



2004 CBCRP Cycle X Awards Compendium

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Introduction

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 causes, prevention, sociocultural aspects, biology, detection, and treatment of breast cancer. With these new awards we are **investing over \$14.7 million for research projects being performed at 27 institutions across the state**, including universities both public (e.g., University of California campuses) and private (e.g., Stanford University), national laboratories (e.g., Lawrence Livermore National Laboratory), research institutes (e.g., The Burnham Institute), medical centers (e.g., Long Beach Memorial Medical Center), and community organizations (e.g., Mendocino Cancer Resource Center).

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

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

This is our tenth year (or cycle) of grant funding, **and through 2004 we have awarded nearly \$165 million to fund 611 research projects**. The CBCRP is administered by the University of California, Office of the President, in Oakland. Our overall objectives, strategies, and priorities are developed with the assistance of a volunteer advisory Council, which also makes recommendations on the applications to be funded. The Council consists of 16 members: five are representatives of breast cancer survivor/advocacy groups; five are scientists/clinicians; two are members from nonprofit health organizations, one is a practicing breast cancer medical specialist, two are members from private industry, and one is an *ex officio* member from the State of California, Department of Health Services Breast Cancer Early Detection Program: Every Women Counts.

The Goals of Our Research Funding

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

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

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

- Respond to feedback on breast cancer research needs and **expectations of the CBCRP** as identified by scientists and the public in California

Additionally, we utilize several award types that:

- Encourage multi-disciplinary, collaborative, and community-based **participatory research**
- Allow researchers to explore speculative, **“high reward” opportunities**
- Bring new researchers into breast cancer
- Focus on **underserved communities**
- **Encourage special topics** not well covered by other funding agencies

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

CBCRP Funding Changes for 2005

We recently completed a three-year priority-setting process during which we asked ourselves, “How successful were we at funding breast cancer research that met our stated goals?” We observed certain of our research topics, such as *Health Policy & Health Services*, *Etiology* (which we revised to focus on environmental and lifestyle issues), and *Racial & Ethnic Differences in Breast Cancer* attracted very few applications. These were topics where California offered tremendous opportunities, but we concluded the conventional style of grant funding did not address very well. In addition, despite our attempts to stimulate collaborative, translational, and cross-disciplinary projects, the CBCRP was funding few grants in these areas. Some of our career development award types received little interest. Finally, despite our best intentions, it was apparent that our larger innovative grant applications (STEPs) were not true “high risk-high reward” projects. These issues limited us in fulfilling the CBCRP’s mission.

In order to maximize our impact and build on our strengths, the CBCRP and our advisory Council have instituted substantial changes to our research grant program starting next year in Cycle 11. We are taking two paths to support critical breast cancer research in California. First, the CBCRP will set aside 30 percent of our funding for the next five years to tackle research questions that California is uniquely positioned to address. Through an intensive evaluation, we identified the following critical research topics: (1) defining the influence of the **environment and lifestyle** on breast cancer and (2) uncovering the reasons for the **unequal burden (disparities)** of breast cancer. Over the next year, we will convene a task force comprised of researchers and advocates to identify the knowledge gaps and available California resources in these areas. With the help of the task force, we will determine how California’s resources can be leveraged to make the biggest leaps forward in tackling breast cancer and launch high-impact program initiatives. At present **we are not soliciting grant applications for these initiatives**.

The remaining 70 percent of our future research funding will support traditional grant applications. We are focusing our “core funding” efforts in the areas of innovative research, career development, and community participation. The CBCRP award types will now include four categories:

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

We will no longer offer the following award types: RFA, STEP, Translational Research Collaborations (TRCs: both Pilot & Full Awards), Scientific Perspectives Research Collaborations (SPRCs, both Pilots and Full Awards), New Investigator, Career Enrichment, Mentored Scholar, and Training Program.

The CBCRP Funding Process

In this Compendium, we present the outcome of our 2004 grant application review and funding process. In 2004 we received 232 grant applications in response to our “call” for new research on breast cancer. These applications were reviewed and scored by our out-of-state scientific and advocate reviewers. Our review committee membership lists and the review process are described at the end of this booklet. After the peer review scores those applications having sufficient scientific merit were rated by our advisory Council for responsiveness to stated CBCRP programmatic criteria. The end result is that the CBCRP’s advisory Council balances the scientific merit and programmatic ratings to arrive at a funding recommendation for each application. Thus, the successful applicant has responded both in terms of presenting a high quality research project and by meeting the interests of CBCRP stakeholders.

The Outcome

Below and in the sections to follow are summaries, discussions, and listings of newly funded CBCRP grants for 2004 including:

- Grant applications and new awards shown by CBCRP research topics and award types
- Highlights of 2004 funding
- Portfolio summary, discussion, and list of grants for our Priority Issues and key topics
- Funded California institutions
- Description of the review process and review committee listings

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

Overall CBCRP Funding in 2004

- Applications received = **232**
- Applications judged responsive by peer reviewers and receiving merit scores = **223**
- Applications offered funding = **43**
- Success rate = **18.5%**
- Grants accepted and awarded = **42**
- Community research planning grants awarded in 2004 = **3 (\$30,000)**

Total for new grants awarded in 2004 = \$14,719,446
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2004/Cycle X Funding Highlights

- Three awards to **community groups collaborating with traditional researchers** address health care access and support for underserved rural communities and peer mentors to facilitate participation in clinical trials.
- Eight grants expand our **knowledge of normal breast biology**, development, function, aging, and separate abnormal breast structures from normal ones. These projects lay the groundwork for explaining the source of breast cancer and how **normal breast biology** might be influenced to prevent breast cancer.
- Eight awards focus on **etiology and prevention**, including a study on cancer in younger women and prevention strategies based on phytochemicals, green tea, and grape seeds.
- Two grants investigate the underlying reasons behind **racial and ethnic disparities** associated with breast cancer.
- Eight awards deal with **sociocultural/psychological issues** related to underserved rural communities, survivorship issues, and psychological factors.
- Ten grants further our understanding of **tumor biology**, especially the process of metastasis.

- Five projects explore novel methods to **detect breast cancer and develop novel approaches for treatment**.
- One award focused on **health services communication** between oncologists and acupuncturists.
- Twelve projects for **innovative, exploratory, and high-risk/high reward research** projects push boundaries, challenge existing paradigms, and initiate new research programs.
- Thirteen awards provide opportunities in **career development** at the levels of graduate and postdoctoral training. These researchers bring fresh thinking to their respective disciplines.
- Seven grants in **special-topic RFAs**, which we have identified as under-funded, allow the CBCRP to maximize its overall impact in breast cancer research
- Ten projects involve **collaborative teams** that include community groups and researchers, or cross-disciplinary efforts between researchers



- **Six awards are of special interest**, because they are funded, in part, by revenue from the **California State Income Tax Check-off**. These grants are highlighted in the following sections.

- **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. Faith 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 the annual Faith Fancher Research Award. The recipient of the inaugural Faith Fancher Research Award is **Annette Stanton, Ph.D.**, at the **University of California, Los Angeles**, for her project, *Living Well with Advanced Breast Cancer: a Predictive Model*.

