The effect of antidepressants in this context would be to block to conversion of ingested tamoxifen to its active form, endoxifen, by the liver.

A possible link between organochlorine pesticide exposure and risk for breast cancer has received renewed interest lately with evidence that timing of

exposure with regard to breast development may be crucial to risk later in life. **Paul Mills** with **University of California, San Francisco** (Fresno Campus) will conduct a pilot/feasibility study on the impact of genetic variants and exposures to organochlorine pesticides among Hispanic women residing in the San Joaquin Valley, where exposure to agricultural pesticides is known to be very high. The research team will obtain and compare saliva samples from recently diagnosed cancer patients and non-cancer controls. The DNA from saliva will be genotyped and results analyzed with risk factor data obtained from a questionnaire to establish pesticide exposure. The genes and SNPs/polymorphisms to be studied were chosen by their association with organochlorine metabolism and detoxification.

Finally, **Daniel Donoghue** at the **University of California, San Diego,** received IDEA funding to understand the biological relevance of a SNPs in the Fibroblast Growth Factor Receptor (FGFR2) gene. The fibroblast growth factor receptor (FGFR) family has been found to play a role in the development of several types of cancers. The link to breast cancer comes from Dr. Donoghue's hypothesis that one or more of these novel SNP polymorphisms creates a binding site for an estradiol-responsive transcription factor, resulting in altered FGFR2 amounts or activity.

The other two funded grants represent diverse topics.

First, the Warburg hypothesis from the 1920s made the connection between cancer cells and their preferential, non-oxidative breakdown of glucose (glycolysis) compared to "healthy" cells that mainly generate energy from the more efficient oxidative breakdown pathway. Recently, Warburg's hypothesis has regained attention, especially with evidence that drug-induced changes in cell respiration via the mitochondria can kill cancer cells. A totally novel aspect of this deregulated metabolism in breast cancer is being studied by **Daniel Tamae** at the **Beckman Research Institute of the City of Hope.** In his dissertation project Mr. Tamae will focus on a glycolysis-generated, DNA adduct (i.e., DNA bonded to a cancer-causing chemical) called CEdG. These adducts result in DNA sequence mutations that can lead to deregulation of cellular function. The potential for CEdG as a novel breast cancer biomarker will be evaluated using analytical chemistry, biochemistry, and molecular biology approaches.

Second, folate (Vitamin B9) is needed to synthesize DNA bases, and folate deficiency has been implicated in neural tube defects leading to its recommended use as a supplement during pregnancy. However, folate also participates in cell pathways leading to DNA methylation. A major effect of increased DNA methylation in cancer is believed to be the "silencing" of normal tumor suppressor genes. **Teresa Marple** from the **University of California, Davis,** will investigate the positive correlation of increased dietary folate with breast cancer cell growth, tumor progression, and metastasis using a mouse model system. Results of this work might serve to question whether normal adults or cancer survivors should continue using folate as a supplement.

Etiology & Prevention Grants Funded in 2008

FGFR2 Signaling in Human Breast Cancer Cells
Daniel Donoghue, Ph.D.
University of California, San Diego
Award type: IDEA
$100,000

Antidepressant and Breast Cancer Drug Interactions
Reina Haque, Ph.D.
Kaiser Foundation Research Institute
Award type: IDEA
$163,083

Genes in Hormone Metabolism Pathway and Breast Cancer
Eunjung Lee, Ph.D.
University of Southern California
Award type: Postdoctoral fellowship
$134,996

Folate, DNA Methylation and Breast Cancer Metastasis
Teresa Marple, Ph.D.
University of California, Davis
Award type: Postdoctoral fellowship
$135,000

☑ **Pesticide and Gene Interactions in Latina Farm Workers**
Paul Mills, Ph.D., MPH
University of California, San Francisco
Award type: IDEA
$163,668

➔ **Grapefruit, Hormones, and Postmenopausal Breast Cancer Risk**
Kristine Monroe, Ph.D.
University of Southern California
Award type: IDEA
$244,106

Prognostic Implications of DNA Glycation in Breast Cancer
Daniel Tamae
Beckman Research Institute of the City of Hope
Award type: Dissertation
$67,060

Detection, Prognosis & Treatment: Delivering Clinical Solutions

Overview:

The detection, prognosis, and treatment of breast cancer represents a slowly evolving landscape. Information filtering in from hypothesis-driven basic science is screened for clinical relevance and slowly advanced along the 10+ year "critical path" for translation into practical uses. Better early detection and staging/prognosis for breast cancer remains a critical need. The use of combined imaging modalities is aimed at improving both sensitivity and selectivity to reduce unnecessary biopsies. Genetic profiling of tumors in patients continues to move in the direction of improved "individualized therapy." New tests are in the works to add to the existing two competing technologies on the market: Oncotype DX from Genomic Health Inc. of Redwood City, and MammaPrint from the Dutch firm Agendia. For example, a new 55-gene Breast Bioclassifier™ (University genomics, Inc. and ARUP) will be launched in late 2008 designed to classify ER-positive and ER-negative breast cancers into expression-based subtypes that more accurately predict patient outcome.

New molecularly-targeted therapies that began with the introduction of Herceptin® will require validation in the animal model and clinical setting. In addition, companion technologies to stratify patients to select those most likely to benefit from these expensive drugs are needed to maximize impact and avoid the unnecessary application of these expensive treatments. Advances in nanotechnology promise new methods for both cancer detection and tumor-specific delivery of drugs. However, some clinical scenarios, such as how best to stratify DCIS to determine treatment options, drug resistance, and metastasis to the brain still require more research efforts to make an impact on patient care.

The CBCRP funded 11 new grants in 2008 to advance our Detection, Prognosis & Treatment priority issue. Two of the CBCRP's research topics are represented in this section:

- Improving Detection and Diagnosis
- Innovative Treatment Modalities: Search for a Cure

Detection, Prognosis & Treatment Portfolio Summary

CBCRP funded two new translational research awards in 2008.

First, current management of DCIS (ductal carcinoma in situ) is characterized by over-treatment, since it has been difficult to identify which patients with DCIS will have recurrences, and might benefit from more aggressive therapy. Recent expression profiling and immunohistochemical studies have strongly suggested the presence of molecular subtypes in DCIS, which may parallel the distinct molecular subtypes known to exist for invasive tumors. **Thea Tlsty** at the **University of California, San Francisco** recently found a pre-malignant DCIS subtype with high risk for future malignancy. Expression levels for the p16, Cox-2, and Ki67 genes differentiated DCIS pre-malignant lesions that would either develop into invasive breast cancers or likely remain indolent. In their preliminary studies using archived DCIS samples where the patient outcomes are known, these DCIS molecular phenotypes predicted tumor events up to 10 years in advance. With CBCRP funding and using retrospective and prospective DCIS patient cohorts, Dr. Tlsty's team will expand and confirm these results. In addition, clinical and pathological parameters as well as other potential molecular markers, such as those in the apoptotic (cell death) pathways, will be studied. The overall goal is the development of a rapid, inexpensive prognostic clinical test within three years that will provide individualized risk information for all women diagnosed with DCIS.

Next, tamoxifen is a standard hormonal therapy agent in the adjuvant setting to prevent recurrences of hormone receptor positive breast cancer in premenopausal women and in postmenopausal women who cannot tolerate aromatase inhibitors. CYP2D6, which converts tamoxifen to its active metabolite endoxifen, has significant individual variations in its enzyme activity due to polymorphisms of its gene, ranging from non-functioning to hyper-functioning alleles. Recent studies suggest that patients who carry a non-functioning variant allele, such as

for CYP2D6, do not benefit much from the use of tamoxifen. However, results have not been consistent across separate studies. **Elad Ziv,** also from the **University of California, San Francisco,** is funded to provide further evidence that variation in genes affecting the metabolisms and action of tamoxifen will impact clinical outcomes. The research team will perform detailed analysis of genetic polymorphisms in CYP3A4, CYP3A5, and CYP2C9 enzymes and correlate these results with cancer recurrence in patients who were treated with tamoxifen for at least a year in the adjuvant setting. In addition, they will determine what factors might best determine whether a woman should elect to undergo genetic testing (through questionnaire in consenting patients before and after an education session about genetic testing and CYP2D6 testing), and whether women who receive a genetic test alter their decision to remain on tamoxifen.

