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April 8, 2008

The Honorable Denise Moreno Ducheny
Chair, Joint Legislative Budget Committee
State Capitol, Room 5035
Sacramento, California 95814

Dear Senator Ducheny:

Pursuant to Assembly Bill 3391 (Friedman, 1994), enclosed is the University of California's annual report to the Legislature on the *California Breast Cancer Research Program.*

If you have any questions regarding this report, Associate Vice President Debora Obley would be pleased to speak with you. She can be reached by telephone at (510) 987-9112, or by e-mail at Debora.Obley@ucop.edu.

Sincerely,

Robert C. Dynes

Enclosure

cc: The Honorable Jack Scott, Chair
Senate Budget and Fiscal Review Subcommittee #1
(Attn: Ms. Amy Supinger)
(Attn: Ms. Cheryl Black)
The Honorable Julia Brownley, Chair
Assembly Budget Subcommittee #2
(Attn: Ms. Sara Bachez)
(Attn: Ms. Amy Rutschow)
Ms. Elizabeth Hill, Legislative Analyst
Mr. Mike Genest, Director of Finance
Mr. E. Dotson Wilson, Chief Clerk of the Assembly
Mr. Gregory Schmidt, Secretary of the Senate
Ms. Diane Boyer-Vine, Legislative Counsel
Ms. Sara Swan, Department of Finance
Mr. Steve Boilard, Legislative Analyst's Office
Joint Legislative Budget Committee (18)
Provost Wyatt R. Hume
Executive Vice President Katherine N. Lapp
Vice President Patrick J. Lenz
Associate Vice President Debora Obley
Executive Director Charles L. Gruder
Interim Assistant Vice President Karen French

Annual Report

2007

California Breast Cancer Research Program

EXECUTIVE SUMMARY

During 2007, the California Breast Cancer Research Program (CBCRP) awarded $7.1 million for 35 single- and multiple-year research projects at 21 California institutions. These pages list the studies funded this year, the studies in progress, and summaries of 60 studies funded in previous years that were completed during 2007.

Table 1. Grants Awarded in 2007 by Subject Area

	Number of Grants	Amount	Percentage of Total Funding
Community Impact of Breast Cancer	**6**	**$1,935,241**	**27%**
Etiology and Prevention	**2**	**$911,413**	**13%**
Detection, Prognosis and Treatment	**14**	**$2,825,270**	**40%**
Biology of the Breast Cell	**13**	**$1,429,718**	**20%**
Totals	**35**	**$7,101,642**	**100%**

Designed to push breast cancer research in new, creative directions, the CBCRP is funded primarily by a California state tax on tobacco. Since 1993, the CBCRP has provided over $181 million in research funds.

The need is urgent. Every two hours, on average, a California woman dies of breast cancer. More than 220,000 Californians are living with the disease, and over 19,500 more will be diagnosed this year. Over the past three decades, some progress has been made. Between 1988 and 2004, the breast cancer death rate in California dropped by over 28 percent. While some argue that this is the result of earlier detection, there has been no significant drop in diagnosis of cancers that have spread to other parts of the body. Thus, it is more likely that the lower death rate is due to improvements in treatment, or to more women receiving appropriate treatment.

The rate at which California women get breast cancer has also improved somewhat in recent years, after climbing steeply from 1973-1988 and staying near the 1988 rate for more than a decade. While some attribute this to a drop in detecting breast tumors because women are receiving fewer mammograms, others observe that even women who receive mammograms are being diagnosed with breast cancer at a lower rate. This leads many researchers to believe that the current decrease in breast cancer cases is due to fewer women receiving hormone replacement therapy. This welcome decrease in breast cancer underscores the need to move beyond just stopping a harmful medical intervention; research is needed to find out why so many women still get breast cancer and to develop positive interventions that prevent the disease.

Breast cancer activists have played a leading role in the CBCRP from the beginning. They helped write and pass the statewide legislation that created the Program in 1993. Women with breast cancer and survivors of the disease are involved in all levels of the CBCRP's decision making, including decisions about which projects get funded. With input from these advocates, the CBCRP has established a record for funding cutting-edge studies and jump-starting new areas of research. The Program's goal is to fund the projects that will lead most rapidly to the end of the breast cancer epidemic.

This report has been prepared by the University of California pursuant to Article 1 of Chapter 2 of Part 1 of Division 103 of the California Health and Safety Code, Section 104145; and the Revenue and Taxation Code Sections 30461-30462.1 and 18791-18796. The following required reporting elements will be addressed in this report:

1. **The number and dollar amounts of research grants, including the amount allocated to indirect costs.**
   The CBCRP awarded $7.1 million for 35 single- and multiple-year research projects at 21 California institutions in 2007. A complete list of newly funded grants can be found in Table 2.

2. **The institutions and campuses receiving grant awards.**
   All funded grants are listed with the recipient institutions in the Research Progress and Results section of this report (pages 30-66).

3. **The subject of research grants.**
   All of the investigator-initiated grants funded by the CBCRP involve key questions in one or more of the following research areas:
   - Basic Biology of the Breast (normal breast biology and breast cancer pathogenesis)
   - Breast Cancer Causes and Prevention
   - Earlier Detection, Diagnosis, and Treatment of Breast Cancer
   - Community Impact of Breast Cancer (Socio-cultural behavioral studies and health policy)

   The CBCRP is also setting aside $18 million over five years to fund its Special Research Initiatives, which is a program-initiated endeavor to identify and support research strategies to understand and address both the environmental causes of breast cancer and the unequal burden of the disease across ethnic, racial, and cultural populations in California.

4. **The relationship between federal and state funding for breast cancer research.**
   The CBCRP takes several steps to avoid duplication of funding at the individual grant level and in the Program's research priorities. We identify and attempt to fill important gaps in knowledge about breast cancer. We review priorities yearly in light of changes in the research field, successes and failures of previous funding initiatives, and the results of previous funding. Additionally, as founding members of the International Cancer Research Portfolio and participating members of the Collaborative Summit on Breast Cancer Research, we are able to ensure that CBCRP funding complements rather than duplicates grants bestowed by other funding organizations.

   The CBCRP's Breast Cancer Research Council sets the Program's funding priorities, taking into account:
   - Opinions from national breast cancer experts
   - Opinions from California advocates and activists, healthcare providers, public health practitioners, community leaders, biotechnology scientists, and academic researchers
   - Current literature on breast cancer and current gaps in knowledge

- In-house evaluations of the efficacy of CBCRP grant mechanisms and topic areas in fulfilling program goals.

5. **The relationship between each project and the overall strategy of the research program.**
   The following ten criteria are used to set priorities that push the boundaries of research.

   1. The research helps form and nurture collaboration among California scientists, clinicians, advocates, community members, and others.
   2. The research helps recruit, retain, and develop high-quality California-based investigators who engage in breast cancer research.
   3. The research embodies innovative ideas (e.g., new drugs, new strategies, new paradigms).
   4. The research addresses the public health outcomes of prevention, earliest detection, effective treatments, and quality of life.
   5. The research leads quickly to more effective products, technologies, or interventions and their application/delivery to Californians.
   6. The research helps drive policy in both the private and public sectors on breast cancer in California.
   7. The research reduces disparities and/or addresses the needs of the underserved in California.
   8. The research complements, builds on, feeds into, but does not duplicate the research programs of other organizations interested in breast cancer.
   9. The research addresses a breast cancer need that is specific but not necessarily unique to the burden of breast cancer in California.
   10. The research is responsive to the perceived breast cancer research needs and expectations of the CBCRP as identified by scientists and the public in California.

   Each individual grant is evaluated by our scientific review committees and our advisory Breast Cancer Research Council for essential criteria for addressing these goals, including innovativeness, impact on breast cancer, responsiveness to program priorities, whether it's an underfunded research area, and integration of advocacy issues.

6. **A summary of research findings including discussion of promising new areas.**
   Summaries of all of the completed research grants are included in the body of this report. Listed below are just a few of the findings:

   - **Sonia Ancoli-Israel, Ph.D.**, at the **University of California, San Diego**, discovered that the type and amount of light that women with breast cancer are exposed to during chemotherapy affects their overall level of fatigue. See page 33.
   - **Allison Kurian, M.D.**, at **Stanford University** developed a tool for determining the effectiveness and cost-effectiveness of using breast MRI in addition to mammography in women with BRCA1 and BRCA2 mutations. See page 36.

- **Dale Leitman, M.D., Ph.D.**, at the **University of California, San Francisco**, found that an herbal formula, MF101, which contains 22 different herbs that are often used in Traditional Chinese Medicine to prevent breast cancer and menopausal symptoms in women with breast cancer, prevented the breast cancer cells from growing and forming tumors in mice. See page 42.
- **Bob Liu, Ph.D.**, at the **University of California, San Francisco**, and colleagues in the lab of Dr. Thea Tlsty, found new genetic biomarkers for basal-like breast cancers, which, due to their aggressive nature, have a poor prognosis. See page 56.
- **Alexander Borowsky, M.D.**, at the **University of California**, Davis, and colleagues are using mouse models of mammary cancer that progress from precancerous ductal carcinoma in situ (DCIS) to invasive cancer to explore whether early changes on the path to cancer development can be explained by the presence of cancer stem cells in the tissue. See page 59.
- **Bradford Gibson, Ph.D.**, and **Christopher Benz, M.D.**, at the **Buck Institute for Age Research,** Novato, identified several structural changes in estrogen receptor that had previously been suspected but had never before been detected. The work has the potential to advance our understanding of how ER-positive breast cancer develops and to reveal environmental exposures that contribute to the development and progression of the disease. See page 60.

7. Inclusion of women and minorities in research studies.

Thirty-four percent (12 of 35) of the grants awarded by the CBCRP in 2007 studied either women or tissues from women, while the remaining 66 percent were laboratory studies that did not directly involve women or tissues from women.

Of the 12 grants that involved women or tissues from women, 100 percent (12) of the grants involved women as study participants.

-- Twenty percent (7) are focused on underserved women.
-- Fourteen percent (5) are focused on minority women.

This report describes the CBCRP's recent activities, goals, progress, and plans for the challenges that lie ahead on the road to decreasing the human and economic cost of breast cancer for the people of California.

Table 2. Summary of New Research Funded in 2007

Institution and Investigator	Duration (Years)	Project Title	Direct Costs	Indirect Costs	Total Costs
Afghan Coalition					
Aida Shirazi	1.5	Breast Health Behaviors of Immigrant Afghan Women		$13,360	$99,255
This is a collaborative project with Joan Bloom of University of California, Berkeley					
Alta Bates Summit Medical Foundation					
Lisa Bailey	1	Networking Breast Cancer Navigator Programs in Northern California	$15,000	$0	$15,000
Asian Health Services					
Linda Okahara	3	Breast Cancer Risks in California Nail Salon Workers		$14,839	$322,690
This is a collaborative project with Peggy Reynolds of the Northern California Cancer Center					
Beckman Research Institute of the City of Hope					
Kimlin Ashing-Giwa	1.5	Sister Survivor: African American Breast Cancer Coalition		$51,750	$169,000
This is a collaborative project with Gloria Harmon of Women of Essence					
Cynthie Wong	2	Mechanisms of HSP90 Inhibitor Action in Breast Cancer	$76,000	$0	$76,000
The Burnham Institute of Medical Research					
Lorena Puto	2	Mechanisms of Daxx-Mediated Apoptosis in Breast Cancer	$76,000	$0	$76,000
California Institute of Technology					
John Phillips	2	Polyamide HIF Inhibitors to Block Breast Cancer Metastasis	$76,000	$0	$76,000
Charlotte Maxwell Complementary Clinic					
Beverly Burns and Denise Wells	3	Underserved Women with Breast Cancer at End of Life		$25,000	$337,500
This is a collaborative project with Shelley Adler at University of California, San Francisco					
Dr. Susan Love Research Foundation					
Susan Love	1	Symposium on the Intraductal Approach to Breast Cancer	$25,000	$0	$25,000
Susan Love	3	Intraductal Therapy of DCIS: A Presurgery Study	$750,000	$101,559	$851,559
Northern California Cancer Center					
Peggy Reynolds	3	Breast Cancer Risks in California Nail Salon Workers	$322,184	$27,119	$349,303
This is a collaborative project with Linda Okahara of Asian Health Services					
Northern Sierra Rural Health Network					
Mary Anne Kreshka and Jim Perkins	3	Expanding Rural Access: Distance Delivery of Support Groups	$401,997	$23,853	$425,850
This is a collaborative project with Cheryl Koopman at Stanford University					
Palo Alto Institute for Research and Education					
Robert West	1.5	Determination of Stromal Gene Expression in Breast Cancer	$112,861	$26,580	$139,441

Institution and Investigator	Duration (Years)	Project Title	Direct Costs	Indirect Costs	Total Costs
Scripps Research Institute					
Brunhilde Felding-Habermann	2	Neural Stem Cell Therapy for Breast Cancer Brain Metastases	$311,400	$108,000	$419,400
Florence Schaffner	3	Targeting Tissue Factor in Breast Cancer	$90,000	$0	$90,000
Stanford University					
Steven Artandi	2	Telomerase, Mammary Stem Cells, and Breast Cancer	$291,750	$68,527	$360,277
Deborah Burkhart	2	Novel Regulation of the Rb Pathway in Breast Epithelium	$76,000	$0	$76,000
Karlene Cimprich	1.5	Exploring the Role of PARP Inhibitors in Breast Cancer	$100,000	$57,750	$157,750
Brian Hargreaves	1.5	Multinuclear MRI of Breast Tumors	$183,711	$53,060	$236,771
Cheryl Koopman	3	Expanding Rural Access: Distance Delivery of Support Groups	$254,837	$35,500	$290,337
This is a collaborative project with Mary Anne Kreshka & Jim Perkins at Northern Sierra Rural Health Network					
Jennifer Lahti	2	Engineering EGFR Antagonists for Breast Tumor Targeting	$76,000	$0	$76,000
Tatana Spicakova	3	Determinants of Response to Microtubule Stabilizing Drugs	$90,000	$0	$90,000
University of California, Berkeley					
Joan Bloom	1.5	Breast Health Behaviors of Immigrant Afghan Women	$70,481	$0	$70,481
This is a collaborative project with Aida Shirazi of the Afghan Coalition					
Crystal Marconette	2	Indole (I3C) Control of Breast Cancer by ER Downregulation	$76,000	$0	$76,000
University of California, Irvine					
Connie Tsai	2	The Relationship of BRCA1 and HMGA2 in Breast Cancer	$76,000	$0	$76,000
Min Yang	2	Competition for ADA2 and 3 to Inhibit p53 in Breast Cancer	$76,000	$0	$76,000
University of California, Los Angeles					
Ralf Landgraf	1.5	Lipid Raft Composition in Deregulated ERBB2 Signaling	$100,000	$0	$100,000
Frank Pajonk	1.5	Modulation of Breast Cancer Stem Cell Response to Radiation	$150,000	$0	$150,000
University of California, San Diego					
Ananda Goldrath	1.5	Novel Cytokine Immunotherapy for Breast Cancer	$150,000	$0	$150,000
Georgia Sadler	1.5	Science Literacy & Breast Cancer Clinical Trials Education	$44,003	$0	$44,003
This is a collaborative project with Natasha Riley of the Vista Community Clinic					
Thomas Nelson	2	Early Breast Cancer Detection Using 3D Ultrasound Tomography	$225,000	$0	$225,000
University of California, San Francisco					
Shelley Adler	3	Underserved Women with Breast Cancer at End of Life	$270,000	$0	$270,000
This is a collaborative project with Beverly Burns & Denise Wells at Charlotte Maxwell Complementary Clinic					

Institution and Investigator	Duration (Years)	Project Title	Direct Costs	Indirect Costs	Total Costs
Kelly Harradine	3	Breast Tumor Responses to Novel TGF-beta Inhibitors	$90,000	$0	$90,000
Catherine Jacobson	3	Cytoskeletal Regulation of Invading Breast Cells	$90,000	$0	$90,000
Ella Jones	1.5	Molecular Imaging of Metastatic Lymph Nodes in Breast Cancer	$150,000	$0	$150,000
Catherine Klifa	1.5	Breast Cancer Treatment Monitoring Combining MRI and Optics	$149,927	$0	$149,927
Ching Hang Wong	3	Trask, a Candidate Breast Cancer Metastasis Protein	$90,000	$0	$90,000
Jun Zhang	3	A New Mouse Model of PI3-Kinase Induced Breast Cancer	$90,000	$0	$90,000
University of Southern California					
Jaimie Davis	1.5	Circuit Training to Lower Breast Cancer Risk in Latina Teens	$185,210	$59,290	$244,500
Vista Community Clinic					
Natasha Riley	1.5	Science Literacy & Breast Cancer Clinical Trials Education	$109,353	$12,049	$121,402
This is a collaborative project with Georgia Sadler of University of California, San Diego					
Women of Essence					
Gloria Harmon	1.5	Sister Survivor: African American Breast Cancer Coalition	$55,405	$7,095	$62,500
This is a collaborative project with Kimlin Ashing-Giwa of Beckman Research Institute of the City of Hope					

Table of Contents

California Breast Cancer Research Program
Annual Report to the State of California Legislature 2007

Report prepared by the University of California, Office of the President pursuant to Article 1 of Chapter 2 of Part 1 of Division 103 of the California Health and Safety Code

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About the California Breast Cancer Research Program

Making California a Leader among States

In 1993, California breast cancer activists joined forces with scientists, clinicians, state legislators, and University of California officials to propel the state into national leadership for breast cancer research.