2004 Applications and Awards by CBCRP Research Topics

Research topic	# Applications	# Grants Awarded	Awarded Amount
Community Impact			
Health Policy & Health Services	9	1	\$89,728
Sociocultural, Behavioral, & Psychological	28	8	\$2,800,709
Disparities	10	2	\$190,000
Etiology & Prevention			
Etiology	7	3	\$1,052,287
Prevention and Risk Reduction	22	5	\$2,849,376
Detection, Prognosis, and Treatment			
Imaging, Biomarkers, & Molecular Pathology	11	2	\$1,436,996
Innovative Treatments	33	3	\$748,352
Biology of the Breast Cell			
Biology of the Normal Breast	22	8	\$1,605,672
Pathogenesis	81	10	\$3,916,353

2004 Applications and Awards by CBCRP Award Types

Award Type	# Applications	# Grants Awarded	Award Amount
Collaboration awards:			
Community (CRC)	15	3	\$386,132
Translational (TRC)	21	5	\$2,578,242
Sci. Perspectives (SPRC)	4	2	\$2,066,496
Total Collaboration	40	10	\$5,030,870
Investigator-initiated Awards:			
RFA	27	7	\$6,465,565
STEP	51	4	\$1,143,088
IDEA	31	8	\$1,005,521
Total Investigator-initiated	109	19	\$8,614,174
Career Development Awards:			
Dissertation	10	4	\$234,713
Postdoctoral	50	9	\$809,716
New Investigator	13	0	0
Career Enrichment	1	0	0
Total Career	74	13	\$1,044,429

Description of Award Types Funded in 2004

- **Community Research Collaboration (CRC) Award:** Brings community organizations—such as breast cancer advocacy organizations, community clinics, or organizations serving minority women—together with experienced scientists to investigate breast cancer problems that are important to that community, using culturally-appropriate research methods.
- **Translational Research Collaboration (TRC) Award:** Generates creative, translational research partnerships from several fields of science to push laboratory discoveries towards practical uses.
- **Scientific Perspectives Research Collaboration (SPRC) Award:** Encourages researchers from other disciplines to team up with breast cancer researchers and apply novel tools, insights, and ideas.
- **Requests for Applications (RFA):** Supports full-scale research projects that encourage creative efforts in under-represented topics.
- **STEP Award:** Allows researchers that have done innovative preliminary research to develop their project further, as a “STEP” towards getting funding for a full-scale study.
- **Innovative Developmental and Exploratory Award (IDEA):** Funds promising high-risk/high-reward research to road test innovative concepts.
- **Postdoctoral Fellowship Award:** For advanced training under a breast cancer research mentor.
- **Dissertation Award:** Supports the completion of dissertation research by masters or doctoral candidates.

The Community Impact of Breast Cancer: The Social Context

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

The CBCRP's focus on the **Community Impact of Breast Cancer** has changed during the first ten years of the program, and a survey of grants funded in the early years would show a different profile from those funded in our last two or three cycles. In the **psychosocial and behavioral** areas we are seeing more applications that attempt to find biological correlates of the emotional, psychological, and spiritual states of breast cancer patients. While the connection between severe emotional trauma and subsequent physical health has long been known, investigators are now going far beyond broad descriptions of these associations to looking at things such as stress hormones and immune system functioning, biological responses to cognitive therapy, and mapping brain activity and impairment. Such work can begin to measure the impact of psychological interventions along pathways that lend themselves to clinical interpretation, to strengthening interventions, and to improve health outcomes. In the **health services** area, our applications deal with topics that used to be largely outside of traditional research concerns. These include acupuncture, use of herbal remedies, return to work issues, and patient-oriented studies such as the impact of lymphedema on quality of life.

Funding Data:

		<u>Proportion of Total</u>
Community Impact grants awarded in 2004:	11	26%
Funded amount:	\$3,080,437	21%
Community research planning grants:	3	
Funded amount:	\$30,000	

Community Impact Portfolio Summary:

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

- **Health Policy and Health Services: Better Serving Women's Needs**
- **Disparities: Eliminating the Unequal Burden of Breast Cancer**
- **Sociocultural, Behavioral, and Psychological Issues Relevant to Breast Cancer: The Human Side**

In the **Health Policy and Health Services** topic we funded a postdoctoral fellowship to **Michael Johnston** at the **University of California, Los Angeles**. Dr. Johnson will undertake a project to enhance health services for breast cancer patients by developing an educational program that will empower acupuncturists to initiate care coordination with oncology clinicians treating the same patients. This

research attempts to bridge gaps in care coordination and to enhance collaboration and communication among acupuncturists and oncology providers for this widely used treatment.

Increasingly within the last decade scientists have joined the traditional concepts of epidemiology, whereby differences between populations are examined for clues to explain differences in disease and disease outcomes, with the techniques of molecular biology. In the **Disparities** topic the CBCRP funded two such grants in 2004. **Vinona Bhatia** at the **University of California, San Francisco**, will evaluate the different subtypes (called isoforms) of estrogen and progesterone receptors (proteins that bind estrogen and progesterone to cells) of different ethnic groups to determine if the distributions of these isoforms account for varying aggressiveness of cancers and in survival. This study will focus on defining characteristics of a multiethnic population of low socioeconomic status, and which had similar treatment at San Francisco General Hospital. **Koie Chen** also at the **University of California, San Francisco**, will look for differences in breast cancer mortality between African American and Caucasian women by comparing chromosomal abnormalities from breast tumors in the two ethnic groups.

In the **Sociocultural, Behavioral, and Psychological** topic we funded five career development and investigator-initiated grants, all of which go beyond typical psychological assessments to also consider the physical and psychobiological aspects of breast cancer. **David Wellisch** at the **University of California, Los Angeles**, received IDEA funding to look at women at high-risk for breast cancer, who have lost a sister and/or a mother to breast cancer and for whom grief has been possibly traumatic, to see whether such grief confers increased psychobiological risk for breast cancer. Using fMRI brain scanning and salivary cortisol levels, Dr. Wellisch will study whether grief-driven activation of the brain's emotion centers leads to cortisol dysregulation. The effects of the chronic stress of traumatic grief, brain activation, and cortisol dysregulation may be a pathway to immune system compromise and higher risk for breast cancer. This model has never before been integrated and tested. **Annette Stanton** also at the **University of California, Los Angeles**, received an IDEA grant to examine the quality of life of women with advanced breast cancer. Using established questionnaires, interviews, and a biological marker of stress (cortisol-obtained through saliva collection), Dr. Stanton will examine factors such as hope, approach-oriented involvement in goal-related activities, mood, and quality of life in 140 women with advanced disease. She hypothesizes that active engagement in pursuing cherished life goals will contribute to positive outcomes during the study. Hopefully, this research will help develop interventions to bolster well-being and health of women with advanced breast cancer. **Hillary Klonoff-Cohen** at the **University of California, San Diego**, will investigate the role of sex hormones (menstrual phase at time of surgery), psychological distress, cortisol, and natural killer cell activity (NKCA) in predicting subsequent breast cancer. The hypothesis is that scheduling breast cancer surgery for the luteal phase of the menstrual cycle, low levels of emotional distress, and good NKCA will improve breast cancer survivorship. **Meredith Edwards** of the **University of California, San Francisco**, is funded to complete her dissertation work by developing a method to measure the neurological side effects caused by Taxol or Taxotere. The ultimate goal is to identify the onset of the effects before they have detrimental physical or quality of life consequences. **Joan Bloom** at the **University of California, Berkeley**, will study young breast cancer survivors (50 or younger at diagnosis) ten years after diagnosis in order to disentangle the effects of treatment and chemotherapy from the normal effects of aging. The aim is understand the extent to which time has ameliorated the physical, psychological and emotional impact of their diagnosis and treatment. This will be the first population-based study of the long-term impact of breast cancer in younger women.