The use of chemotherapy and targeted therapies (e.g., Herceptin®) has evolved with the advent of more advanced tests to predict patient sensitivity, aimed to maximize benefit of therapeutic response and outweigh potential side effects. Both Herceptin® and anthracylines (e.g., Doxorubicin, trade name Adriamycin) are associated with cardiac toxicity as the major side effect. **Michael Press** at the **University of Southern California** was funded for an IDEA-competitive renewal to continue evaluating the role of TOP2A gene amplification in predicting the benefit of Adriamycin in the adjuvant treatment of HER2-positive breast cancer. The TOP2A gene encodes topoisomerase II-alpha enzyme, which is a known target of Adriamycin chemotherapy. TheTOP2A gene is close to the HER2 gene on Chromosome 17, such that in about 35 percent of diagnosed Her-2 positive patients they are co-amplified. The results of Dr. Press' preliminary studies have been presented at the San Antonio and ASCO meetings. As a result, there has been a shift away from using Adriamycin for HER2-positive patients receiving Herceptin®, since this research indicates no additional clinical benefit. In January the FDA approved a new genetic test (TOP2A FISH pharmDx™ from Dako in Denmark) for testing TOP2A gene amplification.

Five newly funded grants focus on imaging technologies or the use of imaging to monitor therapy.

All the major imaging technologies (X-ray, MRI, PET, ultrasound, optical) have limitations when used alone, so there is considerable research to improve or combine modalities to mitigate their individual drawbacks. **Rebecca Rakow-Penner** from **Stanford University** received funding for dissertation research to combine the anatomic high resolution of MRI with the physiologic (blood flow differences in tumors) detection abilities or near-infrared optical. Ms. Rakow-Penner will use a technique called Blood Oxygen Level Dependent (BOLD) contrast to enhance breast tumor detection. Traditionally, this technique has been used to study the brain, but has the potential in cancer to verify increases in tumor metabolism and angiogenesis. In addition, BOLD has the potential to monitor therapy, particularly for angiogenesis-targeting drugs, such as Avastin®. However, the use of BOLD will require patients to breathe a mixture of oxygen and carbon dioxide during imaging.

Next, achieving consistency and accuracy in "reading" mammograms and MRI images is a challenge for radiologists, so computer assisted diagnosis (CAD) is an active area of research. CAD acts like a "spell-checker" and assists radiologists by highlighting suspected tumor sites in the breast for a second review. CAD has been in use for mammography since 1998, but remains more in the developmental stages for MRI. **Ke Nie** at the **University of California, Irvine,** will use automated computer algorithms to simulate the entire procedure of radiologists' interpretation for breast MRI. This computer system will detect and segment suspicious regions (possible lesions), then analyze their morphologic and kinetic features. A full panel of features to allow differentiation between malignant and benign lesions will be established by studying a unique database of 250 malignant and 150 benign cases of breast cancer.

Next, although the use of PET (positron emission tomography) probes is not in routine clinical use, the need for such agents is well recognized. For example, in HER2 diagnosis it would helpful to use a detection agent that directly binds to the receptor to report on its abundance, as opposed to the current strategy of assessing gene amplification as an indirect marker of abundance. *In vivo* animal work has shown that tumors not categorized as HER2-positive by immunohistochemistry or FISH may still have significant tumor uptake of radiolabeled Herceptin® and show response to drug therapy. It is also well known that the expression patterns of tumor metastases may differ from that of the primary, suggesting that some patients with HER2-negative primary tumor may harbor HER2-positive metastatic disease. **Zhen Cheng** from **Stanford University** is funded to develop *Novel Small Proteins for PET Imaging of Breast Cancer.* The aim of this project is to develop a 2-helix protein-based PET probe for imaging HER2 status in breast cancer in patients

and eventually translate this technique into a clinical application. With this approach, the HER2 probes will be much smaller than antibody-based probes, which should greatly improve tumor penetration and imaging quality. Further, PET has the potential to monitor therapy by detecting whether drugs or other tumor-targeting strategies actually "home in" on sites of tumor growth and metastasis.

Next, on the related topic of HER2 imaging, **Shannon Sirk** with the **University of California, Los Angeles,** will evaluate the clinical uses of a smaller version of a HER2 antibody. This anti-HER2 cys-diabody is one-sixth the size of Herceptin®, thus it should have enhanced tumor-penetrating ability and reduce background noise for tumor imaging. In addition, the anti-HER2 cys-diabody may have applications for the nanoparticle delivery of drugs to tumors, or be useful in treating patients with Herceptin® -resistant tumors.