The activists, most of them women who had survived or currently had breast cancer, were impatient with the slow pace of progress against the disease. With their allies, they wrote and won passage of statewide legislation to push breast cancer research in new, creative directions. The California Breast Cancer Act, sponsored by then-Assemblywoman Barbara Friedman, raised the tobacco tax by two cents a pack, with 45 percent of the proceeds going to the California Breast Cancer Research Program (CBCRP), which is administered as a public service by the University of California. The CBCRP has since become the largest, most stable state-funded breast cancer research effort in the nation.

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

The CBCRP has provided a total of over $181 million in research funds since 1993. In 2007, the CBCRP awarded $7.1 million for 35 single- and multiple-year research projects at 21 California institutions.

The CBCRP is funded primarily by the tobacco tax, a steadily declining source of revenue due to decreasing consumption of tobacco products. This funding is supplemented with taxpayer donations contributed through state income donations. The CBCRP also receives private contributions.

Pushing the Research Boundaries

During its fourteen-year history, the CBCRP has established a record for filling gaps not covered by other research funders, jump-starting new areas of research, and fostering new types of collaboration. Now the Program is challenging itself to find ways to focus its resources on questions that could change the face of breast cancer research.

The CBCRP's five-year Special Research Initiatives will investigate the role of the environment in breast cancer and the reasons why breast cancer affects some groups of Californians more than others. The CBCRP is investing 30 percent of its funds over this period in these initiatives. During 2007, to assure that the research will have the most impact on breast cancer and to avoid duplication, the CBCRP drafted a review of previous research in the areas to be covered under the Special Research Initiatives. This draft, titled "Identifying Gaps in Breast Cancer Research," has been posted to the CBCRP Web site, www.cabreastcancer.org. Two committees composed of experts of national stature are providing leadership for this research effort. The 6-member steering committee is guiding the Special Research Initiatives. The 33-member strategy team is developing specific recommendations for research to be funded (See Appendix A). During 2007, the public had opportunities to suggest questions to be investigated

under the Special Research Initiatives through four statewide stakeholder town hall meetings, two teleconferences, and via a special section of the CBCRP Web site. The Special Research Initiatives are discussed more fully in the section of this report titled “The CBCRP’s Strategy for Funding Research.”

A Structure That Encourages Public Input

The CBCRP’s structure has set a standard for community involvement that has inspired similar changes in other research funding agencies around the nation. Through example, the CBCRP is encouraging other agencies to include community advocates in the review of research proposals and to involve community members in the design and conduct of research. Breast cancer advocates play a leading role in every aspect of the CBCRP’s work, from setting research priorities to recommending grants for funding to getting out the word about research results.

The CBCRP is under the direction of the University of California, Office of the President, in Oakland, with a staff managing the solicitation, review, award, and oversight of grants.

The CBCRP’s 16-member advisory Breast Cancer Research Council includes scientists, clinicians, representatives of industry and nonprofit health organizations, and breast cancer advocates. The council provides vision, sets research priorities, and determines how the CBCRP invests its funds in research. It also conducts one of two reviews that every proposal must pass to receive funding. The council reviews research proposals for relevance to the CBCRP’s goals, while teams of research scientists and breast cancer advocates from outside California also review all proposals for scientific merit.

In addition, all Californians concerned about breast cancer have opportunities to help set the research agenda via several avenues of feedback created by the Program. The Program’s biennial research symposia bring the scientific and treatment communities into dialog with a broader range of the public than is common at such conferences. Each symposium includes a session for members of the public to provide feedback on the Program’s work and suggest research priorities. The Program's five-year Special Research Initiatives included several opportunities during 2007 for the public to take part in identifying and prioritizing the questions to be investigated. These opportunities included town hall meetings, teleconferences, and a special section on the CBCRP Web site. The CBCRP also encourages public review of its funded research through its *Advances in Breast Cancer Research* report and the Program’s Web site (www.CABreastCancer.org), where members of the public can leave written comments.

By bringing the research, advocacy, and treatment communities into closer collaboration, the California Breast Cancer Research Program pushes the boundaries of research, mobilizing greater creativity and resources, toward decreasing—and ending—the suffering and death caused by breast cancer.

Sharing Research With Scientists and the Public

The sponsors of the legislation that established the California Breast Cancer Research Program recognized that funding high quality research is necessary but not sufficient to fulfill the Program's mission. Therefore the statutory language calls on the CBCRP to disseminate the results of the research it funds. If the research is going to be effective in reducing or ending the suffering caused by breast cancer, then people need to know the results. The scientific community needs to know, to make progress against the disease. The medical community needs to know, to improve prevention and treatment. People with breast cancer need the opportunity to learn about new prevention and treatment options. Breast cancer activists and policy makers need information about research results to shape their advocacy agenda. Communities affected by breast cancer need to know what's been proven to work in other communities. And the taxpayers of California need to know what their taxes are funding.

The scientists whose projects are funded by the CBCRP publish their results in peer-reviewed scientific journals and present them at scientific conferences. The California Breast Cancer Research Program is committed to making the research it funds available to a much wider audience. The CBCRP publishes and distributes summaries of Program-funded research widely, in print and over the Internet. The CBCRP is one of the few research funding programs in the world to publish annual summaries of research while the studies are still in progress, so that scientists and other interested people can make use of the information as soon as possible. Research results and research progress are disseminated in a variety of ways:

Research Symposia

Every two years, the CBCRP holds a statewide symposium, free to the public, where researchers present the results of their CBCRP-funded studies. The Program's sixth symposium, "From Research to Action: Breaking New Ground," was held September 7-9, 2007, in Los Angeles. The symposium brought together nearly 600 scientists, health care and social service professionals, and women and men whose lives have been affected by breast cancer. The CBCRP makes a special effort to bring women who have, had, or are at risk of breast cancer to the symposium. Eighty-two women received scholarships that covered their travel and accommodations. The mix of diverse attendees leads to spirited exchanges of ideas between researchers and the people most affected by breast cancer, as well as increased networking opportunities.

Plenary sessions at the sixth symposium included "Racial and Ethnic Disparities in Breast Cancer" and "New Directions in Breast Cancer Treatment." In these plenary sessions, and in workshops and breakout sessions, researchers presented their latest findings, gave overviews of research fields, and predicted coming trends.

Illustrated posters depicting the results of 80 research projects funded by the CBCRP were on display throughout the symposium. Five researchers presented their results in a plenary session. More researchers were on hand for a poster viewing session where they could answer questions and receive comments about their research directly from the public and their scientific colleagues. Trained advocates were also available to interpret posters for non-scientist attendees.

In addition, the symposium booklet given to all attendees contained abstracts of all research projects presented on posters.

At a Meet the Experts Breakfast, the public discussed breast cancer topics in small groups with research scientists and other experts. Topics ranged from advocacy for young women with breast cancer, to new drug development for treatment, to the environment and breast cancer. Attendees new to breast cancer could get the basics at a workshop called Breast Cancer 101.

The CBCRP's sixth symposium included a workshop for researchers who wanted to learn to navigate the Program's process for applying for a research grant. An extra day of training was also provided for members of community organizations and experienced researchers interested in teaming up to conduct research with funding from the CBCRP's Community Research Collaboration awards.

Representatives from California community organizations staffed over 20 exhibits. They provided information about what women could do for themselves and their communities to reduce the impact of breast cancer, including reducing their risk of getting the disease, finding support groups, and joining advocacy efforts to advance policy changes that improve access to diagnostic services and care.

CBCRP Listens, a town-hall-style meeting, invited feedback on the Program's Special Research Initiatives, which will investigate the role of the environment in breast cancer and the reasons why some groups of women bear a greater burden of the disease than others. Feedback from past CBCRP Listens sessions was one factor that led to the creation of the Special Research Initiatives.

The symposium also included a curated art exhibition of painting, photography, sculpture, graphic art, textile art, and mixed media. Also on view was *Expressions: the Art of Science and Healing*, the CBCRP's collection of wearable breast art, which has been shown in California art galleries.

The symposium was designed to be healthy and environmentally friendly. Free yoga and exercise classes were offered each morning. Organic produce was served when possible. The use of plastic products was reduced and Styrofoam products were eliminated in the symposium food service. All printed symposium materials were produced on recycled chlorine-free paper with soy-based ink. In addition, opportunities for recycling were provided.

A report, free to the public in booklet form and available on the CBCRP Web site, provides summaries of all presentations made at the 2007 symposium.

Web site

The CBCRP Web site (www.CABreastCancer.org) has summaries of all completed research projects and annual progress reports for ongoing projects, in language accessible to the general reader. All research on the CBCRP Web site is fully searchable, and visitors who want to keep up with the latest research can search to access the most recently posted findings. A featured researcher section, which changes 8-12 times per year, profiles one researcher and her or his findings. Visitors to the Web site can ask this expert questions, and receive answers, via email. On the CBCRP Web site home page, two short summaries of interesting research are posted, with links to further information. These short summaries change daily. Progress on the development of the CBCRP's Special Research Initiatives is also reported on the Web site.

Publication abstracts supported by CBCRP funding have links to the National Institutes of Health’s PubMed, a public-access database of biomedical journals. The CBCRP Web site also

contains a list of each year's awards and information on applying for grants. In addition, all CBCRP publications are available and downloadable. A new feature during 2007 allows visitors to listen to a presentation made at the CBCRP's recent symposium.

The Web site includes an opportunity to join our volunteer team, request specific information from the CBCRP and make online donations to the CBCRP.

Publications

All CBCRP publications are available free to the public in printed form and on the CBCRP Web site. Multiple copies are available free of charge to organizations.

Compendium of Awards: To make it easy for scientists and the public to follow CBCRP-funded research from the beginning, a description of newly funded projects is published each year.

Formal Evaluations of CBCRP: Formal evaluations let the public understand the success and need for improvement of CBCRP work.

Community Research Collaboration Awards Abstract Booklet: The CBCRP's Community Research Collaboration awards bring together members of community groups and academic scientists to conduct breast cancer research. This booklet, with abstracts of all community research collaboration research funded by the CBCRP to date, is designed to make community groups aware of this opportunity.

Newsletter: The CBCRP's newsletters report on new awards, research results, scientific meetings where the CBCRP is presenting an exhibit of Program work, and other Program news.

Breast Cancer in California: A Closer Look/El Cancer de Seno en California: Una Mirada Mas de Cerca: A 40-page booklet, provides a picture of breast cancer's effect on the lives of California women. During 2007, the CBCRP published the Spanish-language version.

Identifying Gaps in Breast Cancer Research: This research paper reviews previous research in the areas to be covered under the CBCRP's Special Research Initiatives: the role of the environment in breast cancer and the reasons why some groups of women bear a greater burden of the disease. The draft is available on the CBCRP Web site; a printed version will be published in the future.

California Breast Cancer Research Program brochure: An overview of the CBCRP, our philosophy, and opportunities to get involved. The brochure is available in English and Spanish.

Further Methods of Sharing Research

E-Newsletter: In May, 2007, the CBCRP launched an email newsletter that gives subscribers timely announcements of funding opportunities, early notification of new research resources and breast cancer conferences, and avenues to stay involved, informed, and active in the fight against breast cancer. The email newsletter is distributed to over 2,000 stakeholders.

Expressions: The Art of Healing Breast Cancer: The CBCRP owns a collection of wearable breast art created by California artists to reflect on the breast cancer epidemic. During 2007, portions of *Expressions: the Art of Healing Breast Cancer* were displayed along with the

CBCRP's exhibit at scientific meetings, and the entire collection was on exhibit at the CBCRP's 2007 symposium. An art catalog of this collection is available online at the CBCRP Web site.

Exhibits at Scientific and Community Meetings: The CBCRP presented an exhibit of the Program's work at a number of scientific and community meetings during 2007. The meetings included:

- 5th International Symposium on the Intraductal Approach to Breast Cancer, Santa Monica
- Bay Area Breast Cancer and Environment Research Center's Communities Coming Together to Understand Girls' Development During Puberty Educational Forum, San Francisco
- Cedar Sinai's Sixth Annual Women's Health Conference, Los Angeles
- Just Darling Fashion Event, Oakland
- American Association for Cancer Research Annual Meeting, Los Angeles
- California Black Health Network Statewide Conference, Ontario
- Professional Business Women of California Conference, San Francisco
- African American Women's Each One Reach One Breast Cancer Conference, Oakland
- Cause to Run Marathon, San Francisco
- Women of Color Survivors' Breakfast, Los Angeles
- California Tobacco-Related Disease Program Annual Investigators' Meeting, Sacramento
- Partnership Matters Public Forum, Sacramento
- On the Way to a Cure – Komen on the Go Cancer Health Expo, San Francisco
- Community Breast Health Project's 4th Annual Breast Cancer Conference, Palo Alto
- American Association for Cancer Research/Minorities in Cancer Research Council Conference, Atlanta, GA

Serving the Media: The CBCRP does regular outreach to the media about the Program and about CBCRP-funded research projects that are of interest to the general public. When reporters from TV, newspapers, magazines, or other media need information on breast cancer research, the CBCRP links them with the appropriate experts. During 2007, calls from both the public and the media rose after radio and TV appearances by Program Director Dr. Marion H. E. Kavanaugh-Lynch and a *Sacramento Bee* article that included comments from Dr. Kavanaugh-Lynch.

Speakers and Educational Bureau: When community organizations want speakers on breast cancer research for meetings and public events, the CBCRP provides referrals from the Program's network of researchers and advocates. The Program also refers research experts to teach continuing education classes for healthcare professionals.

Collaborating with Breast Cancer Advocates and California Communities

People with breast cancer and survivors of the disease are involved in every level of the California Breast Cancer Research Program, from deciding which research the Program funds to actually carrying out some of the CBCRP's research. Non-scientist advocates have played a leadership role in the CBCRP right from the start. The CBCRP has been in the forefront of a nationwide trend among research funding agencies toward a greater voice for the people breast cancer affects most, and the CBCRP still sets the standard for having advocates at all levels of leadership.

Breast Cancer Advocates in Leadership

Breast cancer advocates comprise one-third of the CBCRP's highest leadership body, the advisory council. The council recommends the research proposals that best fit the CBCRP's funding strategy. Throughout the CBCRP's fourteen-year history, an advocate has also always served as the council's Chair or Vice-Chair. In addition, out-of-state panels of scientists and advocates review all CBCRP research proposals for scientific merit. Out-of-state breast cancer advocates are full voting members of these review panels and a California advocate observes each one. Advocates are also involved in the development and leadership of the CBCRP's Special Research Initiatives, a five-year effort to investigate the environmental causes of breast cancer and the reasons why some groups of women bear a greater burden of the disease.

Having breast cancer advocates in a wide variety of leadership positions ensures that the CBCRP funds research important to people who face the disease in their day-to-day lives.

Communities Conducting Research

Breast cancer advocates are also investigators on a rising number of the CBCRP's research projects. In 1997, the CBCRP pioneered a new type of research grant that allows community groups and breast cancer advocacy organizations to team up with experienced scientists to pursue a research idea of importance to the community in a scientifically rigorous way. These Community Research Collaboration (CRC) awards are open to nonprofit organizations or ad-hoc community groups in any California community affected by breast cancer. The majority of community collaborators funded by the CBCRP to date have been breast cancer survivors.

Research involving community organizations as active partners is gaining credibility in the United States, and the CBCRP has been a prime mover in extending and supporting the use of this kind of research to breast cancer in California. The Community Research Collaboration awards have provided over $14 million in funding to 59 collaborative projects. Projects funded over the years include:

- Investigating immigrant Afghan women's concerns, knowledge, attitudes, behaviors, and sources of information about breast care, and perceived barriers to care, as well as cultural modifications needed to adapt breast cancer-related education programs for this

group. Information learned from the project has the potential to increase breast health awareness among immigrant Afghan women and also other groups of Muslim women in California and the U.S.

- Educating African American and Hispanic women about the importance of participating in breast cancer clinical trials and developing tools for an educational program entitled Scientific Literacy and Breast Cancer Clinical Trials Education Program.
- Determining the benefits of peer-led African American support groups to address the unmet needs of African American women with breast cancer in a geographically underserved area.
- Assessing the benefits and acceptability of a videoconferencing support group for rural and isolated women.
- Evaluating an ethical will intervention for underserved women at end of life.
- Determining whether Vietnamese nail salon workers have higher breast cancer rates and whether this group of women are exposed to workplace exposures that exceed health-based standards.
- Breast cancer risk factors of lesbians and heterosexual women.
- Culturally-appropriate care for Samoan American and Korean American women.
- The effectiveness of "peer navigators"—trained volunteer breast cancer survivors who work with newly-diagnosed women to understand decisions about treatment and to cope with the disease.
- Testing of a culturally-sensitive DVD to increase knowledge of breast health and breast cancer risk among Native American women.
- The breast cancer experience of Slavic American women.
- The barriers to older Thai American women participating in breast cancer screening.

The CBCRP's Community Research Collaboration awards are designed to have an impact on breast cancer health care:

- The San Joaquin Valley Health Consortium and California State University, Fresno are completing a pilot project to identify barriers in the Fresno County health care process that lead to some groups of women receiving less than optimal and complete breast cancer care. Based on their findings, they intend to design a navigation service that will assist breast cancer patients with accessing health care and making treatment decisions in a manner that responds to the diversity within the community and health system. The pilot project will prepare for a larger research project that tests the health and cost impacts of this navigation service.
- Patient navigators—who provide support, information, and advice to women about breast cancer treatment options and accessing services—need ways to exchange experiences, explore resource sharing, and measure the benefit and quality of services they provide. The Alta Bates Medical Center in Berkeley used a CBCRP grant to bring providers of breast cancer navigation services together for a full-day conference. Navigators were encouraged to network and share research. The conference also facilitated documentation and measurement of navigation services to provide both resources for new navigation programs and evidence-based literature on the value of these services.