Three Community Research Collaboration pilot studies were funded in 2004. These projects bring together traditional researchers with representatives of community organizations to tackle research questions of common interest. **John Link** at **Long Beach Memorial Medical Center**, **Michele Rakoff** with **Breast Friends**, a peer support group, and **Annette Maxwell** at the **University of California, Los Angeles**, aim to develop new ways to increase women's participation in breast cancer clinical trials. They

will use breast cancer survivors, who themselves have participated in such trials, to provide peer support for patients considering participation in clinical trials and will assess whether it results in higher clinical trial participation. **Mary Ann Kreshka**, from Sierra College; **Susan Ferrier**, at the **Northern Sierra Rural Health Network**; and **Cheryl Koopman** from **Stanford University** will examine the feasibility, acceptability, and effectiveness of using videoconferencing to reduce urban/rural inequities in access to psychosocial support for women diagnosed with breast cancer. **Sara O'Donnell** from the **Mendocino Cancer Resource Center**, **Julie Ohnemus** at the **Humboldt Community Breast Health Project**, and **Jeff Belkora** with the **University of California, San Francisco**, plan to evaluate a decision support approach, called Consultation Planning (CP) in a rural setting. This group had previously shown CP as being effective at improving satisfaction/quality in treatment decision-making among newly diagnosed breast cancer patients. This study will test the feasibility of extending the reach of CP, previously delivered in person, to a telephone intervention, and to test its acceptability among Native American and Latina breast cancer patients.

The CBCRP awarded planning grants to three teams of community groups and scientists to further develop applications submitted this year. These small awards enable these groups to improve their methodology, strengthen the collaboration, and gather pilot data as appropriate. **Janice Barlow** with **Marin Breast Cancer Watch** and **Scott Fendorf** from **Stanford University** will further develop the hypothesis that the high incidence of breast cancer in Marin County is due in part to exposures to certain cancer-causing trace elements which are found in serpentinites, soils formed from these rocks, and in related water sources. **Shelly Adler** at the **University of California, San Francisco**, and **Beverly Burns** with the **Charlotte Maxwell Complementary Clinic** wish to develop a patient-centered model of culturally appropriate, end-of-life care for underserved women with breast cancer. They propose to design a narrative intervention aimed at enhancing meaning at the end of life. Specifically, they plan to describe and examine the ways in which critical end-of-life issues are approached and understood by underserved women with breast cancer, their main physicians, their lead CAM providers, and their informal caregivers. **Zul Surani** at **South Asian Cancer Foundation** and **Roshan Bastani** at the **University of California, Los Angeles**, intend to conduct an assessment aimed at understanding the psychosocial and concrete needs of the growing and underserved population of South Asian women (e.g., Indian, Pakistani, Sri Lankan, Bangladeshi) with breast cancer, so that future interventions are more culturally relevant.

Community Impact Grants Funded in 2004:

Health Policy and Health Services

Empowering Acupuncturists to Cooperate with Oncologists

Michael Johnston, Ph.D.
University of California, Los Angeles
Award type: Postdoctoral Fellowship
Duration: 2 years
\$89,728

Disparities

Socioeconomics and Ethnicity Affect Tumor Endocrine Status

Vinona Bhatia, M.D.
University of California, San Francisco
Award type: Postdoctoral Fellowship
Duration: 2 years
\$90,000

Assessment of Recurrent Genomic Aberrations Linked to Ethnicity

Koie Chen, M.D., Ph.D.

University of California, San Francisco

Award type: IDEA

Duration: 1.5 years

\$100,000

Sociocultural, Behavioral, and Psychological Issues



Decision Support in Rural Underserved North Coast Counties

¹Jeff Belkora, Ph.D., ²Sara O'Donnell, and ³Julie Ohnemus

¹University of California, San Francisco, ²Mendocino Cancer Resource Center, and ³Humboldt Community Breast Health Project

Award type: CRC Pilot

Duration: 1 year

\$115,000

Young Breast Cancer Survivors: Ten Years Later

Joan Bloom, Ph.D.

University of California, Berkeley

Award type: RFA

Duration: 3 years

\$944,961

The Functional Implications of Taxane-induced Neuropathy

Meredith Edwards

University of California, San Francisco

Award type: Dissertation

Duration: 2 years

\$54,713

Expanding Rural Access: Distance Delivery of Support Groups

¹Susan Ferrier, R.N.; ²Cheryl Koopman, Ph.D.; and ^{3,1}Mary Anne Kreshka, M.A.

¹Northern Sierra Rural Health Network, ²Stanford University, and ³Sierra College

Award type: CRC Pilot

Duration: 1 year

\$138,914

Hormone, Psychologic, and Immunologic Factors and Breast Cancer Survivorship

Hillary Klonoff-Cohen, Ph.D.

University of California, San Diego

Award type: RFA

Duration: 3 years

\$1,196,166

Peer Mentors Promoting Breast Cancer Clinical Research

¹Annette Maxwell, Dr.P.H., ^{2,3}Michele Rakoff; and ³John Link, M.D.

¹University of California, Los Angeles; ²Breast Friends; and ³Long Beach Memorial Medical Center

Award type: CRC Pilot

Duration: 1.5 years

\$162,344



Faith Fancher Research Award

Living Well with Advanced Breast Cancer: a Predictive Model

Annette Stanton, Ph.D.

University of California, Los Angeles

Award type: IDEA

Duration: 1.5 years

\$99,982

Psychobiological Concomitants of Bereaved Women at Breast Cancer Risk

David Wellisch, Ph.D.

University of California, Los Angeles

Award type: IDEA

Duration: 1.5 years

\$118,755

Community Research Collaboration (CRC) planning grants

Underserved Women with Breast Cancer at End of Life

¹Shelley Adler, Ph.D., and ²Beverly Burns

¹University of California, San Francisco; and ²Charlotte Maxwell Complementary Clinic

Duration: 1 year

\$10,000

Serpentinities & the High Incidence of Breast Cancer in Marin

¹Janice Barlow, and ²Scott Fendorf, Ph.D.