Finally, **Joseph Wu** also at **Stanford University** is using a PET approach to test the feasibility of combined stem cell-based and immune therapy for breast cancer. Using mouse models, Dr. Wu and his team will use embryonic endothelial cells and natural killer immune cells. The natural killer cells are expected to exhibit a localized cytotoxic effect, and the embryonic endothelial cells will be genetically engineered with an enzyme to convert a systemically delivered prodrug at the site of tumor growth into an active cytotoxic agent. The combination of bioluminescence and PET in the CBCRP-funded IDEA grant will allow Dr. Wu to optimize the use of both cell types to advance this novel, potentially less-toxic, cell-based treatment strategy.

Three additional grants cover a wide range of topics.

First, as most breast cancer patients are aware, there are no treatment options for metastasis to the brain, which occurs in about 35 percent of patients diagnosed with advanced disease. Sadly, the incidence of brain metastasis is increasing as overall disease survival time improves. Immunotherapy with cytotoxic T lymphocytes injected directly into intracranial tumors has shown promise in preclinical models of primary brain cancer, glioma, and is currently under active clinical investigation in this context. **Barbara Mueller** from the **Sidney Kimmel Cancer Center** plans to extend this treatment strategy to secondary brain tumors in breast cancer. They will sensitize T lymphocytes (alloCTL) from donors using special brain-tropic human breast tumor cell lines, analyze the MHC (major histocompatibility complex) functionality of these cells, then assess tumor migration and killing activity in mice after intracranial injection of alloCTL. The potential for this novel approach is due to MHC molecules not being generally expressed on normal brain cells, but present on primary brain tumor cells and metastatic breast tumor cells.

Tissue Factor (TF) is the cellular receptor and co-factor of factor VIIa that triggers blood coagulation. However, independent from its role in coagulation, TF also mediates complex intracellular pathways that are believed to be linked to tumor cell growth and survival. **Wolfram Ruf** from **The Scripps Research Institute** has developed a novel antibody that selectively blocks TF signaling. They plan to test the hypothesis that TF signaling synergizes with epidermal growth factor signaling to promote a more aggressive tumor phenotype. They will evaluate the efficacy of anti-TF therapy when combined with standard chemotherapies and/or anti-angiogenesis therapy (Avastin®).

Finally, macrophages are prominent in tumor tissues, comprising up to 80 percent of the cell mass in breast carcinomas. Evidence suggests that tumor-associated macrophages (TAMs) have been "reprogrammed" by cancer cells to augment tumor cell proliferation and metastases by secreting growth factors. These TAMs provide an ideal, but underutilized, target for anti-cancer therapies. Moreover, legumain, a member of the endopeptidase (i.e., cleave peptide bonds within a protein chain) family, is selectively expressed on TAMs at higher levels. **Gaurav Sarma** at **The Burnham Institute for Medical Research** will explore the potential of targeting TAMs with nanoparticles by altering their shape and attaching a legumain antibody to their surface. The goal is to "design" nanoparticles containing chemotherapeutic compounds as a novel strategy targeting TAMs and sparing other macrophages in the body.

Better early detection and staging/prognosis for breast cancer remains a critical need.

Detection, Prognosis & Treatment Grants Funded in 2008

Novel Small Proteins for PET Imaging of Breast Cancer
Zhen Cheng, Ph.D.
Stanford University
Award Type: IDEA
$261,849

Treating BC Brain Metastasis with Cytotoxic Lymphocytes
Barbara Mueller, Ph.D.
Sidney Kimmel Cancer Center
Award Type: IDEA
$292,412

Development of a Breast MRI Computer-Aided Diagnosis System
Ke Nie
University of California, Irvine
Award Type: Dissertation
$76,000

Topoisomerase-IIa as a Predictor of Anthracycline Response
Michael Press, M.D.
University of Southern California
Award Type: IDEA- competitive renewal
$407,500

Functional Breast MRI with BOLD Contrast
Rebecca Rakow-Penner
Stanford University
Award Type: Dissertation
$76,000