Fostering Community-Based Research

The CBCRP has taken major steps over the past five years to enable diverse populations in California to take part in quality scientific research into breast cancer issues of interest to their communities. These efforts resulted in 2007 with the CBCRP receiving a record of 26 applications for CRC grants, the largest number in the eleven years the Program has offered this type of grant. The scientific quality of these applications was also very high. The CBCRP funded six community research collaboration projects which cover a wide range of under-studied research topics. Women whose breast cancer issues have been explored very little, or not at all, will now have their issues systematically addressed.

The effort that led to this success began in 2003. That year, the CBCRP began a series of changes to make the process of applying for CRC grants and conducting CRC research more user-friendly to both the community organizations and scientific researchers who make up the research teams.

Beginning in 2003, the CBCRP has offered a technical assistance program geared to interested community agencies and prospective applicants. The application process and application evaluation process were also changed to better suit the community participation research model. During 2005, the CBCRP added teleconference training for community groups and academic researchers interested in applying for CRC awards.

During 2006 and 2007, the CBCRP held outreach workshops and outreach teleconferences about the opportunity to apply for CRC awards, and also made presentations at community events across the state. Funded CRC teams participated in the outreach workshops, sharing their experiences and the challenges they faced working together. Attendees gave positive feedback about the funded research teams' role in the outreach workshops and reported that they learned from these funded teams.

Over two dozen teleconferences and site visits also provided training and assistance both to research teams who had been awarded grants to plan future research projects, and to teams conducting research.

In addition, the CBCRP highlighted funded CRC grantees during its 2007 symposium. A breakout session presented research on Services and Support for the Underserved. A workshop was devoted to the Theory and Practice of Community-based Participatory Research, the theoretical model upon which the CBCRP's Community Research Collaborations are based. The workshop drew a record number of attendees, many from non-breast cancer specific organizations who were interested in learning more about community-based participatory research.

During 2007, at major national and international conferences, the CBCRP also presented results of the Program's research into the effectiveness of community-based participatory breast cancer research. In 2007, the CBCRP made a presentation alongside funded grantees to an international audience at the 10th Annual Community Campus Partnership for Health Conference in Toronto, Canada. The presentation, *Funders, Communities, & Academia: Creating Authentic Partnerships,* was well received and demonstrated a unique relationship between funders and grantees as an important element of community-based participatory research.

Other CBCRP presentations at conferences during 2007 were based on an evaluation conducted by the CBCRP that found that the Community Research Collaboration awards empowered communities to address questions important to them. This contrasts with past research in underserved communities, which has often left community members feeling left out

of the process, results and potential benefits by scientists who come in from the outside and conduct research that leaves the community with no lasting benefit. The evaluation further found that the CRC awards may be the most appropriate and effective way to perform breast cancer research within California’s diverse communities.

The CBCRP published its third evaluation of the CRC Awards in 2007. Results from this evaluation found that research teams that more closely reflected authentic partnerships had the most successful outcomes evident from their research project and partnership. For more on this evaluation, see the section of this report titled, "Improving the CBCRP Through Evaluation."

As a result of the CBCRP's leadership in community-based participatory research, the Program's Director, Dr. Marion H. E. Kavanaugh-Lynch, serves as the chair of a National Institutes of Health committee that reviews that agency's funding for community-based participatory research.

During 2008, the CBCRP will continue to facilitate diverse communities in California taking part in quality scientific breast cancer research and to take leadership in community-based participatory research.

The CBCRP's Strategy for Funding Research

The CBCRP's Breast Cancer Research Council and staff set the priorities for the Program's research funding. The following ten criteria are used by the Breast Cancer Research Council to set priorities that push the boundaries of research.

1. The research helps form and nurture collaboration among California scientists, clinicians, advocates, community members, and others.
2. The research helps recruit, retain, and develop high-quality California-based investigators who engage in breast cancer research.
3. The research embodies innovative ideas (i.e., new drugs, new strategies, new paradigms).
4. The research addresses the public health outcomes of prevention, earliest detection, effective treatments, and quality of life.
5. The research leads quickly to more effective products, technologies, or interventions and their application/delivery to Californians.
6. The research helps drive policy in both the private and public sectors on breast cancer in California.
7. The research reduces disparities and/or addresses the needs of the underserved in California.
8. The research complements, builds on, feeds into, but does not duplicate the research programs of other organizations interested in breast cancer.
9. The research addresses a breast cancer need that is specific but not necessarily unique to the burden of breast cancer in California.
10. The research is responsive to the perceived breast cancer research needs and expectations of the CBCRP as identified by scientists and the public in California.

To ensure that the CBCRP fulfills all of the criteria, the Council devised a two-part funding strategy, the Special Research Initiatives and Core Funding.

Five-Year Special Research Initiatives

The CBCRP's Special Research Initiatives address two overlapping questions:

- The impact of the environment on breast cancer;
- The reasons why women from some ethnic groups, income levels, and geographic areas of the state of California bear more of the burden of breast cancer than others.

The CBCRP launched the Special Research Initiatives in 2005 because the Program's previous efforts to increase research addressing these questions have not led to enough progress. California is an ideal laboratory for research into the environment's role in breast cancer and the reasons why some groups of women bear an unequal burden of the disease. The state has varied geography, heavily industrialized areas, and a large agricultural area. It has a mix of urban, suburban, small town, and rural communities. The state's population is ethnically diverse. California also has communities with the highest rates of breast cancer in the nation.

The initiatives are the result of a thoughtful, thorough planning process that included analyzing years of nationwide and CBCRP-funded breast cancer research, and collecting feedback from breast cancer advocates, researchers, and the public.

The CBCRP is investing 30 percent of its research funds over five years, which will result in at least $18 million for these investigations.

To select the research that will lead to the most progress against breast cancer, the Program is following a carefully-crafted, two-year, publicly-accessible strategy development process. A steering committee of researchers and advocates from across the nation is guiding this process of developing strategy. The members of this committee include:

- **Olufunmilayo I. Olopade, M.D.,** who recently received a MacArthur fellowship for her work translating findings on the molecular genetics of breast cancer in African American and African women into innovative clinical practices in the United States and abroad.
- **Susan Shinagawa,** who is widely recognized as the nation's leading Asian American cancer and chronic pain advocate and activist.
- **David R. Williams, Ph.D.,** a leader in research into how racial discrimination affects heart disease and other health conditions.
- **Julia G. Brody, Ph.D.,** one of the world's experts on breast cancer and the environment.
- **Sandra Steingraber, Ph.D.,** author of the book *Living Downstream: An Ecologist Looks at Cancer and the Environment*, and an environmental activist with a national reputation.

The CBCRP's director, Marion H.E. Kavanaugh-Lynch, also serves on the steering committee.

The CBCRP has been following a two-year process for developing the SRI funding strategy because the questions selected for investigation hold great promise for progress against breast cancer, but they are also difficult to research. There's no scientific consensus on where to begin. Information about previous research into these questions has up until now been available only through widely scattered sources.

The CBCRP's strategy development process is designed to avoid duplicating previous research and to base the Program's efforts on the most up-to-date knowledge and on the opinions of experts nationwide. The process allows time to make the best use of the state's resources by identifying and involving California institutions and organizations who can join forces to make progress against breast cancer. The goal is an integrated, coordinated statewide approach that ensures statewide solutions.

The process of developing this strategy moved forward in 2007. The CBCRP completed drafting a review of previous research into the impact of the environment on breast cancer and the reasons why some groups of women bear a greater burden of the disease. This draft, titled "Identifying Gaps in Breast Cancer Research," runs to hundreds of pages, considers the results of thousands of research studies, summarizes the latest thinking on these questions, and makes recommendations for research to be pursued under the Special Research Initiatives. "Identifying Gaps in Breast Cancer Research" is available to the public on the CBCRP Web site. A panel of science advisors, composed of experts from across the nation, reviewed and shaped "Identifying Gaps in Breast Cancer Research." A list of the science advisors, staff, and consultants who wrote and shaped "Identifying Gaps in Breast Cancer Research" is found in Appendix B.

During 2007, the CBCRP gathered ideas from a variety of sources concerning research to be conducted under the Special Research Initiatives. Four town hall stakeholder meetings were held in Fresno, Los Angeles, San Francisco, and Ukiah. Interested members of the public viewed a slide presentation summarizing important points from the "Identifying Gaps in Breast Cancer

Research" review. Participants were then invited to submit ideas for research, during the meeting or later online. Two teleconferences and an online opportunity further encouraged the public to submit ideas. Those who participated in this process were later able to rate the ideas submitted. At the CBCRP symposium in September, attendees were also asked to rate submitted research ideas. Participants in this process included women affected by breast cancer, investigators, clinicians, government officials, and interested members of the public across California.

A 33-member strategy team of scientists, advocates, and clinicians from California and across the nation met twice during 2007 to consider input from the public and use the review of previous research to make specific recommendations for research to be funded. The strategy team, the members of which are listed in Appendix B, will make its recommendations during 2008.

As a result of the CBCRP's leadership in research into the role of the environment in breast cancer, the Program's director, Marion H.E. Kavanaugh-Lynch, has been appointed to the nine-member California Environmental Contaminant Biomonitoring Program Scientific Guidance Panel. The panel assists the Department of Health Services and California Environmental Protections Agency by providing scientific peer reviews and making recommendations regarding the design and implementation of the California Environmental Contaminant Biomonitoring Program.

Core Funding

After setting aside 30 percent of CBCRP research funds for the Special Research Initiatives, the remaining 70 percent is dedicated to challenging investigators to use the funds to maximum effect. During its fourteen-year history, the CBCRP has developed and fine-tuned a funding strategy designed to stimulate innovative research.

Each research project must fall under one of the CBCRP's Priority Issue areas:

- The Community Impact of Breast Cancer
- Etiology and Prevention
- Biology of the Breast Cell
- Detection, Prognosis, and Treatment

Each research project must also qualify as one of the CBCRP types of awards:

- **Community Research Collaboration (CRC) award:** Brings community organizations—such as breast cancer advocacy organizations, community clinics, or organizations serving under-represented women—together with experienced scientists to investigate breast cancer problems that are important to that community, using culturally-appropriate research methods. Pilot CRC awards are funded up to 18 months and up to $150,000 in direct costs. Full CRC awards are funded up to three years for up to $600,000 in direct costs.
- **Innovative Developmental and Exploratory Award (IDEA):** Funds promising high-risk/high-reward research to “road test” innovative concepts. Applicants must show how their project is part of a step-by-step research process that will lead to practical applications. IDEAs are funded for up to 18 months and up to $100,000—and for studies using animals or humans, $150,000—in direct costs.
- **IDEA–competitive renewal**: Allows recently-funded recipients of CBCRP IDEA grants to compete for additional funding, if the project has succeeded in meeting key milestones in a research process that will lead to practical applications. IDEA-competitive renewal awards are

available for up to two years and up to $200,000—and for studies using animals or humans, $250,000—in direct costs.

- **Postdoctoral Fellowship award**: Funds advanced training under a breast cancer mentor. Total postdoctoral tenure (prior training plus new CBCRP funding) is limited to five years, and the maximum award duration is three years at $45,000 per year.
- **Dissertation award**: Supports the completion of dissertation research by masters or doctoral degree candidates. Dissertations are funded up to $38,000 per year for up to two years.
- **Joining Forces Conference award**: Supports a conference, symposium, retreat, or other meeting to link breast cancer researchers, non-breast cancer investigators, and community members for the purpose of stimulating new ideas and collaborations.
- **Translational Research award**: Funds research that will take basic science findings quickly toward treatment, diagnosis, prevention or another application that can directly impact breast cancer, either in a medical clinic setting or through a public health measure.

The Translational Research award, offered for the first time during 2007, drew a high response from interested researchers. The CBCRP received over 50 letters of intent and 10 applications. Only one study was funded, due to limitations on CBCRP funds. This award replaces the CBCRP's previous Translational Research Collaboration Award, which was a mixed success. The requirements have been altered to stimulate research that moves most directly and quickly toward applications that will create progress against breast cancer.

Two goals underlying the CBCRP's funding strategy are the leveraging of Program funds to influence the research system nationwide, and enlarging the pool of breast cancer researchers.

Influencing the Research System Nationwide

The CBCRP is part of a much larger research system. The federal government funds breast cancer research through agencies like the National Cancer Institute and the Department of Defense. Nonprofit organizations and for-profit corporations also fund breast cancer research. Although the CBCRP is the largest state funding source for breast cancer research in California, these funds make up only a small part of the funds granted through the larger system. The CBCRP tries to influence this larger research system to move in new, creative directions.

An example is the CBCRP’s Innovative, Developmental, and Exploratory Awards (IDEAs). These awards were specifically designed to fund research that has a high potential for scientific payoff—and also a high potential for failure. When the CBCRP began funding breast cancer research in 1995, less than 10 percent of research proposals submitted to the nation’s funding agencies were successful. This led the people who decided what got funded—panels of research experts—to look for proposals that seemed most likely to succeed. Research scientists had to have done a significant portion of the research, and have strong preliminary data, before they could even get a grant. This made it hard for anyone to get funding in order to try out a high-risk idea. However, high-risk ideas are often the source of scientific breakthroughs.

If the research funded by an IDEA succeeds, the researcher may well be able to get another research funding agency to fund the next step. For example, in 2005, the CBCRP awarded Mark Moasser, M.D., at the University of California San Francisco, an IDEA grant. Dr. Moasser used it to investigate more effective treatments for a subset of breast cancers containing overactive proteins called HER-2 that drive the growth and spread of these tumors. Dr. Moasser's research goal was to discover why medications that effectively block the HER-2 protein do not work against these tumors. He discovered the molecule-level chemical reactions within breast

cancer cells that allow the cells to get around the effects of medications that block the HER-2 protein. The National Institutes of Health recognized the importance of this discovery by awarding Dr. Moasser a grant in 2007 to test several treatment strategies for tumors with overactive HER-2 protein, based on the findings from his CBCRP-funded research. If the strategies Dr. Moasser is investigating succeed in laboratory studies, he plans to propose testing them with breast cancer patients.

The CBCRP uses additional methods to get creative new research going. These include encouraging researchers in California to submit exciting new ideas. The CBCRP also developed a new scoring system to help reviewers read proposals with a perspective toward rewarding high-risk research.

Enlarging the Pool of Breast Cancer Researchers

Another major goal of the CBCRP is to increase the number of talented scientists engaged in breast cancer research. Some of the Program's grants have allowed investigators to specialize in, or concentrate much of their efforts on, breast cancer research. For example, the CBCRP awarded Karlene Cimprich, Ph.D., of Stanford University, two IDEA grants in 2002 and 2007. Dr. Cimprich's work centers on the normal processes within cells that repair damage to DNA that would otherwise lead to cells becoming cancer cells. She uses frog eggs as a model for human cells, because they have similar DNA repair processes. CBCRP funding allowed Dr. Cimprich to apply her research specifically to the DNA damage caused by mutated forms of the BRCA1 and BRCA2 genes. The normal version of theses genes is involved in DNA repair, but women who have inherited mutated versions of these genes are at very high risk for breast cancer. Currently, Dr. Cimprich is attempting to develop a molecular profile of breast tumors that have some of the same defects in cellular DNA repair systems as do tumors from women with BRCA1/2 mutations. The goal is to identify up to 25 percent of breast cancer patients who could potentially benefit from medications called PARP inhibitors that target tumors with defects in cell processes initiated by BRCA genes.

The CBCRP also makes it possible for new scientists to begin their careers as specialists in breast cancer research, through Postdoctoral Fellowship and Dissertation awards. Since the CBCRP's inception, the Program's Postdoctoral and Dissertation awards have launched over 200 new breast cancer research careers.

Funding by Priority Issue and by Award Type

Every research grant funded under the CBCRP's Core Funding must fit within two separate sets of categories, the Priority Issues (research topic) and the Award Types. The Priority Issues are broad, to allow the Program to have an impact across a wide spectrum of breast cancer research. The Award Types, discussed on previous pages, are narrowly targeted to focus CBCRP funding where it will lead to the most rapid progress.

Below, two tables present statistics on the 35 projects funded during 2007 by Priority Issue and by Award Type.

Table 3. 2007 Grants Awarded by Priority Issue

	Number of Grants	Amount	Percentage of Total Funding
Community Impact of Breast Cancer	**6**	**$1,935,241**	**27%**
Etiology and Prevention	**2**	**$911,413**	**13%**
Detection, Prognosis and Treatment	**14**	**$2,825,270**	**40%**
Biology of the Breast Cell	**13**	**$1,429,718**	**20%**
Totals	**35**	**$7,101,642**	**100%**

Table 4. 2007 Grants Awarded by Award Type

Award Type	Number of Grants	Amount	Percentage of Total Funding
Dissertation	**8**	**$599,863**	**8%**
Postdoctoral Fellowship	**6**	**$540,000**	**8%**
Innovative Developmental and Exploratory (IDEA)	**9**	**$1,478,389**	**20%**
IDEA-Competitive Renewal	**3**	**$1.004,677**	**14%**
Community Research Collaboration (CRC) Pilot Award	**3**	**$566,641**	**8%**
Community Research Collaboration (CRC) Full Award	**3**	**$2,020,512**	**28%**
Joining Forces Conference Award	**2**	**$40,000**	**4%**
Translational Research Award	**1**	**$851,559**	**11%**
Totals	**35**	**$7,101,642**	**100%**

Improving the CBCRP through Evaluation

California taxpayers deserve to have the funds they provide for breast cancer research spent wisely. That's why the California Breast Cancer Research Program is conducting a multi-year, formal evaluation of the entire program. Evaluation helps the program target research dollars where they will do the most to reduce and end the suffering caused by breast cancer.