¹Marin Breast Cancer Watch; and ²Stanford University

Duration: 1 year

\$10,000

South Asian Women with Breast Cancer: What are Their Needs?

¹Roshan Bastani, Ph.D., and ²Zul Surani

¹University of California, Los Angeles, and ²South Asian Cancer Foundation

Duration: 1 year

\$10,000

Etiology and Prevention: Finding the Underlying Causes

Overview: Despite the identification of breast cancer genes and other risk factors, the disease strikes most women at random. There are causes of the disease that cannot be explained by the analysis of tumors in the laboratory setting. What are environmental and biological factors that interact to increase a woman's risk of developing breast cancer? How do these factors impact different communities of women in California? Knowing what causes breast cancer will allow us to take steps to prevent it.

Funding Data:

		Proportion of Total
Etiology and Prevention grants awarded in 2004	8	19%
Funded amount:	\$3,901,663	27%

Etiology and Prevention Portfolio Summary:

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

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

Although there has been renewed interest very recently in explanations for the causes of breast cancer based on non-estrogen factors (e.g., viruses, particularly the mouse mammary tumor virus), the view of breast cancer as largely an uncontrolled, estrogen-fueled cell growth process received most of the attention in our **Etiology and Prevention** topic this year. Three newly funded grants look at suppressing the aromatase (an enzyme critical in the biosynthesis of estrogen) pathway, which in turns limits estrogen production. This research interest has received new impetus from the results the ATAC (Arimidex, Tamoxifen, Alone or in Combination) clinical trial that has shown aromatase inhibitors to be superior to antiestrogen compounds in treating breast cancers. **Ikuko Kijima** a doctoral student at the **Beckman Research Institute of the City of Hope** will focus on the aromatase gene and examine its gene regulatory factors. The PI believes that novel regulatory sites may play an important role in acting as enhancers or repressors of aromatase production. This research may aid in refinement of novel therapeutic approaches to reduce aromatase gene activity. **Shiuan Chen** and **Melanie Ruth Palomares** also at the **Beckman Research Institute of the City of Hope** will determine if grape seed extracts (GSE) given to human volunteers will reduce the level of circulating estrogens in normal postmenopausal women at increased risk for breast cancer, and they will look at the safety and tolerability of these extracts. **Shiuan Chen** is funded through a separate grant to study whether a white button mushroom extract is a potent aromatase inhibitor. If this is true, then a readily available and affordable strategy to reduce breast cancer risk would be available to the public.

Two newly funded grants examine the role of estrogen and estrogen receptors. **Dale Leitman** at the **University of California, San Francisco**, will examine the possibility of chemoprevention using substances from Chinese herbal remedies that may interact with a type of estrogen receptor, called ER β . There is some preliminary data showing that activation of this receptor may be protective against breast cancer. Dr. Leitman will screen for compounds that have ER β activity and test them in a mouse model for

effectiveness. This is a necessary step before possible human trials. While most of the research on the effects of estrogen exposure and breast cancer has adult women as its subject, **Peggy Reynolds** with the **California Department of Health Services** will look at whether prenatal exposure to maternal estrogens may play a role in later breast cancer development. This case-control study will test the hypothesis that selected prenatal and perinatal factors are related to subsequent breast cancer risk in young California-born women. Factors such as infant birth weight, gestational age at birth, and maternal characteristics will be looked at in consideration with the possible modifying effects of socioeconomic factors (SES) and region of birth on the relationship between birth characteristics and breast cancer risk.

Two newly-funded grants focus on dietary factors that may modulate breast cancer risk and serve in chemoprevention. **Anna Wu** and her team at the **University of Southern California** is examining soy and green tea intake and breast cancer among Chinese, Japanese, and Filipino women. Dr. Wu has found decreasing breast cancer risk with increasing levels of green tea intake, particularly among women without high soy intake. Confirmation of these findings is important, as are more details on dose response and the timing necessary to reduce risk (i.e., whether soy intake in adulthood vs. childhood). She will also look at variations in certain genes for associated metabolic interactions which may affect risk, and she will determine the relationship between blood estrogen levels and dietary intake of soy and tea. **Mai Brooks** and **Jian Rao**, from the **University of California, Los Angeles**, will look to see if polyphenol compounds in green tea have direct action in the breast to decrease both cell growth and expression of suspected tumor growth factors when taken orally. They propose the use of ductal lavage technology to measure changes in certain angiogenic compounds (those associated with the process of blood vessel formation that supports tumor growth) that are found in nipple fluid. These compounds may also be associated with pre-cancerous breast atypia. If successful, they will then know more about the effect of green tea on breast physiology and whether certain compounds in breast fluid can serve as markers for evaluating the effects of green tea.

Urged on by community concerns, **Myrto Peatras** at the **California Department of Health Services, Public Health Institute** is funded to see if there is a possible link between polybrominated diphenyl ethers (PBDEs) and breast cancer. This study will compare the levels of the byproducts of these compounds (commonly used as flame retardants) in women who have breast cancer to those who do not. PBDEs were introduced in the late 1970s and the PI has already shown that these potentially estrogen-modulating toxins are present in the environment and in human sera.

Etiology and Prevention Grants Funded in 2004:

Etiology

Control of Aromatase Expression in Breast Cancer

Ikuko Kijima

Beckman Research Institute of the City of Hope

Award type: Dissertation

Duration: 2 years

\$60,000



PDBEs in Tissues of Women with and Without Breast Cancer

Myrto Petreas, Ph.D., M.P.H.
California Department of Health Services
Award type: IDEA
Duration: 1.5 years
\$85,901

Birth Characteristics and Breast Cancer in Young Women

Peggy Reynolds, Ph.D.
California Department of Health Services
Award type: RFA
Duration: 3 years
\$906,386

Prevention

Surrogate Markers for Green Tea

Mai Brooks, M.D., FACS and Jian Rao, M.D.
University of California, Los Angeles
Award type: TRC Pilot
Duration: 1 year
\$100,000



Breast Cancer Prevention with Phytochemicals in Mushrooms

Shiuan Chen, Ph.D.
Beckman Research Institute of the City of Hope
Award type: RFA
Duration: 3 years
\$766,376

Grape Seed as Aromatase Inhibitor for Breast Cancer Risk

Shiuan Chen, Ph.D. and Melanie Ruth Palomares, M.D.
Beckman Research Institute of the City of Hope
Award type: TRC Pilot
Duration: 1 year
\$171,996

Breast Cancer Chemoprevention with Dietary Herbal Estrogens

Dale Leitman, M.D., Ph.D.
University of California, San Francisco
Award type: STEP
Duration: 2 years
\$200,000

Tea, Genes, and their Interactions on Breast Cancer

Anna H. Wu, Ph.D.