Inhibition of TF Signaling as Novel Breast Cancer Therapy
Wolfram Ruf, M.D.
The Scripps Research Institute
Award Type: IDEA
$284,250

☑ **Nanotherapy for Breast Cancer Targeting Tumor Macrophages**
Gaurav Sarma, Ph.D.
The Burnham Institute for Medical Research
Award Type: Postdoctoral fellowship
$90,000

Novel Anti-HER2 Fragments for Better Detection and Therapy
Shannon Sirk
University of California, Los Angeles
Award Type: Dissertation
$76,000

☑ **Stratifying DCIS Biopsies for Risk of Future Tumor Formation**
Thea Tlsty, Ph.D.
University of California, San Francisco
Award Type: Translational research
$750,000

Imaging of Novel Stem Cell Therapy Targeting Breast Cancer
Joseph Wu, M.D., Ph.D.
Stanford University
Award Type: IDEA
$239,243

Genetics of Tamoxifen Response
Elad Ziv, M.D.
University of California, San Francisco
Award Type: Translational research
$803,111

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 coordinate migration, proliferation, and apoptosis (cell death) over space and time. In cancer progression these same processes become deregulated, initially at the genetic level that leads to the physiological changes associated with malignancy. An emerging paradigm links progenitor 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. In this context non-malignant mammary progenitor cells form breast-like acinar structures resulting in growth arrest and a polarized morphology, while tumor-like progenitor cells proliferate as a heterogeneous, disorganized mass. If this paradigm proves correct, then only a small fraction (1-2%) of cells in a tumor mass retain stem/progenitor cell properties, and these "cancer stem cells" must be selectively targeted to achieve an effective eradication of the disease. Current therapies where "success" is typically measured by tumor shrinkage appear to mainly target the non-stem cell population in a tumor. Thus, these therapies extend survival without impacting the final outcome of the disease.

The CBCRP funded 9 new grants in 2008 to advance research knowledge in our Biology of the Breast Cell priority issue. 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 Portfolio Summary

Two newly funded grants focus on metastasis.

First, chemokines are critical mediators of leukocyte cell migration during routine immune surveillance, lymphocyte development, homing, and inflammation processes. In a cancer context, chemokines and their receptors have been implicated in metastatic events by directing the migration of tumor cells. The chemokine receptors CXCR4 and CXCR7 are not expressed on normal breast epithelia, but they are frequently expressed on breast cancer cells, and there is preferential metastasis of breast cancer cells to sites where their ligand, called CXCL12, is constitutively expressed. **Morgan O'Hayre** from **University of California, San Diego,** is being support for her dissertation research to study inhibitors of CXCR4 and CXCR7 chemokine receptors to dissect their link to breast cancer. She will study survival and proliferation pathways (e.g., Akt, ERK1/2, NF-κB) for their contribution to chemokine-dependent metastasis.

Next, Twist is a protein that has been shown to have a role in promoting epithelial-mesenchymal transition (EMT) in breast cancer cells. Epithelial cells are non-migratory cells, while their genetic and phenotypic transition to mesenchymal cells results in a loss of cell-to-cell adhesion with a gain in motility typical of cancer cells. **Janine Low-Marchelli,** also at the **University of California, San Diego,** will catalog genes regulated by Twist, validate them for relevance to breast cancer, and examine their functional role (mechanistic properties) at the cellular and tissue level. Defining the molecular targets of Twist could lead to new prognostic tools and drugs.

Three newly funded grants focus on cell growth, signaling, and survival processes. First, although targeted therapeutics for the HER family of receptors are in clinical use, additional basic science studies on these receptors are needed to develop new strategies for overcoming resistance to therapy commonly seen in the clinic. Since HER receptors are membrane proteins, they are difficult to produce and study in biochemical systems due to their insolubility. **Paul Henderson** from the **University of California, Davis**, is developing a new biotechnology application—single step assembly and formation of nanolipoproteins (NLPs) capable of solubilizing membrane-bound, HER receptors associated

with breast cancer. They will adapt a technology, called cell-free protein expression, such that both NLPs and breast cancer-related receptor proteins are produced. The end result will be spontaneously formed, water-soluble NLPs with HER receptors in the center. This resulting NLP disc mimics the normal cell surface, allowing previously impossible functional studies on HER growth receptors in a cell-free system.