Over the past several years, the CBCRP has evaluated several of its award types: the Community Research Collaboration awards, the Postdoctoral Fellowship awards, the New Investigator awards, and the Innovative, Developmental, Exploratory Awards (IDEAs). The results of these evaluations were used by the CBCRP's advisory Breast Cancer Research Council to set priorities. These evaluations are available in print to the public and can also be viewed on the Program Web site.

During 2007, the CBCRP conducted a third evaluation of the Community Research Collaboration Awards. The purpose of this evaluation was to investigate whether the quality of the collaboration between community members and scientific researchers led to better research results and outcomes. The evaluation found that research teams who collaborated most effectively on their projects and involved their communities in the research has the most positive outcomes. Examples of positive outcomes include the research results improving health education or health services, the research results impacting health policy or government programs, the general public or the community being educated as a result of the research project, and the researchers receiving awards or honors for their research.

Over the past year, the CBCRP also began a three-year priority setting process. Previous priority-setting processes have led to major improvements in the type of research the CBCRP funds. In addition, during 2007, the CBCRP evaluated the application process for the Program's Core Funding awards, and used the results to streamline the process.

Evaluation Leading to Improvement

Formal evaluations are used to improve the CBCRP. Examples of changes in the program made as a result of evaluations include:

- The CBCRP's first formal evaluation of the program's Community Research Collaborations, in 2000, led to a multi-year effort that has increased the number of community organizations and scientific researchers collaborating on breast cancer research questions of interest to communities of California women. This effort is discussed more fully in this report in the section titled "Collaborating with Breast Cancer Activists and California Communities."
- The CBCRP's second formal evaluation of the Community Research Collaborations, conducted in 2005, highlighted a problem facing the research teams. Once they had successfully tested an intervention, they encountered difficulty applying their research results because of lack of funds. This led to the CBCRP providing a new grant opportunity, where successful research teams can apply for an additional grant to make their results available to other programs, apply their results to changing public policy, or make the public more aware of their results. The evaluation also resulted in the CRC grant amount being increased to $150,000 for pilot awards and $600,000 for full awards.

- A previous three-year priority-setting process led the CBCRP to discontinue award types that were not meeting the program's goals. It also led to the CBCRP investing 30 percent of its funds for five years in the Program's Special Research Initiatives, in order to answer crucial questions about the influence of the environment on breast cancer, and to uncover the reasons why some groups in California bear more of the burden of the disease. For more on the CBCRP's Special Research Initiatives, see the previous section of this report titled, "The CBCRP's Strategy for Funding Research."
- CBCRP staff and the Program's advisory council informally evaluated how CBCRP-funded research gets translated into new medications, new detection methods, new programs to support patients, policy changes, or other actions that have an impact on breast cancer. As a result, applicants for CBCRP research grants are now required to describe the steps necessary to translate their research project into action that impacts the disease. This has enabled the Program to target its limited funds toward research most likely to lead to progress against breast cancer.

Research Progress and Results

On the following pages, the results of research funded by the California Breast Cancer Research Program and completed during 2007 are presented. Listings of research in progress and research grants awarded this year are also presented.

The Research Progress and Results section is organized by the CBCRP's four major Priority Issues:

- The Community Impact of Breast Cancer
- Etiology and Prevention
- Detection, Prognosis, and Treatment
- Biology of the Breast Cell

The Community Impact of Breast Cancer

California is a blend of diverse communities offering a unique opportunity to investigate disparities and the unequal burden of breast cancer. Critical questions to be addressed include:

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

The CBCRP has been supporting community-based collaborations for over 10 years, and we offer pre-application workshops and technical assistance to facilitate new partnerships and successful grant applications. We are encouraged that many CRC grants focus on underserved populations to address the underlying disparities. We feel that an "evidence-based" community project great potential to lead to a successful intervention.

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

Three 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

Research Conclusions

Breast Cancer Risk Profile of Vietnamese Nail Salon Workers

Vietnamese workers run more than 80 percent of California nail salons. These workers routinely handle cosmetic products that contain carcinogens and endocrine disruptors, which may increase a woman's risk of breast cancer. **Kim Nguyen**, at **Asian Health Services**, Oakland, and **Peggy Reynolds**, **Ph.D.**, at the **Northern California Cancer Center**, Berkeley, conducted focus groups and surveys of Vietnamese nail salon workers about their health concerns and work conditions. They found that nearly all of the women, most of whom were immigrants, were very concerned about the health effects of the chemicals they used. Over half of the women surveyed had been working in the nail salon industry for more than five years, and a majority of these women reported that they had experienced health problems, such as skin and eye irritation, breathing difficulties, headaches, and asthma, as a result of their work. Eighty-four percent of the women said they had some type of health insurance, and among women over 40 years of age, 89 percent said they had been screened for breast cancer, most (83%) within the last two years.

These results will be used to guide future interventions to reduce breast cancer risk among Vietnamese women.

Partnership to Reduce Cancer Disparities in Spanish Speakers

Latinas often do not have access to the breast cancer education and support available in more affluent communities. Lay Health Workers (LHWs), also known as *promotoras*, are widely used in community clinics as a valuable link between the health care system and the Latino community. However, these *promotora* programs vary significantly, and there is little research that identifies common challenges and synthesizes their solutions. **Rena Pasick, Dr.P.H.**, at the **University of California**, San Francisco, and **Peggy McGuire** at the **Women's Cancer Resource Center**, Oakland, conducted an 18-month project in Alameda County to prepare for a 3-year evaluation of *promotora* programs. This work included interviewing directors of agencies that used *promotoras*, *promotora* managers, and *promotoras* themselves. They also trained members of the Alameda City Latino Center Coalition (ACLCC) in the qualitative research methods they would use in this project. The initial study found that LHW programs empower *promotoras*, increase awareness of specific health issues and access to health care, and foster social change. The team will now develop, implement, and evaluate breast cancer *promotora* programs at two primary clinics in Alameda serving Latinos.

Correlates of Lymphedema Severity and Access to Intervention

Data previously collected by **Rani Eversley, Ph.D.,** at the **University of California**, San Francisco, **Linda Wardlaw**, at the **Charlotte Maxwell Complementary Clinic**, Oakland, and **Dolores Moorehead**, at the **Women's Cancer Resource Center**, Oakland, suggested that ethnic minority women report more arm swelling and pain (lymphedema) after their breast cancer treatment. The researchers also found that many of the women with arm swelling and pain said they had not been informed about the possibility of developing lymphedema prior to their breast cancer surgery and thus were unable to take any preventive measures. This project allowed the research team to develop and pilot test a simple, low-cost, culturally sensitive program, called Total Arm Care Intervention (TACI), to help reduce the risk for lymphedema among women undergoing treatment for breast cancer. The team intends to continue to study the effectiveness of their TACI program.

Consultation Support for Diverse Rural Breast Patients

It is not enough to help patients prepare a list of questions before meeting with a breast care specialist, as the answers they receive can be overwhelming. **Jeffrey Belkora, Ph.D.**, at the **University of California**, San Francisco, **Sara O'Donnell**, at the **Mendocino Cancer Resource Center**, Mendocino, and **Dawn Elsbree**, at the Humboldt Community Breast Health Project, Arcata, investigated which procedures best help patients absorb, remember, and act upon the information and advice they get from breast specialists. Their team interviewed 12 doctors, 10 community health agency staff, and 12 diverse (4 Native American, 4 Latina, and 4 White) breast cancer survivors about what could improve these interactions. Some of the key themes that emerged included: changes to the physical infrastructure, such as the provision of DVDs and recording devices; changes in institutional policies, such as arranging for interpreters; change in patient, doctor, or accompanier practices or behaviors, which could include providing patients with more information on how to select an accompanier as well as instituting training programs for caregivers; development of new tools, such as databases of community resources and

psychotherapists. This work could lead to new programs that help patients, accompaniers, and their doctors make the most of consultations leading to major treatment decisions.

Racial Disparity in Breast Cancer Mortality

Substantial variation exists in breast cancer outcomes by race and ethnicity. **Rebecca Smith-Bindman, M.D.**, at the **University of California**, San Francisco, investigated the reasons for these differences by analyzing the records of 95,000 women with breast cancer diagnosed between 1992-2001. Dr. Smith-Bindman and her team found that, overall, minority women underutilize mammography in comparison to White women. The team found no significant differences in advanced cancer rates and total cancer rates between White and African American women who had been screened between 1-3 years prior to diagnosis. They also found that most, but not all, of the differences in tumor characteristics at diagnosis were due to later use of mammography, rather than underlying biology. Lastly, they found that patients from minority groups were less likely to receive appropriate treatments for early-stage breast cancer. This work expands on what is known about, and could help decrease, racial disparities in breast cancer mortality. Findings from this research were published in *Cancer* 104(2005)2347, *Annals of Internal Medicine* 144(2006)541, and the *American Journal of Preventative Medicine* 2(2006)142.

Dialogue with Breast Cancer Survivors

Studies have shown that African American women and White women have very different breast cancer experiences, from their diagnosis and treatment to their knowledge about the disease and their participation in their care. **Grace Yoo, Ph.D.**, at **San Francisco State University,** coordinated a three-day symposium for 44 African American women with breast cancer living in the San Francisco Bay Area and 20 researchers, clinicians, and advocates to identify and address issues and problems faced by African American women with breast cancer. Topics discussed at the retreat included environmental health, sexuality, exercise, nutrition, spirituality, psycho-social needs, and clinical and diagnostic concerns. Based on information gathered at the retreat, Dr. Yoo and her colleagues designed and successfully piloted an eight-week diet and exercise intervention for African American breast cancer survivors. The team hopes to conduct another symposium for African American survivors that will focus on spirituality, nutrition, exercise, and psycho-social concerns. They also intend to develop a second diet and exercise program.

Expanding Rural Access: Distance Delivery of Support Groups

Women with breast cancer living in rural areas have less access to psychosocial support than their urban counterparts. **Mary Anne Kreshka, M.A.** and **Susan Ferrier, R.N.**, at the **Northern Sierra Rural Health Network,** Nevada City, and **Cheryl Koopman, Ph.D.**, at **Stanford University**, Palo Alto, collaborated with the Stanford University School of Medicine to determine the feasibility of using their videoconferencing network to provide leader-led support groups for women living with breast cancer. The research team recruited 27 women living with breast cancer living in rural northeastern California for this pilot study. Each woman participated in an eight-session support group led by an experienced oncology social worker. Up to four videoconferencing sites were connected for each support group so participants could interact with each other and the facilitator. Participants reported that the groups were beneficial in facilitating informational support and promoting emotional bonds with other women with breast

cancer. These findings suggest that support groups provided through a videoconferencing network have the potential to improve the lives of rural women with breast cancer.

Effect of Bright Light on Fatigue in Breast Cancer

Women with breast cancer undergoing chemotherapy often report disturbed sleep and increased symptoms of fatigue and depression. These patients also exhibit a disruption of their circadian rhythm, or biological clock. This clock is driven by exposure to bright light. **Sonia Ancoli-Israel, Ph.D.**, at the **University of California**, San Diego, previously found that women with breast cancer are exposed to less bright light during chemotherapy, and that less light exposure is related to increased fatigue. To follow-up on that finding, Dr. Ancoli-Israel and her team had 20 women undergoing chemotherapy self-administer either bright white light (BWL) or dim red light (DRL) for 30 minutes on the morning of their first four cycles of chemotherapy to measure the effect of exposure to bright light. The study found that increased light exposure during chemotherapy increased total sleep time by 22 minutes and decreased wake time during the night by 12 minutes. In addition, the women reported decreased fatigue and an improved quality of sleep. Dr. Ancoli-Israel has received funding from Litebook, Inc., to continue this study in a greater number of patients.

Living With Advanced Breast Cancer: A Predictive Model

Women diagnosed with Stage IV breast cancer (cancer that has spread to the bone, brain, and soft tissues) have a poor prognosis. These women face not only the likelihood of an uncertain future, but also the prospect of having nearly continuous medical treatments and cancer-related problems. **Annette Stanton, Ph.D.**, at the **University of California**, Los Angeles, followed more than 100 women with metastatic disease for more than three months in order to identify both their central concerns and the factors that aid or hinder their lives. She found that these women's greatest concerns involved fear of mortality, loss of independence, the impact being ill had on their interpersonal relationships, and the effect of treatment on their lives. She also found that the women who said they were actively engaged in pursuing cherished life goals and who were able to express their emotions had fewer depressive symptoms. Dr. Stanton intends to develop an educational program to help improve the quality of life of women living with advanced disease.

Psychobiological Concomitants: Bereaved Women at Breast Cancer Risk

Grief affects the lives of many women who are at high risk for breast cancer due to a family history of the disease. Some women have a more complicated process for adjusting to the death of a mother or sister. The chronic stress of what psychiatrists refer to as complicated grief may increase the psychobiological risk for women already at high risk for breast cancer. **David Wellisch, Ph.D.**, at the **University of California**, Los Angeles, explored whether grief-driven activation of emotion centers of the brain increases breast cancer risk by causing cortisol dysregulation, which can compromise the immune system. Dr. Wellisch and his team interviewed women who had lost a mother or a sister in the past five years and had them provide daily saliva samples to measure cortisol levels. They also had these women undergo a functional magnetic resonance imaging scan while looking at pictures of their deceased loved one so that they could measure brain activation during the feeling of grief. Dr. Wellisch is now analyzing the data they have collected. Preliminary findings demonstrated differences in the regional brain

activity and cortisol pattern levels between the women who were more resilient and those with complicated grief. This work could lead to new programs that address grief in high-risk women.

Peer Mentors Promoting Breast Cancer Clinical Research

Clinical trials provide opportunities for breast cancer patients to obtain state-of-the-art treatment. However, only a small number of breast cancer patients enroll in these studies. **Annette Maxwell, Dr.P.H**., at the **University of California**, Los Angeles, and **John S. Link**, and **Michelle Rakoff**, at Long Beach Memorial Medical Center/University of California, Los Angeles, investigated whether a Clinical Research Mentoring program could increase patients' interest in clinical trials. The team conducted focus groups with breast cancer survivors to learn what they believed patients needed to know to make an educated decision about enrolling in a clinical trial and what factors influenced their own decision-making. Based on their findings, the team developed a one-day Clinical Research Mentor training program, which was attended by 10 breast cancer survivors. The team intended to study whether pairing a mentor with a newly diagnosed breast cancer patient would impact patient enrollment in two clinical trials offered by the MemorialCare Breast Cancer Research Group. However, both of those trials closed and no new suitable trials became available. Even so, the interest breast cancer survivors expressed in the Clinical Research Mentoring program suggests that peer mentors might help increase patient enrollment in clinical trials.

Psychosocial Support Services for Latinas with Breast Cancer

Latina breast cancer patients infrequently use cancer support services, even though they may be at higher risk of psychosocial problems than White women. **Carmen Ortiz, Ph.D.**, at **Círculo de Vida (CDV),** San Francisco, which provides services to Latinos living with cancer, and **Anna Napoles-Springer, Ph.D., MPH**, at the **University of California**, San Francisco, investigated what encourages or dissuades Spanish-speaking Latinas with cancer from using support service, the psychosocial needs of these women, and the type of peer support counselor program they would find most useful. The team surveyed 89 Spanish-speaking Latina cancer patients, 29 Latina breast cancer survivors, and 17 community advocates working with Latinas with breast cancer at CDV. Based on these findings, Drs. Ortiz and Napoles-Springer developed and then pilot tested a training program and resource manual for community organizations interested in starting a peer support counselor program. Next, they will study a peer-delivered intervention that has been adapted for use with Spanish-speaking Latinas with breast cancer. If proven effective, this program could serve as a model to meet the psychosocial needs of other vulnerable women diagnosed with breast cancer.

Treating Insomnia with CBT in Women with Breast Cancer

Studies have found that up to 70 percent of breast cancer survivors experience insomnia. This insomnia is often associated with depression, anxiety, fatigue, and low quality of life. **Lavinia Fiorentino, M.S., M.A.**, at the **University of California**, San Diego, investigated whether cognitive behavioral treatment for insomnia (CBT-I) could improve sleep and quality of life and decrease fatigue, depression, and anxiety. She randomly assigned 14 breast cancer survivors to either six weeks of CBT-I followed by six weeks of follow-up, or to six weeks of regular treatment followed by 6 weeks of CBT-I. The study found that the women who received CBT-I in the first six weeks had improved self-rated insomnia after treatment compared to the participants who had regular treatment. The study also found that the sleep benefits gained

during treatment were maintained at follow-up, and that quality of life had improved. If these findings are successfully replicated in larger studies, it could lead to expanded use of CBT-I to decrease insomnia and improve quality of life in women with breast cancer.

Underserved Women with Breast Cancer at End of Life

End-of-life care, in general, is extremely inadequate in the U.S. For low income, underserved women, this problem is more acute, since the risk of recurrence and death is higher and their needs are less likely to be met. **Shelley Adler, Ph.D.,** at the **University of California**, San Francisco, and **Beverly Burns, M.S., B.A., L.Ac.**, at the Charlotte Maxwell Complementary Clinic (CMCC), Oakland, interviewed 10 underserved women with metastatic breast cancer along with an oncologist, complementary and alternative medicine (CAM) provider, or informal caregiver the client selected, to learn more about underserved women's beliefs and concerns about end of life of care. Although the analysis of the data is still ongoing, a number of major themes in patients' experiences have emerged, including the enormous impact of cancer on a woman's finances, how difficult it is for women, especially mothers, to be in the "sick" role, and how concerned women are about not having done enough to prepare for death. The research team also found that most CMCC clients had not made decisions about care during end of life or their wishes for what should be done after they die. The team now intends to develop an "ethical will" to improve the quality of CMCC clients' end of life and to implement a community peer-based system to support women through the process of completing this document.