University of Southern California

Award type: RFA

Duration: 3 years

\$1,611,004

Detection, Prognosis, and Treatment: Delivering Clinical Solutions

Overview: The “war on cancer” is over 30 years old, yet progress comes slowly despite the many billions of dollars invested. Since President Nixon signed the National Cancer Act into law in 1971, we have seen the emergence of an innovative biotechnology industry, the completion of the human genome project, and Nobel prizes were awarded for the landmark work on (cancer-causing) oncogenes to **J. Michael Bishop** and **Harold Varmus** from the **University of California, San Francisco**. Still, much of this research is awaiting actual translation into human cancer therapy and prevention. Sadly, X-ray mammography, a basic radiology method devised over a century ago, and toxic chemotherapeutic drugs, many in use for decades, remain the frontline weapons in our “war.” Despite the technologies of the “information age”, new drug development and clinical testing can take 10-15 years and cost up to \$1 billion. A ten-year wait for a new breast cancer “cure” might eventually cost over 50,000 lives in California alone! Fortunately, breast cancer is one disease that has seen the emergence of patient advocates and activists that are willing to ask tough questions to researchers and demand that public research funding seek new avenues for progress.

The CBCRP encourages lab researchers and clinicians to engage in more cross-disciplinary research projects to link discovery efforts with the clinical issues important to breast cancer.

Funding Data:

		<u>Proportion of Total</u>
Detection, Prognosis, and Treatment grants awarded in 2004:	5	12%
Funded amount:	\$2,185,348	14%

Detection, Prognosis, and Treatment Portfolio Summary:

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

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

Both of the CBCRP-funded grants in the imaging topic are full Translational Research Collaborations (TRCs) that have a focus on optical imaging. **Bruce Tromberg** and **John Butler** at the **University of California, Irvine**, are teaming with **Nola Hylton** from the **University of California, San Francisco**, to expand the clinical potential of previous work by Dr. Tromberg (partially supported by the CBCRP) to develop a non-invasive, optical detection-based Laser Breast Scanner (LBS). In this new project they will find ways to make the functional parameters from optical imaging complementary to high anatomic resolution images derived from the magnetic resonance imaging (MRI) work from Dr. Hylton’s laboratory. In terms of breast cancer prognosis/diagnosis, they will study the impact of menopausal status, hormone replacement therapy (HRT), and neoadjuvant chemotherapy on physiological properties in normal and high risk subjects; and develop Tissue Optical Indices that report on functional parameters related to metabolism, angiogenesis, and cell/matrix density. Dr. Butler is the clinician who will supervise the selection of patient groups and correlation of imaging data with disease parameters. **Gregory Faris**, a medical physicist at **SRI International** in Menlo Park, is collaborating with **Robyn Birdwell**, a clinical

radiologist from **Stanford University**. They are taking an optical (infrared) method, called differential vasoactive optical imaging (DVOI) from animal models of breast cancer to human studies. The DVOI method depends on the metabolic differences in normal breast tissue vs. tumor tissue before and during inhalation of mixtures of oxygen and carbon dioxide. This imaging method works because of (1) tumor blood pooling, and (2) the oxy- and deoxy-hemoglobin-dependant (tumor hypoxia) properties. Besides being non-invasive, the advantages of optical-based detection methods are the low cost and the portability of the basic instrumentation.

Three other funded projects in 2004 are novel treatment strategies. **Sylvia Fong** at the **California Pacific Medical Center Research Institute** in San Francisco was awarded a postdoctoral fellowship to study a group of genes, called FKBP, for their potential to alter the angiogenic and metastatic properties of breast cancer cells. The FKBP genes are reduced in expression in aggressive cancers, and Dr. Fong is exploring their connection to metastasis-regulatory genes, such as syndecan-1 and MMP9. In this project the FKBP genes will be surveyed from patient tumor samples. The FKBP genes are good candidates for gene therapy as developed in the lab of Dr. Fong's mentor, **Dr. Robert Debs**. Next, Her-2 is recognized as an important oncogene for promoting breast cancer growth, and its presence is a prognostic marker for poor patient survival. However, even after the development of Herceptin® (Trastuzumab) by Genentech, there continues to be much research interest in advancing other therapeutic modalities to treat breast cancer patients with elevated Her-2. Although Herceptin® is a remarkable drug, only about 30 percent of patients eligible for its use will respond well to therapy. **Joseph Lustgarten** from the **Sidney Kimmel Cancer Center** is funded to develop a vaccine approach against Her-2 that is based on the use of synthetic peptides from on the Her-2 protein sequence. Using this approach combined with special immune-stimulating "adjuvants", Dr. Lustgarten hopes to avoid the problem of T-cell tolerance, which handicaps many attempts at developing anti-tumor vaccines. **Maurizio Pellecchia** from **The Burnham Institute** is funded to study a metabolite of Gossypol, a polyphenol derived from the cottonseed plant used as a male oral contraceptive in China, as a possible new drug to stimulate apoptosis (programmed cell death) in breast cancer. Dr. Pellecchia hopes to develop synthetic derivatives of Apogossypol that interfere with the biology of the apoptosis inhibitory protein, called Bcl-xl. The goal is to sensitize breast cancer cells to death-inducing stimuli in either a chemopreventive or a therapeutic strategy.

Detection, Prognosis, and Treatment Grants Funded in 2004:

Imaging, Biomarkers, and Molecular Pathology

Differential Optical Mammography

¹Gregory Faris, Ph.D. and ²Robyn Birdwell, M.D.

¹SRI International and ²Stanford University

Award type: TRC Full

Duration: 3 years

\$936,996



Breast Cancer Functional Imaging with Optics and MRI

¹Bruce Tromberg, Ph.D., ²Nola Hylton, Ph.D., & ¹John Butler, M.D.

¹University of California, Irvine, and ²University of California, San Francisco

Award type: TRC Full

Duration: 3 years

\$500,000

Innovative Treatment Modalities

FKBP Proteins as Molecular Targets in Breast Cancer Therapy

Sylvia Fong, Ph.D.

California Pacific Medical Center Research Institute

Award type: Postdoctoral fellowship

Duration: 2 years

\$89,988

Her-2/Neu Crossreactive Analogs as Targets for Breast Cancer

Joseph Lustgarten, Ph.D.

Sidney Kimmel Cancer Center

Award type: STEP

Duration: 2 years

\$372,600



Apogossypol Derivatives for Breast Cancer Therapy

Maurizo Pellecchia, Ph.D.

The Burnham Institute

Award type: STEP

Duration: 2 years

\$285,764

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-neoplastic causative events in the normal breast. We need to understand the cancer-related genetic and physiological changes associated with breast development, aging, pregnancy, and the influence of lifestyle and dietary factors. Breast cancer is a complex disease, and the underlying genetics of disease heterogeneity seen in the clinic need clarification at the basic science level. We need more relevant cell and pre-clinical animal models of breast cancer. The key genetic and molecular signatures of the disease may provide useful biomarkers for better diagnosis and prognosis, so treatments can be individualized and women spared the use of ineffective drugs. The underlying cellular signaling pathways for growth control, cell death, DNA repair, and cell migration/metastasis require exploration to develop into new targets for therapy and prevention.