Next, the PI3K/Akt signaling pathway is pivotal for cell growth, survival, and proliferation. Since it can block apoptosis (programmed cell death), and thereby promote cell survival, Akt has been implicated as a major player in many types of cancer. PI3K serves to activate Akt, while the tumor suppressor PTEN removes Akt from its membrane-bound state to reduce activity. **Holly Hantz** at the **University of California, Berkeley,** will study the mechanism by which 3,3′-diindolylmethane (DIM), a metabolic conversion product of a dietary component in Brassica vegetables (e.g., broccoli), inhibits the PI3K/Akt pathway. DIM is in clinical trials as a treatment for numerous forms of cancer, and its relatively nontoxic profile, classification as a "natural product", and low cost ($10.98 for 30, 100mg tablets from the vitaminshoppe.com) makes it an appealing alternative to conventional chemotherapeutics.

Finally, anterior gradient 2 (AGR2), originally identified in the frog *Xenopus*, is a cancer cell biomarker. Elevated levels of AGR2 are known to increase the metastatic potential of cancer cells, but conditions leading to increased expression of AGR2 are not well understood. **Mikhail Geyfman** from the **University of California, Irvine,** will test whether the AGR2 gene affects the behavior of normal breast epithelial cells by either removing or overexpressing the AGR2 gene in mice. Then, he will determine the effect of reducing of AGR2 gene expression on tumor cell proliferation and invasion. Additionally, changes in ER (estrogen receptor)-signaling pathways and the activity of several downstream ER-regulated genes will be examined using molecular analysis.

Tumor progression and novel breast cancer genes are the focus of four newly funded grants.

More research is needed on the normal breast biology to provide insight into the origins of cancer, especially with respect to stem/progenitor cell renewal. The Wnt/beta-catenin signaling pathway has been the subject of much interest with respect to its role in embryology, stem cell biology, and mammary tumors. **Bingnan Gu** at the **University of California, Irvine,** will study the Pygopus 2 (Pygo2) gene, an activator of the Wnt pathway. Dr. Gu plans to determine whether Pygo2 acts to control beta-catenin signaling through epigenetic modifications. Pygo2 is a potential regulator of methylation and acetylation of histones, a group of small proteins that package long DNA molecules into repetitive units inside the cell nucleus. Differences in DNA packaging influence gene expression on a global scale.

Ubiquitin is a small protein that occurs in all cells, and its main function is to "mark" other proteins for destruction (proteolysis) in a cell structure called the proteosome. Increased intracellular proteolysis is a characteristic of cancer, and a proteosome inhibitor called bortezomib (Velcade®) is an approved drug for the treatment of multiple myeloma. However, proteosome inhibitors for other cancers are still in clinical testing. **Stefan Grotegut** at the **Sidney Kimmel Cancer Center** will use a novel protein microarray chip developed by Invitrogen Corp. to identify known and unknown targets of the ubiquitination system—comparing primary and metastasized breast tumor samples. Such information may identify novel diagnostic/prognostic markers as future therapeutic targets.

Next, p53 is a well established tumor suppressor, and either loss of p53 function or defects in the associated pathways, are critical in allowing genetic mutations to accumulate within tumor cells. **Aaron Boudreau** from the **Lawrence Berkeley National Laboratory** will study 14-3-3sigma, a direct transcriptional (gene regulatory) target of the p53 tumor suppressor. 14-3-3sigma is highly expressed in "basal-like" breast cancers and contributes to malignant progression by modulation of motility and invasiveness. Mr. Boudreau will identify 14-3-3 sigma interacting partner proteins and evaluate whether these are involved in regulation of motility and invasion.

Finally, the maternal leucine zipper kinase (MELK) gene is a potential marker of proliferating mammary epithelial progenitor cells that are highly expressed in many human cancers, including human breast cancer. **Robert Oshima** from **The Burnham Institute for Medical Research** will determine if loss of MELK expression can block the effects of activation of the HER2 growth signaling pathway. This project employs genetically engineered mouse models to assess the growth dependence of MELK expression for HER2-positive tumors, thus advancing MELK as a candidate for additional studies as a potential therapeutic target.