Filipina Breast Cancer Support: What Model is Meaningful?

Breast cancer among Filipina American women represents a major but largely neglected cancer disparity. In 2004, a collaboration between West Bay Pilipino Multi-Service Center (West Bay), the UCSF Comprehensive Cancer Center, and the San Francisco General Breast Care Program, resulted in the establishment of Sinag Tala, the first Filipina breast cancer support group in San Francisco. **Edwin Jocson, B.A.,** at the **West Bay Pilipino Multi-Service Center**, San Francisco, and **Nancy Burke, Ph.D.**, at the **University of California**, San Francisco, used this planning grant to strengthen their proposal for a study that would investigate which type of support programs would best serve the needs of women in Sinag Tala. During the planning process, meetings with community partners helped them to shift their research focus to one that would be better able to assess the most effective peer education programs. Mr. Jocson and Dr. Burke submitted a new grant application titled, "Filipina Breast Cancer Survivors as Peer Educators."

New Breast Cancer Approaches: Integration, Communication

Timely integration of proven new information into clinical practice and quality communication with patients about this new information is needed to ensure that all women with early-stage breast cancer receive quality care, including women in California with limited English proficiency. **Leah Karliner, M.D.**, at the **University of California**, San Francisco, is exploring how breast surgeons and oncologists incorporate new approaches to care, how they communicate with patients about these new approaches, and how language barriers affect that communication. Dr. Karliner and her team mailed a 32-question survey to 662 surgeons and 588 oncologists in California. To date, they have received 314 surveys that have been completed by a surgeon or an oncologist. The team is currently attempting to get more physicians to complete the survey. This work has the potential to facilitate improved communication between breast cancer doctors and their patients.

Cost-effectiveness of Breast MRI Screening by Cancer Risk

Breast magnetic resonance imaging (MRI) is increasingly used as a screening tool for breast cancer. Although breast MRI has been shown to detect cancers when they are smaller, MRI is more costly than mammography and can lead to a high rate of unnecessary breast biopsies. **Allison Kurian, M.D.**, at **Stanford University**, Palo Alto, investigated the effectiveness (measured in terms of breast cancer mortality reduction) and cost-effectiveness (measured as a ratio of cost versus effectiveness) of using breast MRI in addition to mammography by adapting a computer simulation model of mammography screening to reproduce the natural history of breast cancer in women at high risk due to a BRCA1 or BRCA2 mutation. Dr. Kurian and her team found that adding MRI yielded a cost-effectiveness ratio that is similar to that of other widely accepted interventions in breast cancer management. The results of this research may inform both individualized patient recommendations as well as screening guidelines for women with a BRCA1 or BRCA2 mutation. Findings from this research were published in the *Journal of the American Medical Association* 295(2006)2374.

Empowering Acupuncturists to Cooperate with Oncologists

Many breast cancer patients seek treatment from acupuncturists, yet this care is often not coordinated with the care the patients are receiving from their physicians. **Michael Johnston, Ph.D.**, at the **University of California**, Los Angeles, interviewed 100 acupuncturists who treat breast cancer patients to learn more about the problems they face coordinating care with physicians. Based on these findings, Dr. Johnston developed an educational program for acupuncturists, oncology clinicians, and breast cancer patients. Dr. Johnston also published a manuscript on acupuncture for chemotherapy-associated cognitive dysfunction. He expects to publish additional articles on the evidence in support of acupuncture, coordination of care from the acupuncturist's perspective, and health communication and informed medical decision-making by breast cancer patients. By helping acupuncturists and oncology professionals improve health services coordination, this project could improve quality of care.

Multilingual Access to Breast Cancer Early Detection

Public medical facilities must provide equal access to health care for increasing numbers of ethnically diverse women. In order to make California's "Every Woman Counts" program a reality, medical systems need to make changes that promote equal access to breast health services, regardless of a woman's language. **Susan Stewart, Ph.D.**, at the **University of California,** San Francisco, and **Linda Engelstad, M.D.**, at the **Alameda County Health Care Foundation**, Oakland, used this planning grant to strengthen their proposal for a Pilot Study that would address the challenges faced by public healthcare facilities to provide improved access to health care for increasing numbers of ethnically diverse women with limited English proficiency. During the planning process, meetings with experts in this research field led Drs. Steward and Engelstad to identify a more appropriate scientific model for their study design and to expand their Community Advisory Committee. Dr. Stewart and Engelstad submitted a revised grant application to the CBCRP.

Grants in Progress: 2007

Assessing Recurrent Genomic Aberrations Linked to Ethnicity

Koie Chin

University of California, San Francisco

A Blueprint for Advancing Quality in Breast Cancer
Laura Esserman
University of California, San Francisco

Hormone, Psychologic & Immunologic Factors & BC Survivorship
Hillary Klonoff-Cohen
University of California, San Diego

Latinas and DCIS: Treatment Decisions and Quality of Life
Celia Kaplan
University of California, San Francisco

Lifestyle Factors & Breast Ca Prognosis in Asian-Americans
Anna H. Wu
University of Southern California

South Asian Women with Breast Cancer: What are Their Needs?
Zul Surani, Roshan Bastani & Beth Glenn
South Asian Cancer Foundation and University of California, Los Angeles

Young Breast Cancer Survivors: Ten Years Later
Joan Bloom
University of California, Berkeley

Addressing Cultural & Tribal Issues in Breast Cancer
Linda Navarro and Marlene von Friedrichs-Fitzwater
Turtle Health Foundation and University of California, Davis

Breast Cancer Education for Deaf and Hard-of-Hearing Women
Heidi Kleiger and Barbara Berman
Greater Los Angeles Council on Deafness, Inc. and University of California, Los Angeles

The Breast Cancer Experience of Slavic Women
Roman Romaso and Debora Paterniti
Slavic Assistance Center and University of California, San Diego

Breast Health Literacy and Health Care Decision Making
Joel San Juan and Suzanne Lindsay
Operation Samahan Health Clinic and San Diego State University Research Foundation

Fresno Breast Cancer Navigator Pilot Program
Mary Wallace and John Capitman
San Joaquin Valley Health Consortium and California State University, Fresno

Increasing Mammography Among Latinas with Disabilities
Elsa Quezada and H. Stephen Kaye
Central Coast Center for Independent Living and University of California, San Francisco

Informal and Formal Support and Needs Among Samoan Survivors
Sala Mataalii and Sora Tanjisiri
Samoan National Nurses Association and CSU Fullerton Auxiliary Services Corporation

Introducing Acupuncture to Black Survivors for Wellness
Carolyn Tapp and Michael Johnston
Women of Color Breast Cancer Survivors Support Project and University of California, Los Angeles

Mammography Screening for Latinas with Diabetes
Christine Noguera and Stergios Roussos
Golden Valley Health Centers and California State University, Fullerton

Neighborhood Environment and Obesity in Pre-adolescent Girls
Irene Yen
University of California, San Francisco

Social Capital, Social Support and Long-Term Quality of Life
Dana Peterson
University of California, Berkeley

Social Support and QOL in Older Minority Women with Breast Cancer
Yoshiko Umezawa
University of California, Los Angeles

Southeast Asian Breast Health Navigation
Mary Ann Foo and Marjorie Kagawa-Singer
Orange County Asian &Pacific Islander Community Alliance and University of California, Los Angeles

Telephone-Based Decision Support for Rural Patients
Sara O'Donnell and Jeff Belkora
Mendocino Cancer Resource Center and University of California, San Francisco

Research Initiated in 2007

Breast Health Behaviors of Immigrant Afghan Women
Joan Bloom and Aida Shirazi
University of California, Berkeley and Afghan Coalition

Expanding Rural Access: Distance Delivery of Support Groups
Cheryl Koopman, Mary Anne Kreshka and Jim Perkins
Stanford University and Northern Sierra Rural Health Network

Networking Breast Cancer Navigator Programs in Northern California
Lisa Bailey
Alta Bates Summit Medical Foundation

Science Literacy & Breast Cancer Clinical Trials Education
Georgia Sadler and Natasha Riley
University of California, San Diego and Vista Community Clinic

Sister Survivor: African American Breast Cancer Coalition
Kimlin Ashing-Giwa and Gloria Harmon
Beckman Research Institute of the City of Hope and Women of Essence

Underserved Women with Breast Cancer at End of Life
Shelley Adler and Beverly Burns
University of California, San Francisco and Charlotte Maxwell Complementary Clinic

Etiology and Prevention

Although our foundation of knowledge for the basic science aspects of breast cancer has expanded greatly over the past decade, gaps still remain in our strategies for large-scale prevention due to uncertainties over the underlying causes of the disease and their relative importance. There is an extensive list of factors associated with increased and decreased risk for breast cancer. However, the relative importance of diet, exercise, family history, pregnancy, alcohol, hormone replacement therapy, and other factors remains controversial.

Two 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

Research Conclusions

Epstein-Barr Virus in Breast Cancer Tissues

While some studies have reported a link between breast cancer and the Epstein-Barr virus (EBV), others have not. This could be because it is very difficult to measure EBV in breast tumors. **Sally Glaser, Ph.D.**, at the **Northern California Cancer Center**, Fremont, tested a battery of laboratory tests she developed to detect EBV on stored breast cancer tissues. Applying the tests to tumor tissue from non-Hispanic white and Latina breast cancer patients, Dr. Glaser and her team found very low levels of EBV in only a small number of patients, which indicated that EBV could have caused the tumors to develop. They also found that Latinas were more likely than non-Hispanic white women to have higher levels of the virus; that tumors with EBV tended to occur in women with more advanced and aggressive disease at diagnosis; and that there was no indication that EBV affected survival. These findings suggest that EBV may play some role in increasing breast cancer aggressiveness in a proportion of breast cancer patients.

HER-2/neu Gene Variations and Breast Cancer Risk

Women whose cancer cells make too much of the protein produced by the gene called HER-2/neu tend to have more aggressive tumors. The HER-2/neu gene can be present in one of two "normal" forms (or polymorphisms). One of these polymorphisms has been found to be associated with a higher risk of breast cancer in Chinese women. The role of this polymorphism in African American and White women has not been determined. **Michael Press, M.D., Ph.D.**, at the **University of Southern California**, Los Angeles, and colleagues studied normal forms of the HER-2/neu gene in blood cells taken from 1582 African American and White women. They investigated a single inherited polymorphism in Codon 655 (a codon is that part of DNA or RNA that codes for a single amino acid). To date, 1414 samples have been analyzed. When completed, this research could lead to a greater understanding of whether and to what extent an inherited HER-2/neu polymorphism increases breast cancer risk.

PBDEs in Tissues of Women With and Without Breast Cancer

Polybrominated diphenyl ethers (PBDEs) are a class of chemicals used as flame retardants in many commonly used consumer products, such as electronics and home furnishings. They persist in the environment and they accumulate in our fatty tissues. California women have the highest levels of PBDEs in the world, probably because of their extensive use to meet the State's fire safety standards. PBDEs disrupt thyroid function and impair development in animal studies. It is not yet known if there is any connection between PBDEs and breast cancer. **Myrto Petreas, Ph.D., M.P.H**., at the **California Department of Health Services**, Sacramento, and colleagues measured PBDEs in 152 samples of breast fat collected from women with and without breast cancer. Their preliminary analysis found no statistically significant differences in PBDE levels between the two groups. They also found no significant difference in dietary habits, reported residential proximity to potential sources of PBDEs and PCBs, or occupational exposures. The team plans to conduct further research into whether there were certain habits or characteristics common in the women who had the highest levels of PBDE exposures.

USC/NCCC Breast Cancer Research Training Program

The University of Southern California/Norris Comprehensive Cancer Center (USC/NCCC) is one of 41 federally designated comprehensive cancer centers nationwide. **Michael Press, M.D., Ph.D.**, at the **University of Southern California,** Los Angeles, implemented a formal interdisciplinary graduate research training program led by epidemiologists and prevention scientists, behavioral scientists, tumor biologists, molecular geneticists, and radiation, surgical and medical oncologists. The training program matched 14 trainees to an appropriate faculty mentor with an active breast cancer research program. The trainees conducted research and also participated in an array of breast cancer programs at the USC/NCC, including Breast Center Rounds and Cancer Center Grand Rounds. Findings from the trainees' research were published in *Differentiation* 27(2004)474, *International Journal of Developmental Biology* 48(2004)181, and *Molecular and Cellular Biology* 25(2005)5965.

Breast Cancer Risk Associated with High Mammographic Density

Mammographic density has been found to be one of the strongest predictors of breast cancer risk. **Thea Tlsty, Ph.D.**, at the **University of California**, San Francisco, explored whether this increased risk could be due to biological processes that result in altered cell-cell and/or cell-extracellular matrix interactions. These interactions, which are influenced by genetic, physiological, and environmental factors, are known to generate tissue with the same characteristics seen in mammographic density. Dr. Tlsty and her team identified molecular differences between low density and high density associated fibroblasts (the cells that give rise to connective tissue) that have the potential to link mammographic density to cancer risk. They demonstrated that a protein called Transforming Growth Factor-beta (TGFß) is increased in tissue with high mammographic density, and that TGFß appears to alter the expression of a receptor called CD36 in mammary fibroblasts. Dr. Tlsty believes this suggests that increased TGFß activity, working through a CD36 pathway, could lead to increased mammographic density and increased cancer risk. This work could lead to new methods of detecting breast cancer or decreasing mammographic density that could reduce breast cancer risk.

Breast Cancer Chemoprevention with Dietary Herbal Estrogens

It is widely recognized that exposure to estrogens increases the risk of developing breast cancer. Estrogens enter breast cells from the blood and then bind to proteins, called estrogen receptors (ER), that are in the cell nucleus. Once estrogen binds to the ER, it increases the production of several proteins that can cause breast cells to grow and form tumors. It was initially thought that there was only one ER. Then, in 1996 a second receptor, ERß was discovered. **Dale Leitman, M.D., Ph.D.**, at the **University of California**, San Francisco, is investigating the role of Erß in breast cancer. For this project, Dr. Leitman and his team began by studying cells that only contained ERalpha. They found that estradiol, the estrogen that is made in the body, stimulated the proliferation of these cells and produced tumors in mice. They then took the cells that made only ERalpha and infected them with a virus that produces ERß. They found that estradiol inhibited growth and tumor formation in these cells, which suggested that estrogens that interact only with ERß could be used to prevent breast cancer. The team then studied the effects of an herbal formula, MF101, which contains 22 different herbs that are often used in Traditional Chinese Medicine to prevent breast cancer and menopausal symptoms in women with breast cancer. They found that MF101 prevented the breast cancer cells from growing and forming tumors in mice. This suggests that further research into herbal estrogens could lead to the development of new drugs to prevent breast cancer.

Estrogen Receptor Beta Agonists to Prevent Breast Cancer

The drug tamoxifen is able to block the production of all types of breast cancer when given early in life to rodents. However, tamoxifen cannot be given to young women as a chemopreventive because it puts them into menopause. Tamoxifen targets both the alpha and beta estrogen receptors (ER). New drugs that target only the ERß receptor block the ability of estrogen to drive cancer-causing cell proliferation without causing menopause. **Peter Kushner, Ph.D.**, at the **University of California**, San Francisco, found that some ERß ligands (a hormone is the ligand for its specific protein receptor) could inhibit estrogen-stimulated growth in human breast cancer cells. Dr. Kushner and his team also discovered that ERß increases the efficacy of anti-estrogens, like tamoxifen, because it affects programmed cell death (apoptosis) and cell cycling. This work could lead to new ways to diagnose and treat breast cancer. Findings from this research appeared in *Breast Cancer Research and Treatment* 2007 July 19[Epub ahead of print].

Breast Cancer Prevention with Estrogen

A full term pregnancy at an early age is the only natural physiological condition that drastically reduces breast cancer risk. **Satyabrata Nandi, Ph.D.**, at the **University of California**, Berkeley, investigated the biological basis of the protective effect of pregnancy by mimicking its effect in rats that had never given birth. Dr. Nandi and his team found that there was a decreased ability for cancer cells to grow in the rats that had been given the estrogen treatment that mimicked a pregnancy; that the treatment induced changes in the protein levels of the genes that regulate growth of the mammary glands; and that the rats that received estrogen had a decreased secretion of hormones from the pituitary gland, which provided protection against mammary cancer. They also found that the protective hormonal treatment had no harmful effects on the health or reproductive physiology of the rats. This research raises the possibility that correctly timed simulated pregnancy can be preventive for breast cancer. The findings from this research were published in *Proceedings of the 4th International Symposium on Hormonal Carcinogenesis*

(2003), and *Proceedings of the 94th Annual Meeting of American Association for Cancer Research* (2003).

The IGF Pathway & Breast Cancer Risk in African Americans

Studies have found that African American women are more likely than White women to be diagnosed with aggressive breast cancer, to be diagnosed at a younger age, and to die from their disease. **Susan Neuhausen, Ph.D.**, at the **University of California**, Irvine, studied genes in the insulin-like growth factor (IGF) pathway in African American and Nigerian women with and without breast cancer to investigate whether genetic changes might be one reason for these differences. Dr. Neuhausen and her team specifically looked for inherited variations in a single site in the DNA. This is called a Single Nucleotide Polymorphisms or SNP. The team found statistically significant associations between two sets of inherited variants, called IGFBP2 and IGFBP5, and breast cancer risk. This work provides evidence that genetic variation in the IGF signaling pathway plays a role in breast cancer risk in two independent populations of African descent. This finding could lead to new ways of preventing and treating breast cancer in African American women.