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

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

Biology of the Normal Breast: The Starting Point

Biology of the Normal Breast Funding Data:

		<u>Proportion of CBCRP's Total</u>
Grants awarded in 2004:	8	19%
Funded amount:	\$1,605,672	11%

Biology of the Normal Breast Portfolio Summary:

The job of the breast appears to be quite straightforward, to produce milk for babies. However, in actuality the process requires a complicated structure responding to an intricate combination of cell signals and hormones. The breast (or mammary gland in animals) is composed of a collection of different types of cells, each of which must function properly for milk to be produced. The gland cells respond to the myriad hormonal signals during the menstrual cycle and throughout life by growing, maturing, and dying off. Researchers have had difficulty identifying the key changes that occur during tumor development because of the complex interactions that already exist in the normal mammary gland. The CBCRP applications funded in the **Biology of the Normal Breast** topic seek to understand the behavior of normal cells in hopes of eventually identifying the critical changes during tumor development.

The mammary gland is composed of branching ducts made of epithelial cells which are embedded in stromal cells and a network of extracellular matrix consisting of proteins. The epithelial cells are responsible for producing milk and delivering it to the nipple. They also are the origins of 98 percent of breast tumors. The stromal cells, which include fat cells and blood vessel cells, provide nutrients to the epithelial cells. The extracellular matrix provides a structure onto which cells attach and move. Research has shown that the interactions of these components are complex, and a change in one affects the behavior of the others.

The communication between cell types begins at the earliest stages of mammary gland development. **Lindsay Hinck** of the **University of California, Santa Cruz**, will undertake a three-year study to determine whether the Slit/Rob growth factor system, which is involved in attracting or repelling axons in nerves, is guiding the branching structure in the normal breast. This study could help us understand the factors affecting the movement of breast cells as they develop. **Jacqueline Veltmaat** from the **Children's Hospital Los Angeles/Saban Research Institute** will be studying the genetic control of mammary cells as they form the earliest vestiges of the mammary gland. She will investigate the role of Gli3 in early breast development by creating mice with mutant Gli3 and looking for effects on cell division, breast size, shape and production of breast-specific proteins.

The CBCRP funded two projects to study the different cell types and extracellular matrix interactions in the mammary gland. The manner in which cells connect to each other and the extracellular matrix can determine how they function. **John Muschler** of the **California Pacific Medical Center Research Institute** will explore the possibility that there are as yet undiscovered methods for cells to adhere to the basement membrane. He will generate cells lacking the major adherence proteins (dystroglycan and integrin beta) in transgenic mice and test whether there are any basement membrane receptors still functioning in the normal gland. **Nancy Boudreau** from the **University of California, San Francisco**, will test whether the loss of breast tissue organization acts as a trigger for the development of new blood vessels. These findings could help us to understand the tissue-related control points for tumor progression and metastasis.

Mammary gland growth and development is also controlled by hormones and growth factors. Hormones have often been found to have different forms, some of which encourage the mammary cells to proliferate and others of which signal them to mature or die. Situations that cause cells to produce or react to the maturation versions of the hormones may also be the ones that cause the breast to be resistant to tumor development. Two CBCRP-funded studies will investigate the protective role of hormones in the mammary gland. Postdoctoral fellow **Leslie Hodges** of the **University of California, San Francisco**, hypothesizes that ER β (estrogen receptor beta) protects the mammary gland from developing tumors, because it is lost in the majority of breast tumors. She will use high throughput genetic screens to determine the molecular pathways that are modulated by ER β and then test the physiological effects of the loss of ER β in the mouse. **Ameae Walker** from the **University of California, Riverside**, is funded to investigate the potentially protective role of prolactin. Prolactin is the growth hormone responsible for causing breasts to grow, mature during pregnancy and produce milk. A growth inhibitory version of prolactin is found at elevated levels in breast milk, but the significance of its presence has not been explained. Dr. Walker will investigate the role of inhibitory prolactin on the milk side of the breast duct. This investigation could determine whether it contributes to the effect of early pregnancy on lowering a woman's subsequent risk for breast cancer.

There are thousands of genes that are being activated and inactivated inside the mammary cells in response to cell-cell interactions, hormones or growth factors. Two CBCRP investigators will look at the methods of gene regulation and their implications for breast cell behavior. **Hosein Kouros-Mehr** of the **University of California, San Francisco**, will examine the gene activation in different cell types of the developing mammary gland using a combination of histochemical techniques (for identifying the different cell types) and microarray (for studying the profiles of many genes at the same time). **David Liston** from **The Salk Institute for Biological Studies** will pursue a postdoctoral fellowship to examine the normal pattern of p16 (a gene involved in cell aging) inactivation through a chemical process called DNA methylation. These studies could lead to a better understanding of which genes are crucial for tumor development.

Biology of the Normal Breast Grants Funded in 2004:

Epithelial Polarity, Organization and the Angiogenic Switch

Nancy Boudreau, Ph.D.
University of California, San Francisco
Award type: IDEA
Duration: 1.5 years
\$75,000

Axon Guidance Proteins in Mammary Gland Development

Lindsay Hinck, Ph.D.
University of California, Santa Cruz
Award type: RFA
Duration: 3 years
\$449,228

Protective Role of Estrogen Receptor Beta in the Mammary Gland

Leslie Hodges, Ph.D.
University of California, San Francisco
Award type: Postdoctoral fellowship
Duration: 2 years
\$90,000

Gene Expression Profiling in the Developing Mammary Gland

Hosein Kouros-Mehr
University of California, San Francisco
Award type: Dissertation
Duration: 2 years
\$60,000

Targeting of DNA Methylation in Mammary Epithelial Cells

David Liston, Ph.D.
Salk Institute
Award type: Postdoctoral fellowship
Duration: 2 years
\$90,000

Discovering Novel Cell-ECM Interactions in Breast Cells

John Muschler, Ph.D.
California Pacific Medical Center Research Institute
Award type: IDEA
Duration: 1.5 years
\$160,000

The Role of Gli3 in Mouse Embryonic Mammary Gland Formation

Jacqueline Veltmaat, Ph.D.
Childrens Hospital, Los Angeles
Award type: Postdoctoral fellowship
Duration: 2 years
\$90,000

Normal Mammary Biology of Phosphorylated Prolactin

Ameae Walker, Ph.D.

University of California, Riverside

Award type: RFA

Duration: 3 years

\$541,444

Pathogenesis: Understanding the Disease

Basic science research, while often appearing to be unrelated to clinical problems and practical application, is the entry point for expertise from other research disciplines. Arthur Kornberg, the 1959 Nobel Laureate in Medicine, had these enduring thoughts, (1) “No matter how counter-intuitive it may seem, basic research has proven over and over to be the lifeline of practical advances in medicine,” and (2) “The pursuit of curiosity about the basic facts of nature has proven, with few exceptions throughout the history of medical science, to be the route by which the successful drugs and devices of modern medicine were discovered. Though it seemed unreasonable and impractical, counter-intuitive even to scientists, to solve an urgent problem of disease by exploring apparently unrelated questions in biology, chemistry and physics, these basic studies proved time and again to be utterly practical and cost-effective.” As novel paradigms and technologies in cell and molecular biology are advanced, we provide innovative project funding to explore their relevance to breast cancer.