Biology of the Breast Cell Grants Funded in 2008

Tumor Suppressor 14-3-3sigma in Breast Cancer Progression
Aaron Boudreau
Lawrence Berkeley National Laboratory
Award type: Dissertation
$63,334

Role of Estrogen-modulated Protein AGR2 in Breast Cancer
Mikhail Geyfman
University of California, Irvine
Award type: Dissertation
$71,491

Global Analysis of Protein Ubiquitination in Breast Cancer
Stefan Grotegut, Ph.D.
Sidney Kimmel Cancer Center
Award type: Postdoctoral fellowship
$135,000

Regulation of Breast Stem-Progenitor Cell Chromatin by Pygo2
Bingnan Gu, Ph.D.
University of California, Irvine
Award type: Postdoctoral fellowship
$135,000

Dietary Metabolite Inhibition of Breast Cancer Cell Survival
Holly Hantz
University of California, Berkeley
Award type: Dissertation
$76,000

Nanolipoproteins to Study Breast Cancer Growth Receptors
Paul Henderson, Ph.D.
University of California, Davis
Award type: IDEA
$99,000

Dissecting the Role of Twist in Breast Cancer Metastasis
Janine Low-Marchelli
University of California, San Diego
Award type: Award type: Dissertation
$76,000

Chemokine Receptor Signaling in Breast Cancer
Morgan O'Hayre
University of California, San Diego
Award type: Award type: Dissertation
$74,660

Maternal Embryonic Leucine Zipper Kinase in Mammary Tumors
Robert Oshima, Ph.D.
The Burnham Institute for Medical Research
Award type: IDEA
$286,500

2008 CBCRP Funding by Institution

The following 22 California research institutions and community organizations were awarded new CBCRP funding in 2008. Some community collaborative (CRC) grants were structured either as separate awards that are split between institutions or as sub-contracts (shown at bottom of page).

Institution	# Awards	Amount
Asian Health Services (Oakland)	1	$25,000
Beckman Research Institute of the City of Hope (Duarte)	4	$241,604
The Burnham Institute for Medical Research (La Jolla)	2	$376,500
Golden Valley Health Centers (Merced)	1	$493,666
Kaiser Foundation Research Institute (Pasadena)	1	$163,083
Lawrence Berkeley National Laboratory	1	$63,334
San Diego State University	2	$461,460
The Scripps Research Institute (La Jolla)	1	$284,250
Sidney Kimmel Cancer Center (San Diego)	2	$427,412
Stanford University	3	$577,092
University of California, Berkeley	2	$143,872
University of California, Davis	3	$244,000
University of California, Irvine	3	$282,491
University of California, Los Angeles	5	$525,380
University of California, San Diego	5	$444,292
University of California, San Francisco	5	$2,081,185
University of Southern California	3	$786,602
Vista Community Clinic	1	$372,421
WISE & Healthy Aging (Santa Monica)	1	$93,750

These community groups and organizations received funding as sub-contracts from the indicated institutions:

Partnered for Progress ..... $92,106 (UCLA)
South Asian Cancer Foundation ..... $55,000 (UCLA)
Turtle Health Foundation ..... $4,626 (UC Davis)

2008 CBCRP Evaluation Process and Review Committees

The CBCRP thanks the participants in our 2008 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 in a "study section" format 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 does not review or vote, but represents the California advocacy community. The observer gains insight into our process and provides feedback to the Program. 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. In contrast, the CBCRP uses 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 have the highest career development potential. 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. Applications in the upper two-thirds of average scientific merit are rated by the CBCRP's advisory council for programmatic responsiveness. 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 & Translational Research Award), career plan/mentoring (dissertation, postdoc), or dissemination and translation potential (CRC)