Grants in Progress: 2007

Androgen Receptor Gene and p21 Gene in Breast Cancer
Wei Wang
University of Southern California

Birth Characteristics and Breast Cancer in Young Women
Peggy Reynolds
Northern California Cancer Center

Breast Cancer Lymphedema: Role of Insulin Resistance/FOXC2
Stanley Rockson
Stanford University

Breast Cancer Metastasis: a Heritable Trait?
Alice Whittemore
Stanford University

Breast Cancer Prevention with Phytochemicals in Mushrooms
Shiuan Chen
Beckman Research Institute of the City of Hope

Grape Seed as a Natural Breast Cancer Chemopreventive Agent
Melanie Ruth Palomares
Beckman Research Institute of the City of Hope

Hereditary Breast Cancer and Novel Hispanic BRCA Mutations
Jeffrey Weitzel

Beckman Research Institute of the City of Hope

The Hygiene Hypothesis and Breast Cancer Risk
Christina Clarke Dur
Northern California Cancer Center

A Novel Biological Framework for the Role of Xenoestrogens
Shanaz Dairkee
California Pacific Medical Center Research Institute

Structural Characterization of Aromatase
Yanyan Hong
Beckman Research Institute of the City of Hope

Targeted Chemoprevention in a Mouse Model for DCIS
Jeffrey Gregg
University of California, Davis

Tea, genes and their interactions on breast cancer
Anna H. Wu
University of Southern California

USC/NCCC Breast Cancer Research Training Program
Ronald Ross
University of Southern California

Research Initiated in 2007

Breast Cancer Risks in California Nail Salon Workers
Peggy Reynolds and Linda Okahara
Northern California Cancer Center and Asian Health Services

Circuit Training to Lower Breast Cancer Risk in Latina Teens
Jaimie Davis
University of Southern California

Detection, Prognosis, and Treatment

The detection, prognosis, and treatment topics funded by the CBCRP continue to change as novel technologies and approaches come under investigation. CT (computerized tomography) scanning is emerging with new instruments being designed that are dedicated to breast imaging. Also digital tomosynthesis (a new type of mammography), ultrasound, and PET technologies are being used to better image the breast and to allow more accurate excision of tumors. For better disease prognosis, several gene expression profiling tests are coming into both commercial use and clinical testing. The expected benefits of genetic testing performed on tumor samples are to allow individualized therapy to spare women the unnecessary side-effects of treatments with no potential benefit—a common outcome with most non-targeted chemotherapeutics. Cancer therapeutic development continues to evolve with a focus on (i) the validation of novel cell targets and an improved understanding of the disease at the genetic and molecular levels, and (ii) an enhanced ability to match patient subgroups with individual drugs or drug combinations to assess efficacy earlier in pre-clinical testing. Alternative therapies and drugs, especially those derived from plants, engender intriguing areas of investigation.

The detection, prognosis, and treatment of breast cancer is a constantly evolving landscape where information filtering in from basic scientists is selectively advanced along the 5-to-10 year stepwise “critical path” for translational application. Cancer stem cells (CSCs), first established in 2003 for breast cancer, are already gaining attention as possible novel targets for therapy. The inability to provide a durable cure for breast cancer is thought to be due to the chemo- and radiotherapy resistance of CSCs to current treatments. And, stem cells might even emerge as a delivery vehicle for therapeutics. Better early detection of disease remains a critical need. Using combined imaging modalities aims to improve both sensitivity and selectivity to reduce unnecessary biopsies and facilitate informative disease staging and prognosis. Genetic profiling of patients continues to move in the direction of “individualized therapy.” New targeted therapies that began with the introduction of Herceptin® require validation of novel targets in the clinical setting and technologies to select patients most likely to benefit from these expensive drugs. Advances in nanotechnology promise new methods for detection and tumor-specific delivery to reduce drug side-effects. However, some clinical scenarios, such as “triple-negative” (ER, PR, and Her-2 negative) breast cancers and the “basal-like” gene expression pattern still account for a significant number of new diagnoses that have fewer treatment options.

Two research topics are represented in this section:

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

Research Conclusions

Breast Stromal Genes Act as Early Markers of Malignancy

The breast epithelial cells—the cells from which breast cancers arise—grow within a matrix of breast stroma. The stroma is made up of fibroblasts, the cells that give rise to connective tissue.

The cell-to-cell signaling that takes place between stromal fibroblasts and malignant breast epithelium contributes to the growth and spread of breast cancer. **Thea Tlsty, Ph.D.,** and **Stefanie Jeffrey, M.D.**, of the **University of California**, San Francisco, studied 36 fibroblast cell lines from breast cancer specimens, normal mammary tissue samples, and breast reduction tissue, to see if they could identify an early marker of malignancy. They found that the fibroblasts in the breast cancer specimens (carcinoma associated fibroblasts or CAFs) stimulated the growth and altered the structure of normal breast epithelial cells. In addition, a complex gene analysis they performed showed that the expression of several proteins that activate white blood cells, called chemokines, as well as a chemokine receptor, was lower in the CAFs than in the other tissue samples. Drs. Tlsty and Jeffrey are now exploring when in a tumor's development the CAF's characteristics appear. This work could lead to the discovery of a molecular pattern in the stroma that could be used to not only detect breast cancer at an earlier stage but also to predict the risk of disease progression.

Molecular Imaging of Breast Cancer Using Breast PET/CT

Combining the information obtained from the physiological images derived from positron emission tomography (PET) with the anatomical detail provided by breast computed tomography (CT) could provide physicians with a way to quantitatively assess a breast cancer's aggressiveness. This could, in turn, aid treatment decisions. **Ramsey Badawi, Ph.D.**, at the **University of California**, Davis, combined a PET detector system with a CT scanner to create a well-integrated PET/CT system dedicated to breast imaging. Dr. Badawi has received funding from the American Cancer Society to start a human trial in 10 patients with suspected breast cancer to test the accuracy of this new breast PET/CT. Findings from this research were published in *Nuclear Science Symposium Record* 4(2006)2335 and 3(2005)1524.

Novel Agents for Breast Cancer Therapy

Scientists are trying to identify molecular targets that are specific to cancer cells. This would allow them to develop treatments that could home in on cancer cells and leave normal cells alone. One potential target is a protein called Bcl-xl. It is part of a family of proteins called Bc1-2, which help regulate programmed cell death (a process known as apoptosis.) Bcl-xl has the ability to help cancer cells proliferate even when targeted by radiation or chemotherapy. **Maurizo Pellecchia, Ph.D.**, at **The Burnham Institute for Medical Research**, La Jolla, is trying to develop a way to target Bcl-xl. Dr. Pellecchia and his team discovered that Gossypol, a natural product with demonstrated anti-breast cancer activity, works by selectively blocking Bcl-xl. They then identified and studied a new compound, Apogossypol, and found that it had less toxicity and appeared to be even more effective than Gossypol. This work could lead to the development of more effective breast cancer treatments.

Dietary Indole Analogs Inhibit Breast Cancer Cell Invasion

Up to half of all patients who have a breast cancer recurrence will eventually have metastatic disease. Scientists believe that a cancer recurrence is probably the result of undetectable residual cancer cells left after breast cancer surgery. **Ling Jong, Ph.D.,** at **SRI International**, Menlo Park, is trying to develop a maintenance therapy that could indefinitely suppress these residual cancer cells and, essentially, cure the cancer. Dr. Jong and his team discovered and developed an oral anti-cancer agent, called SR13668. This agent is similar to indole-3-carbinol, an anti-cancer agent found in cruciferous vegetables. The team had previously found that SR13668 could

inhibit phospho-Akt (pAkt) in breast cancer cells in cell cultures and in mice. This is significant because patients that are pAkt-positive are more likely to have a recurrence that involves distant metastasis. This research project, a safety study in rats, found no drug-related deaths or organ toxicity when the drug was administered at a level 30-60 times higher than what has been found to be effective. Based on these findings, the National Cancer Institute has agreed to support additional preclinical studies on this new anti-cancer agent.

HER3 Infidelity and Resistance to Tyrosine Kinase Inhibitors

The human epidermal growth factor receptor (HER) family is known to play a role in cancer progression. The family has four members, HER1-4. The most well known in breast cancer is HER2. There is evidence to suggest that HER2-positive cancers should respond to drugs that inhibit an enzyme called HER2 kinase. However clinical trials of HER family tyrosine kinase inhibitors (TKIs) have not found these drugs to be effective. **Mark Moasser, MD**, at the **University of California,** San Francisco, and colleagues discovered previously that HER family TKIs effectively inhibit HER1, HER2, and HER4 but not HER3. This is a problem because HER3 works with HER2 in cancer tumors. This study allowed Dr. Moasser's team to explore why HER3 does not respond to these therapies. They discovered that the HER2-HER3 partnership is protected by specific feedback signaling mechanisms that allow HER3 to continue to function when targeted by TKIs. They also discovered that although cancer cells can survive when HER2 is weakened, they are unable to survive when it is completely inactivated. Dr. Moasser is now developing and testing inhibitors that can completely inactivate HER2 in preclinical models. This work could lead to the development of new treatments for women with HER2-positive breast cancer. Findings from this research appeared in *Nature* 445(2007)437.

ID4: a Prognostic Factor of Breast Cancer Metastasis

Metastasis of breast cancer to regional lymph nodes is one of the most important factors in predicting disease outcome. **David Hoon, M.Sc., Ph.D.**, at the **John Wayne Cancer Institute**, Santa Monica, and colleagues discovered that when a gene, called ID4, is inactivated, the tumor is likely to have metastasized to the sentinel lymph node (SLN). To validate this finding, Dr. Hoon and his team analyzed primary breast tissue and SLN samples to see whether ID4 inactivation correlates with cancer progression. They also studied the cancer cells to learn more about how ID4 functions. If the team finds that ID4 is predictive of tumor metastasis to the SLN, it could be used to determine which breast cancer patients needs SLN surgery, which could help improve survival and disease management.

Inhibition of Brain Metastases in Breast Cancer

Up to 30 percent of breast cancer patients will have their cancer metastasize to the brain. Because current treatments for breast cancer metastases are not very successful, new approaches are needed. **Brunhilde Felding-Habermann, Ph.D.**, at the **Scripps Research Institute**, La Jolla, and colleagues have created new human breast cancer cell models and analytical systems that allow them to follow the development of breast cancer brain metastases step-by-step and evaluate treatment response. This work led them to identify a new molecular target on metastatic breast cancer cells. The target is a cell adhesion receptor, called the activated conformer of integrin avß3. The team found that this receptor promotes breast cancer cell metastases to the brain and central nervous system. They also showed that treatment with antibodies against activated avß3 could reach target organs of breast cancer metastasis, including the brain. This

work could lead to the development of a new therapy for brain metastases in breast cancer patients. Findings from this work were published in *Clinical Cancer Research* 13(2007)1656.

cAMP Antagonists of Protein Kinase as Breast Cancer Drugs
Mounting evidence suggests that an enzyme called cAMP-dependent protein kinase (PKA) plays a role in breast cancer. But since this enzyme also plays a role in many normal cell processes, it's not a good drug target. There is however, a subunit of PKA, called RIalpha, that cell and animal models have established is a good target, and phase II cancer clinical trials testing a therapy that prevents RI synthesis are now underway. **Sanjay Adrian Saldanha, Ph.D.**, first at **Scripps Research Institute,** La Jolla**,** and then at the **University of California**, San Diego, is trying to identify a small molecule that would target RIalpha and provide an alternative way to target PKA. Dr. Saldanha and his team developed a new assay for the identification of PKA agonists or antagonists that could help them identify this molecule. They tested a series of drug-like small molecules and marine natural products, but only found that those that were analogs of cAMP were active towards PKA. These findings lay the groundwork for future studies to validate PKA as a drug target.

Grants in Progress: 2007

An Approach to Antiestrogen Resistance in Breast Cancer
Oksana Tyurina
University of California, San Diego

Artemisinin Disrupts Estrogen Receptor-Alpha and Cell Growth
Gary Firestone
University of California, Berkeley

Breast Cancer Functional Imaging with Optics and MRI
Bruce Tromberg, Nola Hylton and John Butler
University of California, Irvine and University of California, San Francisco

Breast Tumor Inhibition by Vitamin D in a Mouse Model
David Feldman
Stanford University

Chemical Inhibitors of Hsp70 for Breast Cancer
Chung-Wai Shiau
The Burnham Institute of Medical Research

Combined Imaging Modalities for Breast Cancer
Gultekin Gulsen
University of California, Irvine

Differential Optical Mammography
Gregory Faris and Christopher Comstock
SRI International and University of California, San Diego

Early Breast Cancer Detection Using 3D Ultrasound Tomography
Edward Nelson
University of California, Irvine

Factors Influencing Breast Cancer Screening Among Older Thai
Bulaporn Natipagon-Shah and Mary Jo Clark
Thai Health and Information Service and University of California, San Diego

ID4: A Prognostic Factor of Breast Cancer Metastasis
Dave Hoon
John Wayne Cancer Institute

In Vivo MRS for Cancer Diagnosis and Treatment Monitoring
Hyeon-Man Baek
University of California, Irvine

Inhibition of the BRCA2-RAD51 Interaction in Breast Cancer
Jiewen Zhu
University of California, Irvine

Inhibition of Brain Metastases in Breast Cancer
Brunhilde Felding-Habermann
Scripps Research Institute

Inhibition of Breast Cancer Aggressiveness by Cannabidiol
Sean McAllister
California Pacific Medical Center Research Institute

Intraoperative Assessment of Surgical Lumpectomy Margins
Armando Giuliano
John Wayne Cancer Institute

Molecular Imaging of Breast Cancer Using Breast PET/CT
John Boone
University of California, Davis

Neural Stem Cell Therapy for Breast Cancer Brain Metastases
Brunhilde Felding-Habermann
Scripps Research Institute

New Technology to Enhance PET Imaging of Breast Cancer
Craig Levin
Stanford University

Nur77-derived Peptides as a Novel Breast Cancer Therapy

Xiao-kun Zhang
The Burnham Institute of Medical Research

rADDs: Novel Disintegrins Targeting Breast Cancer
Stephen Swenson
University of Southern California

Real-Time 3D Ultrasound Image-Guidance for Breast Surgery
Michael Bax
Stanford University

Removing Respiratory Artifacts in Nuclide Breast Imaging
Brian Thorndyke
Stanford University

Sulforaphane: Its Potential for Treatment of Breast Cancer
Olga Azarenko
University of California, Santa Barbara

A Targeted Therapy for Wound-like Breast Cancers
Howard Chang
Stanford University

Topoisomerase-IIa as a Predictor of Anthracycline Response
Michael Press
University of Southern California

Vascular Targeting Therapy for Breast Cancer
Albert Deisseroth
Sidney Kimmel Cancer Center

Research Initiated in 2007

Breast Cancer Treatment Monitoring Combining MRI and Optics
Catherine Klifa
University of California, San Francisco

Determinants of Response to Microtubule Stabilizing Drugs
Tatana Spicakova
Stanford University

Early Breast Cancer Detection Using 3D Ultrasound Tomography
Thomas Nelson
University of California, San Diego

Engineering EGFR Antagonists for Breast Tumor Targeting
Jennifer Lahti
Stanford University

Exploring the Role of PARP Inhibitors in Breast Cancer
Karlene Cimprich
Stanford University

Intraductal Therapy of DCIS: a Presurgery Study
Susan Love
Dr. Susan Love Research Foundation

Mechanisms of HSP90 Inhibitor Action in Breast Cancer
Cynthie Wong
Beckman Research Institute of the City of Hope

Modulation of Breast Cancer Stem Cell Response to Radiation
Frank Pajonk
University of California, Los Angeles

Molecular Imaging of Metastatic Lymph Nodes in Breast Cancer
Ella Jones
University of California, San Francisco

Multinuclear MRI of Breast Tumors
Brian Hargreaves
Stanford University

Neural Stem Cell Therapy for Breast Cancer Brain Metastases
Brunhilde Felding-Habermann
Scripps Research Institute

Novel Cytokine Immunotherapy for Breast Cancer
Ananda Goldrath
University of California, San Diego

Polyamide HIF Inhibitors to Block Breast Cancer Metastasis
John Phillips
California Institute of Technology

Symposium on the Intraductal Approach to Breast Cancer
Susan Love
Dr. Susan Love Research Foundation

The Biology of the Breast Cell

To understand the origin of breast cancers, more research is needed on the pre-cancerous, causative events in the normal breast. In breast development, cell populations must co-ordinate migration, proliferation, and apoptosis (cell death) over space and time. In cancer progression, these same processes become dysregulated, initially at the genetic level, it leads to the physiological changes associated with malignancy. To better mimic breast and tumor architecture, 3-D cell culture models provide a means to explore potential underlying mechanisms and show the structure of the breast and interaction of its different cell types lead to the development of a tumor. An emerging paradigm identifies “stem cells” as the key to the origin of tumors. Stem cell populations reside in body organs to provide the raw material for tissue regeneration, repair, and for the cyclic proliferation responses to hormones and pregnancy in the breast. If this theory proves correct, then only a small fraction (1- 2 percent) of cells in a tumor mass retain stem cell properties, and these “cancer stem cells” must be selectively targeted to achieve an effective eradication of the disease.

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

Two research topics are presented in this section.

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

Research Conclusions

Discovering Novel Cell-ECM Interactions in Breast Cells

Breast cancer begins in the epithelial cells that line the breast duct. Normal epithelial cells are in contact with a complex mixture of proteins released from the basement membrane (BM) of the

extracellular matrix, a framework that surrounds and supports these cells. Normal epithelial cells use proteins, known as receptors, to communicate with the BM. This communication organizes the cells into tissues and prevents uncontrolled cell growth. In cancer cells this communication process has stopped functioning properly, which allows the cells to break through the BM and invade surrounding tissue. Two types of proteins, called integrins and dystroglycan receptors, are known to contribute to cancer progression. **John Muschler, Ph.D.**, at the **California Pacific Medical Center Research Institute,** San Francisco, established six new human breast epithelial cell lines that lack ß1 integrin and dystroglycan receptors. By looking at how cancer develops in cells that lack these receptors, Muschler and his colleagues hope to find and identify currently unknown receptors and signaling pathways involved in breast cell-BM communication.