The CBCRP encourages innovative and cross-disciplinary research on breast cancer tumor and stromal biology, including: (1) studies of relevant proteins and genes with an emphasis on their relationship to the actual disease and (2) elucidating key cell signaling, growth control, cell cycle, and apoptosis pathways. We especially encourage new research on the process of metastasis and the development of tools and models to better understand the key metastatic events that impact patient survival.

Pathogenesis Funding Data:

		<u>Proportion of CBCRP's Total</u>
Grants awarded in 2004:	10	24%
Funded amount:	\$3,919,643	27%

Pathogenesis Portfolio Summary:

The predominant basic science topic funded by the CBCRP in 2004 was cancer invasion and metastasis, but the underlying approaches are quite varied. Two full-scale collaboration projects will link basic scientists in different disciplines and clinicians to tackle key research issues. **Brunhilde Felding-Habermann** and **John Yates** from the **Scripps Research Institute** are teaming with **Evan Snyder** at **The Burnham Institute** to explore the emerging theory that a small population of stem cells in breast tumors can seed the growth of new cancers. The stem cells make up a tiny fraction of the tumor and have properties similar to those of other pluripotent embryonic and organ stem cells. The CBCRP-funded project to Drs. Felding-Habermann, Yates, and Evans will use state-of-the-art proteomic, genetic, and immunochemical tests to characterize breast cancer stem cells, and determine whether these cells actually “seed” metastases to distant organs. Dr. Evans brings his expertise in neuronal stem cells as the “synergistic component” to this type of funding. If more effective ways of detecting and killing breast cancer stem cells can be devised, then disease recurrence might be greatly diminished. **Benjamin Cravatt**, a chemist-cell biologist at the **Scripps Research Institute**, is collaborating with **Stefanie Jeffrey**, a surgeon-cancer geneticist from **Stanford University**, to detect cell invasion-specific proteases using a new “functional proteomics” assay. In previous funding from the CBCRP, Dr. Cravatt has shown the ability of this new assay to detect and measure the activity of proteases in breast cells and animal tumor models. In the current project, they hope to translate these findings closer to a clinical application using primary tumor samples. Prior work from Dr. Jeffrey and colleagues at Stanford has shown that breast cancers can be genetically classified into five specific sub-types, so the addition of a proteomics-based assay will serve to develop new information to make individualized metastasis-based prognosis closer to reality.

It has been known for decades that many cancer patients have tumor cells that circulate in the blood, but the clinical and prognostic significance remains uncertain. The CBCRP is funding two innovative projects to study circulating tumor cells (CTCs). **Kristen Kulp**, a basic scientist at **Lawrence Livermore National Laboratory**, will use imaging mass spectrometry (TOF-SIMS). The proof-of-principle for this approach will be to detect the protein fingerprints that distinguish metastatic and non-metastatic breast cancer cells spiked into whole blood samples as an initial *in vitro* model for CTCs. If successful, Dr. Kulp would extend these studies to tumors grown in animals, and eventually to detect CTCs from blood samples from human patients. **Robert Carlson**, an oncologist at **Stanford University**, plans to use advanced fluorescence-activated cell sorting (HiD-FACS) to simultaneously detect up to 12 biomarkers of interest. He will be comparing the CTCs biomarker profile to tumor cells obtained from patient bone marrow aspirates, a common metastatic site. Dr. Carlson is interested in refining a panel of biomarkers and ultimately developing a blood test that would be informative as to whether breast cancer might be recurring in patients several years following initial diagnosis. Novel paradigms are represented in the final two metastasis projects funded by the CBCRP. We awarded a fellowship grant to **Lucy East** from **University of California, San Francisco**, to determine the role of Hox genes in breast tumor angiogenesis. Dr. East is studying the normal endothelial cells that are induced by the tumor to form new blood vessels. Two master gene regulatory proteins, called HOX D3 and HOX D10, might become specific endothelial targets to modulate angiogenesis in breast tumors. **Jeffrey Smith** from **The Burnham Institute** will explore a link between the cell's protein-degrading machinery (the proteasome) and a mammary serine protease inhibitor, called "maspin." The new paradigm to be tested is that maspin serves to alter the protein turnover in cancer cells by "tagging" of cell proteins by ubiquitin. These studies ultimately will address the effect of maspin's tumor suppressor activity in preventing cancer cell metastasis.

Even though the estrogen receptor (ER) is the most successful molecular target for treating breast cancer, it remains of high interest in basic research, especially the application of new technologies. We need new ER-targeted therapeutics, since SERMs and other estrogen antagonists fail to help many patients, and even those patients that benefit will often develop drug resistance. The CBCRP funded two grants that focus on ER biology. **Alex So** from **University of California, San Francisco**, will look at an alternate way of modulating the ER. Cells are believed to have mechanisms of maintaining the ER in an inactive state in the absence of estrogen. Working in laboratory of **Dr. Keith Yamamoto**, Mr. So will use a novel assay to determine whether a protein, called Hsp90, serves in this ER inactivation capacity. Understanding the "inactivation mechanisms" of the ER could provide alternate strategies for therapy. Next, the ER has long been thought to be a target for breast cancer-causing environmental agents, but many compounds in food or other sources might exert subtle influences on the ER that are difficult to detect. **Bradford Gibson** and **Christopher Benz** at **Buck Institute for Age Research** in Novato are funded to use new, state-of-the-art mass spectrometry to study the ER at the level of individual amino acids. They will test whether quinone oxidants, common in the human diet and endogenously produced by estrogen catabolism, serve to alter the arylatation and phosphorylation pattern on the ER. Their initial aim is to correlate the pattern of ER structural changes with known oxidant stress. Their ultimate goal is to better associate the environmental, dietary, and lifestyle effects for new model of breast cancer based on structural modifications of the ER.

Cancer progression is the topic of two other newly funded grants. First, **Jason Bush** at **The Burnham Institute** is using protein-based "proteomics" technology to study the transformation of epithelial cells into mesenchymal cells, the so-called EMT transformation that is an early physiological-morphological "switch" in cancer initiation. An adhesive receptor integrin, called $\alpha 6 \beta 4$, is a receptor for basement membrane components and is the interest for Dr. Bush's study of EMT. Using new inhibitory RNA technology (iRNA) and special protein "affinity tags", he will be able to assess the role of this receptor in critical breast epithelial adhesion processes. Finally, apoptosis (programmed cell death) is involved in

many aspects of cancer progression and failures of therapy. **Beatrice Bailly-Maitre** also from **The Burnham Institute** will study a novel pathway in breast cancer cell apoptosis. An anti-apoptotic protein, called BI-1 (Bax Inhibitor-1), appears to regulate a cell death pathway linked to stress in the endoplasmic reticulum. Working in **Dr. John Reed's** laboratory, Dr. Bailly-Maitre will study BI-1 in animal models and tumor samples. By using BI-1 as a window into this poorly understood endoplasmic reticulum-apoptosis pathway, she eventually hopes to devise strategies for bypassing the roadblocks to cell death that commonly arise as cancer progresses.