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

CRC-Sociocultural and CRC Concept Paper Review Committees

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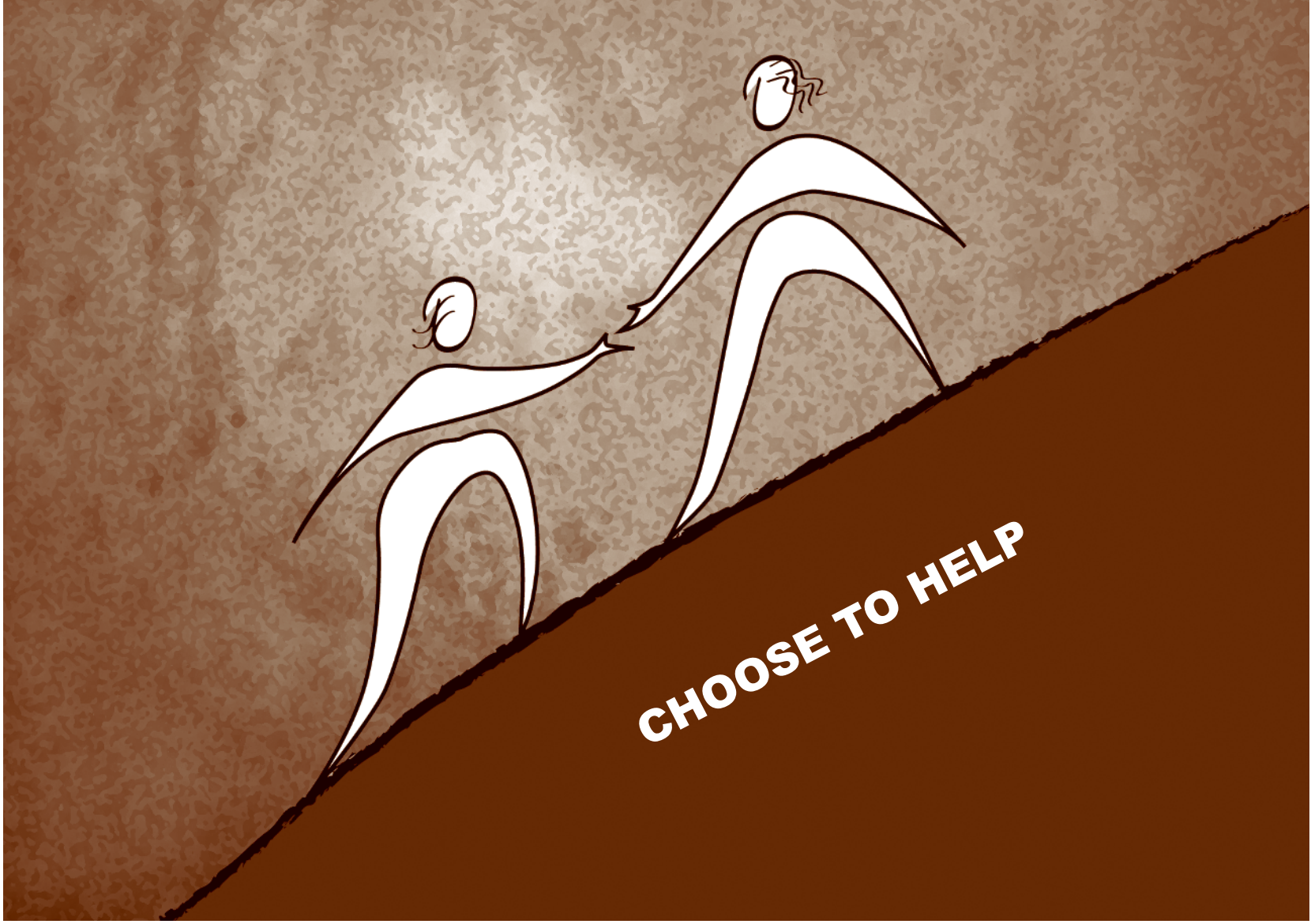

This year nearly 20,000 Californians will be diagnosed with breast cancer

This Tax Season, Choose to Help MAKE A DIFFERENCE IN THE FIGHT AGAINST BREAST CANCER

How?

You can help us conquer breast cancer in your community with a contribution to the California Breast Cancer Research Fund on your state income tax form 540. Your contribution is automatically tax deductible for the following year, and the money goes directly to the California Breast Cancer Research Program to support new approaches to diagnose, treat, and prevent breast cancer.

Previous contributions have supported all or part of 45 grants investigating critical areas of breast cancer research, including:

- Finding extremely early genetic changes that can be used to eliminate cancer cells before they become tumors
- Developing targeted therapies to block breast cancer from spreading to other organs
- Exploring the potential of natural products in preventing and treating breast cancer
- Improving support networks and empowering breast cancer patients within the healthcare system

We need your help to advance farther and faster against the disease.

You can see a full list of research supported by California Breast Cancer Research Fund contributions at endbreastcancer.org. Join us in our fight!

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