The Role of Gli3 in Mouse Embryonic Mammary Gland Formation

Scientists recognize that tumors arise when the genes that play a role in normal development stop functioning properly. Mutant mice in which the genes Gli3, Fgf10, or Fgfr2b do not properly function have similar defects in breast development. **Jacqueline Veltmaat, Ph.D.,** at **Childrens Hospital**, Los Angeles, used these mutant mice to study the role that these three genes play in the developing breast. Normal mice form five pairs of breasts. Dr. Veltmaat and her team found that in the Gli3 and Fgf10 mutant mice, the fourth breast pair developed, but the third pair did not. In addition, in the Gli3 mutants, the second breast pair developed abnormally. The team also found that when Gli3 was absent, the production level of Fgf10 remained too low to induce signaling between Fdf10 and another molecule called Wnt. This finding suggested that there is an optimal level of signaling between Fgf10 and Wnt that needs to occur to maintain a breast cell's identity. It also suggested that Gli3 might start to function as a breast cancer gene when its levels get too high. The team is now investigating how to return Gli3 functioning that is too high to normal levels.

Epithelial Polarity, Organization, and the Angiogenic Switch

For a tumor to become invasive, it first must develop the new blood vessels that will allow it to grow and spread, a process known as angiogenesis. **Nancy Boudreau, Ph.D.,** at the **University of California,** San Francisco, explored whether there is a process that occurs in early tumor development that triggers breast epithelial cells (the cells in which breast cancer begins) to start producing the special molecules, called angiogenic factors, that a cell needs to create new blood vessels. Dr. Boudreau and her team found that normal cells, which appear organized (or polarized) inside, suppressed expression of angiogenic factors whereas disorganized cells and breast tumors cells had higher levels of these factors. They also found that by restoring expression of a gene, called HoxD10, which is missing in aggressive tumors, they could revert tumor cells back to an organized, polarized state. The team is now exploring the role that a receptor called ß4 integrin, which interacts with HoxD10, plays in this process. They are also investigating whether cells need a protein called ß-catenin to grow new blood vessels. This work could lead to the development of new breast cancer treatments that stop tumor cells from growing by inhibiting angiogenesis.

Role of Telomerase in Mammary Stem Cell Function

Telomeres are the protective caps on each end of a chromosome’s four arms. Each time a chromosome splits during cell division, the telomeres get shorter; when they get too short, the cell dies. Telomerase is an enzyme that tells the telomeres to grow. It is expressed in stem cells

and in cancer cells, but not in the vast majority of normal cells. **Steven Artandi, M.D., Ph.D.**, at **Stanford University**, Palo Alto, and colleagues discovered that telomerase could activate inactive tissue stem cells, such as those found in the mammary gland. To further explore this finding, the team created a genetically engineered mouse (GEM) in which a protein subunit of telomerase, called TERT, could be switched on and off. They found that when TERT was on, it led to excessive cell growth and early breast cancers. Dr. Artandi and his team also showed that mice that don't have telomerase exhibit telomere shortening that impairs mammary gland development during pregnancy; that they could reconstitute the mammary gland when stem cells from one GEM mouse were transplanted into a normal mouse; and that the function of mammary stem cells is impaired when the telomeres in mice without TERT become very short. These studies provide important insights into the role telomerase plays in maintaining telomeres and preserving mammary stem cell function when cancer starts to develop.

Identification of BRCA1 Ubiquitylation Targets

The tumor suppressor gene BRCA1 is mutated in 50-90 percent of hereditary breast and ovarian cancers. Although how BRCA1 suppresses tumor growth is not fully understood, ubiquitin-ligases, which help attach the small protein ubiquitin to other proteins, are believed to play a role. **Peter Kaiser, Ph.D.**, at the **University of California**, Irvine, and colleagues developed a procedure to identify which target proteins in BRCA1 are attached to ubiquitin. By comparing cells with BRCA mutations to normal cells, they were able to identify many ubiquination sites and to measure quantitative changes in ubiquination profiles in response to DNA damage. This work could provide a way to identify the meaningful mutations in BRCA1. This could, in turn, lead to more reliable genetic counseling of individuals with an extensive family history of breast cancer. Findings from this research were published in *Molecular and Cellular Proteomics* 2(2005)366 and 5(2006)737, *Genome Biology* 6(2005)233, *EMBO Journal* 8(2007)817, and *Biochemistry* 11(2007)3553. Dr. Kaiser recently received funding from the National Institutes of Health to purchase an instrument, called a mass spectrometer, which will permit his team to better identify BRCA1 ubiquitination targets.

Modulation of TGF-beta Signaling in Mammary Epithelial Cells

Transforming Growth Factor-beta (TGFß) strongly inhibits the growth of mammary epithelial cells. Although it has the ability to suppress tumor growth, TGFß also can promote invasion and metastases of tumor cells as breast cancer progresses. To develop effective TGFß-based treatments, it is necessary to understand how TGFß converts from a tumor suppressor to a tumor promoter. **Xiaoman Xu**, **B.S.**, at the **University of California**, Irvine, and colleagues investigated whether a gene regulatory protein, called LMO4, which is found at high levels during mammary gland development and in over half of all breast cancer cases, transforms TGFß in breast cancer. The team showed that LMO4 affects cell growth by helping TGFß put the brakes on cell proliferation, and that increasing or removing LMO4 enhances TGFß-stimulated transcription. This suggests that LMO4 regulates the transcriptional response to TGFß in two different ways. Mr. Xu and his team also showed that LMO4 associates with a gene promoter, called PAI-1, in a way that could mediate the effects of LMO4 on TGFß signaling. And they found that a protein that is a member of the TGF-ß superfamily of proteins, called BMP7, is a direct target of LMO4. This work, which shows that LMO4 has a role in TGFß signaling, has the potential to advance our understanding of how breast cancer progresses and could lead to the

development of new breast cancer treatments. Findings from this research appeared in *Oncogene* 25(2006)2920 and 26(2007)6431.

Isolation of Cancer Precursors from Normal Human Breasts

Cancer researchers are trying to identify biomarkers that can be used for early detection, prognosis, and prevention. **Bob Liu, Ph.D.**, at the **University of California**, San Francisco, and colleagues in the lab of Dr. Thea Tlsty are using a cell culture model system to grow normal human mammary epithelial cells (HMEC) that allows them to study the earliest events in breast cancer development. The research team has identified a population of cells that have abnormal growth control and malignant characteristics, which they call "variant" HMEC (vHMEC). These cells do not express an important tumor suppressor gene, called p16INK4a. Dr. Liu and his team developed cell surface markers, CD73+ and CD90-, that allowed them to identify vHMEC in women without breast cancer who have pre-malignant characteristics. They then characterized the cell populations that were identified by the CD73 and CD90 markers by whether or not they had malignant characteristics. The team found that there were sub-populations of breast cells that appeared to be able to silence tumor suppressors genes. They also found that CD73 "high" and CD90 "low" cells appear to overlap with basal-like breast cancers, which, due to their aggressive nature, have a poor prognosis. If future research confirms that CD73 and CD90 are good biomarkers, this work could lead to new ways of identifying and treating basal-like breast cancer.

Stem Cells in Breast Cancer Metastasis

Many scientists believe that stem cells may play a role in breast cancer. **John Yates, M.D., Ph.D.**, and **Brunhilde Felding-Habermann, Ph.D.**, at the **Scripps Research Institute**, La Jolla, and **Evan Snyder, M.D., Ph.D.**, at **The Burnham Institute for Medical Research**, La Jolla, tried to identify a population of aberrant stem-like cells within breast tumors that might play a critical role in the initiation of metastatic disease. They found that the majority of cells from patients with metastatic breast cancer display several of the properties associated with small subpopulations of cells found in primary tumors. Using a mouse model, the team showed that these tumor cells have multiple ways of homing in on different organs. The mouse model also revealed that breast cancer cells that have the ability to spread to the brain, which has a unique microenvironment, derive their energy predominantly from glucose oxidation, which is a hallmark of brain cell metabolism. These brain-homing breast cancer cells also are able to activate pathways that enhance their ability to survive and grow in the brain. The team is now studying whether normal human brain stem cells could be used to deliver treatments for metastatic brain lesions. This work could lead to the development of new approaches to prevent and treat metastatic breast cancer. Findings from this research were published in *Molecular and Cellular Proteomics* 5(2006)53, *Clinical Cancer Research* 13(2007)1656, and *Cancer Research* 67(2007)1472.

Histone Methylation as a Marker of Breast Cancer Progression

Histone methylation is a normal cell event that is often altered during breast cancer progression. Histones are proteins that organize the DNA in our cells. When they undergo a chemical change called methylation it results in gene misregulation, DNA damage, cell cycle defects, and genomic instability – all of which are hallmarks of cancer. **Judd Rice, Ph.D.,** at the **University of Southern California**, Los Angeles, and colleagues investigated whether histone methylation could be a breast cancer biomarker. They began by identifying locations on the genome of breast

cancer cells where changes in histone methylation had occurred. They then looked at these locations on normal cells. However, no significant differences were present. The team then conducted the study again, using a panel of histone methylation-specific antibodies. This time they found that specific methylated forms of the histones were dramatically altered on the cancer cells, which suggested that the antibodies themselves could be used as a biomarker. To explore this further, Dr. Rice has begun looking for correlations between cancer progression and degrees of histone methylation. This work could lead to new methods of breast cancer detection, assessment, and treatment.

Apaf-1 is a Transcriptional Target for the ZNF217 Oncogene

An oncogene is a gene that has the ability to transform normal cells into cancer cells. In 20-30 percent of early stage breast tumors, an oncogene called ZNF217 has too many copies (amplification) of the gene and too many proteins (overexpression) on its surface. This amplification and overexpression appears to play a key role during the early transformation of normal breast epithelial cells into cancer cells. Studies have shown that putting ZNF217 into normal breast epithelial cells not only allows them to reproduce indefinitely but it protects breast tumor cells from the chemotherapy drug doxorubicin. **Sheryl Krig, Ph.D.,** at the **University of California,** Davis, identified target genes for ZNF217 in three different cell lines and showed that ZNF217 targets genes in a cell-type specific manner. These findings led Dr. Krig and her team to hypothesize that the normal function of ZNF217 may be to help keep cells in a proliferative state. Findings from this research were published in *Genome Research* 16(2006)890 and *Journal of Biological Chemistry* 282(2007)9703.

Integrated Proteomic and Metabolic Analysis of Breast Cancer

Proteins, such as proteases, play a central role in promoting the aggressive properties of metastatic breast tumors. To better understand how proteases and related enzymes impact breast cancer, **Kyle Chiang, B.S.**, at the **Scripps Research Institute**, La Jolla, and colleagues developed a new way to measure proteins called activity-based protein profiling (ABPP) that can analyze changes in activity in large enzyme families. Using this technique, they identified a new enzyme, called KIAA1363, which appears at increased levels in aggressive breast cancer cells. The team also identified a KIAA1363 inhibitor, but it only inactivated KIAA1363 in lab studies and not in living organisms. The team is now trying to develop a better KIAA1363 inhibitor. Using breast and ovarian cancer cell lines with reductions in KIAA1363 expression, Mr. Chiang and his team showed that by interfering with KIAA1363 they could significantly reduce tumor growth rates in mouse models. The team is now investigating models of human breast cancer development and metastasis in KIAA1363 (-/-) mice. Findings from this research were published in *Chemistry and Biology* 12(2006)1041.

Novel Approach to Analyze Estrogen Action in Breast Cancer

Estrogen promotes breast cancer by inducing cell proliferation through estrogen receptors (ERs) and their associated signaling pathways. Anti-estrogen therapy is widely used to treat ER-positive breast tumors and is assumed to work by blocking estrogen-induced cancer cell division. **Brian Eliceiri, Ph.D.,** at the **La Jolla Institute for Molecular Medicine,** and colleagues explored whether estrogen also influences host tissues, such as blood vessels, to promote tumor metastasis independent of its effects on the tumor cells themselves. They began by identifying a breast cancer cell line that does not respond to estrogen. They then injected these cells into mice

with very low estrogen levels and mice with normal levels of estrogen. (They control the estrogen levels in the mice by removing the ovaries, the organs that produce the most estrogen; they then implant slow-release estrogen pellets in half the mice.) They found that the estrogen promoted metastasis to the lungs, a finding that could have significant implications for the treatment of ER-negative and ER-positive breast cancers. Findings from this research were published in *Cancer Research* 66(2006)3667.

Survivin: Target for Breast Cancer Brain Metastases

Metastatic breast cancer to the brain, which affects about 10-15 percent of patients with advanced breast cancer, has a poor prognosis. Part of the problem is that the chemotherapy agents that are used to treat breast cancer are unable to penetrate the blood-brain barrier. Survivin is a protein that is found in tumor blood vessels. It is also present at high levels in tumor-associated brain endothelial cells (TuBEC), where it makes these cells drug resistant. Studies have shown that blocking survivin production can induce cell death. **Florence Hofman, Ph.D.**, at the **University of Southern California**, Los Angeles is exploring whether reducing survivin in tumor-associated blood vessel cells will disrupt the blood-brain barrier thereby allowing chemotherapy to kill the tumor cells. Dr. Hofman and her team have shown that reducing survivin levels in TuBEC increases their sensitivity to a cancer treatment called temozolomide. Now, they are using a mouse model of human breast cancer to determine how human tumor-associated blood vessel cells with reduced survivin support human breast cancer growth. These studies will show whether survivin can be implanted into the rodent brain. This research could open the possibility for using a wide range of chemotherapy agents for brain metastases. In addition, if anti-survivin therapy is found to be effective in stopping the formation of new blood vessels, it could lead to the development of new drug combinations for blocking tumor growth as well as treating brain metastases. Findings from this research were published in *Neurosurgery Focus* 20(2006)E22.

The Role of B-Myb in Human Breast Cancer Progression

Myb-related proteins play a role in various aspects of normal chromosome biology. Clinical studies have shown that B-Myb is one of a small number of genes that can predict disease recurrence in breast cancer patients who are lymph node negative and treated with the anti-estrogen drug tamoxifen. **Joseph Lipsick, M.D., Ph.D.**, at **Stanford University**, Palo Alto, and colleagues investigated whether high levels of B-Myb are predictive of recurrence because of the role it plays in aneuploidy—the additions or deletions of chromosomes —in breast cancer cells. The team created two versions of the human B-Myb gene. One version produced a full-length B-Myb protein; the other produced a truncated Myb protein that contained only its DNA-binding domain. The team found that high levels of B-Myb caused cell death (apoptosis) in a MCF-7 human breast cancer cell line, whereas moderate levels caused more rapid entry into the cell cycle and increased invasion into the extracellular matrix, the framework that surrounds cells. They also found that inhibition of B-Myb caused an increase in aneuploidy without apoptosis. Dr. Lipsick and his colleagues are continuing to explore the role of B-Myb. They also are currently testing rabbit antibodies they prepared against human B-Myb as potential diagnostic agents. This work could lead to new ways of diagnosing and treating breast cancer.

Defining Mammary Cancer Origins in a Mouse Model of DCIS

The more scientists understand about early events in breast cancer progression, the easier it will be for them to develop new prevention therapies and strategies. **Alexander Borowsky, M.D.**, at the **University of California**, Davis, and colleagues are using mouse models of mammary cancer that progress from precancerous ductal carcinoma in situ (DCIS) to invasive cancer to explore whether genetic changes that commit a mammary cell to become a cancer cell occur before an actual lesion is formed. They are also investigating whether these changes commit the cell to become a cancer cell with specific behavioral properties. This research confirmed the stability of their mouse model system. It also indicated that there were significant differences in the ratio of "stem"- like cells in their pre-cancer mouse model and tumor tissues, and that both ratios differed from normal mammary gland tissue. Dr. Borowsky is now collaborating with the Kent Erickson laboratory at UC Davis in an effort to identify new stem cell markers. He is also collaborating with several other laboratories to use the mouse model in a variety of contexts. This work could lead to a better understanding of how breast cancer develops. Findings from this research appeared in *BMC Cancer* 6(2006)275 and *Clinical Cancer Research* 12(2006)2613.

Role of Oxidative DNA Damage to Breast Tumor Progression

For decades, scientists have believed that cancer is caused by environmental factors that result in mutations in the DNA code. A more contemporary theory suggests that oxygen metabolism produces free radicals, such as hydrogen peroxide, that produce a type of DNA damage, called oxidation, that can result in cancer. In some breast cancers, increased levels of oxidative DNA damage have been associated with tumor progression. However, it has been hard to measure this damage accurately, as the most commonly used marker of DNA oxidation, 8-oxoG, is chemically unstable. **Paul Henderson, Ph.D.**, at **Lawrence Livermore National Laboratory** previously found that the secondary products that 8-oxoG produces when it is oxidized are both chemically stable and easily result in mutations. This project explored the role these products might play in the development of breast cancer. Dr. Henderson and his team found, in part, that exposure to the hormone estradiol (E2), which is present in breast tumors, damages 8-oxodG in the DNA. They also found that a key repair enzyme, called MTH1, which targets 8-oxodG metabolites in cells, increases in concentration with increasing E2 concentration. This work could lead to the identification of molecular markers that could be used to diagnose breast cancer or monitor treatment response. Findings from this research were published in *Chemical Research in Toxicology* 18(2005)12, *Bioorganic Medical Chemistry* 15(2005)3627-31 and *Proceedings of the National Academy of Sciences of the United States of America* 104(2007)11203.