Pathogenesis Grants Funded in 2004:

Role of BI-1 Protein in Breast Cancer Apoptosis

Beatrice Bailly-Maitre, Ph.D.

The Burnham Institute

Award type: Postdoctoral fellowship

Duration: 2 years

\$90,000

Oxidative Stress and Estrogen Receptor Structural Changes

Christopher Benz, M.D. and Bradford Gibson, Ph.D.

Buck Institute for Age Research

Award type: SPRC Full

Duration: 3 years

\$1,122,520

Proteomic Profiling of Adhesive Structures in Breast Cancer

Jason Bush, Ph.D.

The Burnham Institute

Award type: Postdoctoral fellowship

Duration: 2 years

\$90,000



Characterizing Breast Cancer Cells in Blood and Bone Marrow

Robert Carlson, M.D.

Stanford University

Award type: IDEA

Duration: 1 year

\$156,108

Profiling Enzyme Activities in Human Breast Cancer

¹Benjamin Cravatt, Ph.D.; and ²Stefanie Jeffrey, M.D.

¹Scripps Research Institute and ²Stanford University

Duration: 2 years

Award type: TRC Full

¹\$469,250 and ²\$400,000

Hox Transcriptional Regulation of Breast Tumor Angiogenesis

Lucy East, Ph.D.

University of California, San Francisco

Award type: Postdoctoral fellowship

Duration: 2 years

\$90,000

Stem Cells in Breast Cancer Metastasis

¹Brunhilde Felding-Habermann, Ph.D.; ¹John Yates, M.D., Ph.D.; and ²Evan Snyder, M.D., Ph.D.

¹Scripps Research Institute and ²The Burnham Institute

Award type: SPRC full

Duration: 2 years

\$906,990

Identifying Metastatic Breast Cells from Peripheral Blood

Kristen Kulp, Ph.D.

Lawrence Livermore National Laboratory

Award type: IDEA

Duration: 1 year

\$210,159

Maspin: Breast Cancer Suppression through Enzyme Inhibition?

Jeffrey Smith, Ph.D.

The Burnham Institute

Award type: STEP

Duration: 1 year

\$285,266

A Novel Approach to Inactivate the Estrogen Receptor

Alex So

University of California, San Francisco

Award type: Dissertation

Duration: 2 years

\$60,000

2004 CBCRP Funding by Institution

The following 27 California research institutions and community organizations were awarded new CBCRP funding in 2004. Some grants were structured as separate awards that are split between institutions.

Institution	# Awards	Amount
Beckman Research Institute of the City of Hope, Duarte	3	\$998,372
Buck Institute for Age Research, Novato	1	\$1,122,520
Burnham Institute, La Jolla	5	\$1,067,396
California Department of Health Services, Oakland	2	\$992,287
California Pacific Medical Center Research Inst., San Francisco	2	\$249,988
Charlotte Maxwell Complementary Clinic, Oakland	1	\$10,000
Childrens Hospital, Los Angeles	1	\$90,000
Humboldt Community Breast Health Project, Arcata	1	\$37,500
Lawrence Livermore National Laboratory, Livermore	1	\$209,775
Long Beach Memorial Medical Center	1	\$89,197
Marin Breast Cancer Watch, San Rafael	1	\$10,000
Mendocino Cancer Resource Center, Mendocino	1	\$37,500
Northern Sierra Rural Health Network, Nevada City	1	\$75,306
Salk Institute, La Jolla	1	\$90,000
Scripps Research Institute, La Jolla	2	\$1,096,318
Sidney Kimmel Cancer Center, San Diego	1	\$372,600
South Asian Cancer Foundation, Los Angeles	1	\$10,000
SRI International, Menlo Park	1	\$936,996
Stanford University	3	\$619,716
University of California, Berkeley	1	\$944,961
University of California, Irvine	1	\$500,000
University of California, Los Angeles	5	\$451,486
University of California, Riverside	1	\$541,444
University of California, San Diego	1	\$1,196,166
University of California, San Francisco	10	\$859,713
University of California, Santa Cruz	1	\$499,228
University of Southern California, Los Angeles	1	\$1,611,004

2004 CBCRP Application Evaluation & Review Committees

In the first phase of the funding process, grant applications were reviewed and scored for scientific merit in seven peer review committees using a model that follows established practice at the National Institutes of Health (NIH). 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 includes a California Advocate observer, who is not assigned applications for review and does not vote, but represents the California advocacy community. The observer gains insight into the research evaluation process and provides feedback to the Program on this process. Ad Hoc members participate by teleconference and bring their specialized expertise to the review of individual applications.

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

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

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

- Responsiveness to the CBCRP's priority issues and award types
- Multidisciplinary approach, translational potential, and focus on the underserved
- Strength of individual scientific merit component scores (e.g., innovation for IDEA applications)
- Balance of overall portfolio
- Emphasis on relatively under-funded areas
- Quality of the lay abstract
- Inclusion of advocates and sensitivity to advocacy issues/concerns

In addition, we place some of our research topics and award types into a "primary" category, and these applications are given first consideration for funding.

In summary, the advisory Council recommends the grants to be funded, based upon (1) the review committee scientific average and component merit scores and (2) the programmatic relevance. This two-tiered process ensures **both** scientific excellence and relevance of the research to CBCRP's mission and goals.

The CBCRP wishes to thank the participants in our 2004 Review Committees for their service and dedication to our Program.

Basic Breast Biology Committee

Chair:

Lewis A. Chodosh, M.D., Ph.D.
Associate Professor of Medicine
University of Pennsylvania, School of Medicine
Philadelphia, PA

Members:

Philip Bernard, M.D.
Director, Solid Tumor Molecular Diagnostics
University of Utah, Department of Pathology
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Priscilla Furth, M.D.
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Georgetown University School of Medicine
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Nelson D. Horseman, Ph.D.
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Russell Hovey, Ph.D.
Assistant Professor
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Aloysius J. Klingelhut, Ph.D.
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Advocate Members:

Ann E. Fonfa, BPS
The Annie Appleseed Project
Palm Beach Gardens, FL

Michele W. Ganon, M.B.A., Ph.D.
National Breast Cancer Coalition
Danbury, CT

Karin Noss, M.A., M.P.A.
Y-ME, National Capital Area
Round Hill, VA

California Advocate Observer:

Carol Johnson-Davis

Hospice of the Valley

San Jose, CA

Ad-Hoc Members:

Christopher J. Langmead, Ph.D.

Assistant Professor

Computer Science Department

Carnegie Mellon University

Pittsburgh, PA

Lee Niswander, Ph.D.

Investigator and Department Head

Developmental Biology Program

Sloan-Kettering Institute

New York, NY

CRC Concept Paper Review Committee

Chair:

Julia H. Rowland, Ph.D.

Director, Office of Cancer Survivorship
National Cancer Institute
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The mission of the California Breast Cancer Research Program is to eliminate breast cancer by leading innovation in research, communication, and collaboration in the California scientific and lay communities.



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