A Role for p53 and Splicing Factor SAP145 in Breast Cancer

Two of the proteins known to play a role in breast cancer are p53, which helps suppress tumor growth, and Cyclin E, which helps regulate the cell cycle. Both are found at higher than normal levels in aggressive human breast cancers. **Lan Truong, B.S.**, at the **University of California**, Irvine, and colleagues investigated how these two proteins work together to modify, or splice, the genes involved in the initiation and progression of breast cancer through a splicing factor called SAP145. Their initial findings suggested that another cell cycle regulatory protein, p21, may also be involved in this process. This led them to examine how SAP145, p53, p21 and Cyclin E interact. The research team found that SAP145 only interacts with p53 and p21 under conditions of no or low stress-induced cell death. They also found that following high stress or damage, activated p53 decreases SAP145 protein levels, an effect that cannot be rescued by

Cyclin E. In addition, they showed that the loss of SAP145 is p53-dependent following conditions of high stress and that it results in apoptosis, or programmed cell death. These findings, which suggest that p53's work as a tumor suppressor protein may also include mediating apoptosis, could lead to new approaches for treating breast cancer.

Breast Cancer Studies in a 3-D Cell Culture System

Breast tumors exist in a complex environment where cells are growing, dividing, and invading other tissues. As a result of these changes, cancer cells are subjected to stresses, such as limiting amounts of oxygen and nutrients. These so-called metabolic stresses affect how the cells communicate with each other, how they respond to signals from the environment, and how they respond to breast cancer treatment. **Kristiina Vuori, M.D.,Ph.D.,** at **The Burnham Institute of Medical Research**, La Jolla, and colleagues developed a three-dimensional (3-D) culture system that captures the metabolic stresses seen in living tissue better than the single-layer cell dishes currently used to study tumor growth. After investigating a number of cell lines, Dr. Vuori's team found that the human breast cell line T47D worked best in this 3-D model, and they are now using this cell line in their model to explore how breast cancer cells respond to radiation and chemotherapy and whether cell death is more likely to occur in nutrient- and oxygen-stressed cells.

Evaluating the Role of the RIN1 Gene in Breast Cancer

Ras proteins help regulate the pathways that control cell growth, differentiation, and cell death. These proteins alternate between inactive (GDP-bound) and active (GTP-bound) states. In about 30 percent of tumors RAS becomes "activated." **Marc Milstein, B.S.**, at the **University of California**, Los Angeles, and colleagues are studying what occurs downstream in the RAS pathway. Their lab previously identified an unknown breast tumor suppressor protein, called RIN1. This protein is a Ras "effector" that regulates epithelial cell functions. The team has determined that RIN1 expression is frequently blocked in breast cancer cell lines and human breast tumors, and they have characterized two mechanisms that silence RIN1. The team also found that restoration of RIN1 inhibits the growth of tumor cells in cell culture and in mice. In addition, they have shown that the RIN1 gene is tightly clustered with two other tumor suppressor genes, BRMS1 and B3GNT1, and that the three genes display coordinated silencing in multiple breast tumor cell lines and a tissue sample. Additional studies showed that treatment with the protein TGFß caused a reduction in B3GNT1, BRMS1 and RIN1 expression in normal mouse epithelial cells and tumor cells, and that B3GNT1, RIN1, and BRMS1 each independently acted as negative regulators of cell migration. The discovery of this tumor suppressor gene cluster could lead to the development of new breast cancer treatments.

Oxidative Stress and Estrogen Receptor Structural Changes

There is extensive evidence showing that the estrogen receptor alpha (ER, alpha isoform) plays a critical role in driving both the initiation and promotion of most human breast cancers. Oxidative stress induces aging and age-related diseases, and there is biological and clinical evidence to suggest that oxidative stress changes ER structure and function in ways that could help promote the development of breast cancer. **Bradford Gibson, Ph.D.**, and **Christopher Benz, M.D.**, at the **Buck Institute for Age Research,** Novato, used an analytical technique called mass spectrometry to monitor the effect of oxidative stress chemical changes on the ER structure. Their research identified several structural changes in ER that had previously been suspected but

had never before been detected. They also showed that two of these newly detected structural changes in ER could be translated into a potential new method of diagnosing ER-positive breast cancers. This work has the potential to advance our understanding of how ER-positive breast cancer develops and to reveal environmental exposures that contribute to the development and progression of the disease. Findings from this research were published in *American Association for Cancer Research* 45(2005)a560, *Drug Metabolism Reviews* 38(2006)601, and *Analytical Chemistry* 79(2007)3083.

Profiling Enzyme Activities in Human Breast Cancer

Developing new ways to diagnose and treat breast cancer relies heavily on the discovery of new protein biomarkers and therapeutic targets. To streamline analyses of human breast tumors and cells, **Benjamin Cravatt, Ph.D.**, and **Stefanie Jeffrey, M.D.**, at the **Scripps Research Institute**, La Jolla, combined a chemical methodology called activity-based protein profiling (ABPP), which was developed in their laboratory to identify enzyme activities, with a multidimensional protein identification technology (MudPIT). Using this new methodology, Drs. Cravatt and Jeffrey and their team identified more than 50 enzyme activities in human breast tumors, nearly a third of which represented previously uncharacterized proteins. They also embarked on a project to disrupt the function of these enzymes in breast cancer models. These studies led to the discovery that the enzyme KIAA1363 regulates an ether lipid signaling network in human breast and ovarian cancer cells. Using a mouse model, Drs. Cravatt and Jeffrey showed that disruption of the KIAA1363-ether lipid network reduced breast and ovarian tumor growth, suggesting that this enzyme could be a therapeutic target. This is one example of how this new technology could advance our ability to diagnose and treat breast cancer. Findings from this research were published in *Journal American Chemical Society* 126(2004)15640, *Proceedings of the National Academy of Scien*ces 101(2004)13756, *Nature Method* 2(2005)691, and *Chemical Biology* 13(2006)1041.

Defining Mutagenesis Pathways in Breast Cancer Evolution

Breast cancer is a genetic disease that begins with the mutation of DNA. It has long been believed that these mutations occur due to failure of the DNA replication and repair systems. More recently, researchers have come to believe that the cell itself must also influence the proteins that help induce mutations. **Ewa Lis, B.A.**, at the **Scripps Research Institute**, La Jolla, and colleagues studied mutation processes in yeast, which is an excellent model organism for studying cell cycle and DNA repair pathways, and then translating these finding to human breast cancer. The team screened 4,847 yeast gene deletion strains to identify 10 genes involved in the mutation of a gene called CAN1. The team was able to identify new pathways that appear to play a role in inducing genetic mutations. They also showed that they could use a small molecule to inhibit a specific genetic mutation. This suggests that if similar pathways exist in human cells, intervention in some forms of mutation may be possible.

Reactivation of the Inactive X Chromosome and Breast Cancer

In females, one of the two X chromosomes is inactivated to equalize X-linked gene dosage with XY males. Specific types of human breast cancer, including basal-like cancer, have acquired X chromosomal abnormalities such as the loss of the inactive X (Xi) and/or a gain of active X (Xa) chromosomes. These abnormalities are associated with an increased expression of at least 30 X-linked genes, including some that have previously been shown to be involved in breast cancer.

These observations suggest that deregulation of X inactivation may play a role in breast cancer. **Angela Andersen, Ph.D.**, at the **University of California**, San Francisco, and colleagues analyzed X inactivation in different mouse models of breast cancer. Xist is an X-linked gene expressed exclusively from the Xi; this non-coding RNA coats the Xi and plays a role in maintaining the silent state. Loss of Xist RNA enrichment from the Xi correlates with human basal-like cancer. Dr. Anderson and her team found that most cells from each mouse model had Xist RNA coating a single Xi, and that genes normally subject to X inactivation were expressed exclusively from the single Xa. This work could lead to new screening techniques and new treatment strategies that utilize assays for the presence of multiple Xa chromosomes.

Structural Analysis of Cancer-Relevant BRCA2 Mutations

Inherited mutations in BRCA1 and BRCA2 are responsible for about 5-10 percent of all breast cancer cases and about one-half of all familial cases of breast and ovarian cancer. While evidence for a role of BRCA2 in the recombinational repair of DNA damage is mounting, the precise molecular functions of this protein and its biochemical properties remain unknown. **Henning Stahlberg, Ph.D.**, at the **University of California**, Davis, and colleagues developed a three-dimensional structure to test the hypothesis that a subgroup of mutations results in a folded BRCA2 protein that has a reduced ability to bind to Rad51, the central protein in recombinational repair. This, in turn, could elevate cancer risk. Dr. Stahlberg has successfully developed a new sample preparation method that will enable his team to work with the very fragile BRCA2 protein. This new preparation method has the potential to advance other breast cancer protein research projects. It also could lead to the identification of mutant BRCA2 proteins and, in turn, new drug treatments.

Grants in Progress: 2007

Analysis of MicroRNA Expression in Breast Cancer Stem Cells
Yohei Shimono
Stanford University

Axon Guidance Proteins in Mammary Gland Development
Lindsay Hinck
University of California, Santa Cruz

Breast Cancer Studies in a 3-D Cell Culture System
Robert Abraham
The Burnham Institute of Medical Research

A Candidate Marker of Mammary Tumor Initiating Cells
Alexey Terskikh
The Burnham Institute of Medical Research

Defining Mammary Cancer Origins in a Mouse Model of DCIS
Alexander Borowski
University of California, Davis

Functional Analysis of BORIS, A Novel DNA-binding Protein
Paul Yaswen
Lawrence Berkeley National Laboratory

Identification of Metastasis Competent Breast Cancer Cells
Barbara Mueller
La Jolla Institute for Molecular Medicine

Identifying Metastatic Breast Cells from Peripheral Blood
Kristin Kulp
Lawrence Livermore National Laboratory

Imaging RhoC-induced Breast Cancer Invasion and Angiogenesis
Konstantin Stoletov
University of California, San Diego

Inflammation Alters Transcription by ER in Breast Cancer
Eliot Bourk
University of California, San Diego

Modeling, Targeting Acetyl-CoA Metabolism in Breast Cancer
Chen Yang
The Burnham Institute of Medical Research

MYC and CSN5 in the Breast Cancer "Wound Signature" Profile
Adam Adler
Stanford University

A New Marker for Mammary Epithelial Stem Cells?
Robert Oshima
The Burnham Institute of Medical Research

Normal Mammary Biology of Phosphorylated Prolactin
Ameae Walker
University of California, Riverside

Novel Approach to Analyze Estrogen Action in Breast Cancer
Brian Elicieri
La Jolla Institute for Molecular Medicine

A Novel Epithelial-Stromal Model of Metastatic Breast Cancer
Richard Neve
Lawrence Berkeley National Laboratory

Profiling Drug Metabolism (P450) Proteins in Breast Cancer

Aaron Wright
Scripps Research Institute

Reactivation of the Inactive X Chromosome and Breast Cancer
Angela Anderson
University of California, San Francisco

Regulation of Mammary Epithelial Invasion by MMPs and FGFs
Andrew Ewald
University of California, San Francisco

Role of Cell Division Asymmetry in Breast Cancer Stem Cells
Claudia Petritsch
University of California, San Francisco

The Role Chk1 in Breast Cancer DNA Damage Repair
Jennifer Scorah
Scripps Research Institute

The Role of the ECM in Breast Cancer DNA Damage Repair
Albert Davalos
Lawrence Berkeley National Laboratory

The Role of Estrogen-Related Receptors in Breast Cancer
Anastasia Kralli
Scripps Research Institute

Role of Integrins in Lymphangiogenesis During Breast Cancer
Barbara Susini
University of California, San Diego

The Role of LMO4 in Breast Cancer
Zhengquan Yu
University of California, Irvine

The Role of Podosomes in Breast Cancer Metastasis
Barbara Blouw
The Burnham Institute of Medical Research

The Role of Serine and Metallo-Hydrolase's in Breast Cancer
Sherry Niessen
Scripps Research Institute

Stem Cells in Breast Cancer Metastasis
Brunhilde Felding-Habermann, John Yates & Evan Snyder
Scripps Research Institute and The Burnham Institute of Medical Research

Stem Cells of Molecularly Diverse ER Negative Breast Cancers
Stefanie Jeffrey
Stanford University

Structural Analysis of Cancer-Relevant BCRA2 Mutations
Henning Stahlberg
University of California, Davis

Twist Activation in Breast Cancer Metastasis
Jing Yang
University of California, San Diego

Research Initiated in 2007

Breast Tumor Responses to Novel TGF-beta Inhibitors
Kelly Harradine
University of California, San Francisco

Competition for ADA2 and 3 to Inhibit p53 in Breast Cancer
Min Yang
University of California, Irvine

Cytoskeletal Regulation of Invading Breast Cells
Catherine Jacobson
University of California, San Francisco

Determination of Stromal Gene Expression in Breast Cancer
Robert West
Palo Alto Institute for Research & Education

Indole (I3C) Control of Breast Cancer by ER Downregulation
Crystal Marconett
University of California, Berkeley

Lipid Raft Composition in Deregulated ERBB2 Signaling
Ralf Landgraf
University of California, Los Angeles

Mechanisms of Daxx-Mediated Apoptosis in Breast Cancer
Lorena Puto
The Burnham Institute of Medical Research

A New Mouse Model of PI3-Kinase Induced Breast Cancer
Jun Zhang, Ph.D.
University of California, San Francisco

Novel Regulation of the Rb Pathway in Breast Epithelium
Deborah Burkhart
Stanford University

The Relationship of BRCA1 and HMGA2 in Breast Cancer
Connie Tsai
University of California, Irvine

Targeting Tissue Factor in Breast Cancer
Florence Schaffner
Scripps Research Institute

Telomerase, Mammary Stem Cells, and Breast Cancer
Steven Artandi
Stanford University

Trask, a Candidate Breast Cancer Metastasis Protein
Ching Hang Wong
University of California, San Francisco

Relationship between Federal and State Funding for Breast Cancer Research

The California Breast Cancer Research Program is distinct from research programs funded by the federal government in both the CBCRP's source of funding and in the types of research funded.

Sources of Funding

Funding for breast cancer research in the U.S. is available from a variety of sources:

- **Federal Agencies** (National Institutes of Health, Department of Defense) receive funding through Congress from the national budget and from voluntary purchase of more expensive postage stamps.
- **National Voluntary Health Organizations** (such as the American Cancer Society, Komen Foundation, Breast Cancer Research Foundation) receive funding through charitable contributions from individuals, corporations, and foundations.
- **Regional Nonprofit Organizations** (such as the Entertainment Industry Foundation, The Wellness Foundation) also receive funding through charitable contributions.
- **State Agencies** (such as the New Jersey Breast Cancer Research Fund, Illinois Ticket for the Cure State Lottery) receive funding from state general funds, auto license fees, lottery ticket sales and voluntary donations on individual state income tax returns.

The California Breast Cancer Research Program is unique in its funding source. Rather than coming from the state general fund or solely from voluntary donations, almost all of the Program's funds come from a 45 percent share of revenue from a two-cent State tax on cigarettes. This source of funds is declining and temporary. In the past, measures were proposed in the California State Legislature that would have had the indirect effect of decreasing funding for the CBCRP by $5 million; similar measures may be proposed, and may pass, in the future.

The CBCRP also receives some funding from individual contributions and from the income tax check-off program, which allows individuals the opportunity to make voluntary donations on state income tax returns. Voluntary tax contribution funding is a result of legislation passed by the California State Legislature that authorizes donations for five years. During 2007, AB28, a bill authored by Assembly Member Jared Huffman, became law. This legislation provides individuals the opportunity to make donations to the CBCRP through voluntary tax contributions for the coming five years.

To increase this source of revenue, the CBCRP conducts a public outreach and fundraising effort, the Community Partners Program. A distinguished panel of Californians provides leadership to the Community Partners Program as members of the Community Partners Executive Team. The Executive Team is chaired by Sherry L. Lansing, Founder, Sherry Lansing Foundation, and Regent, University of California.

Since 2002, the CBCRP's Community Partners Program has pursued two goals: increasing donations through the income tax voluntary contribution program and new sources, and increasing public awareness of the CBCRP.

Community Partners Program: Increasing Voluntary Donations

More than 43,000 individuals donated over $569,000 to the CBCRP during 2007 through the state income tax check-off program. This made the CBCRP one of the check-off program's top beneficiary organizations for the year.

The following grants were funded in part through voluntary tax contributions in 2007:

Breast Cancer Risks in California Nail Salon Workers
Peggy Reynolds and Linda Okahara
Northern California Cancer Center and Asian Health Services

Intraductal Therapy of DCIS: a Presurgery Study
Susan Love
Dr. Susan Love Research Foundation

Modulation of Breast Cancer Stem Cell Response to Radiation
Frank Pajonk
University of California, Los Angeles

Molecular Imaging of Metastatic Lymph Nodes in Breast Cancer
Ella Jones
University of California, San Francisco

Multinuclear MRI of Breast Tumors
Brian Hargreaves
Stanford University

Science Literacy & Breast Cancer Clinical Trials Education
Georgia Sadler and Natasha Riley
University of California, San Diego and Vista Community Clinic

The Relationship of BRCA1 and HMGA2 in Breast Cancer
Connie Tsai
University of California, Irvine

The CBCRP also provides a number of other opportunities to make financial contributions to the Program's work. The CBCRP is a participant organization in the Community Campaign of the United Way of California, which allows residents of the state to make donations at their place of work. During 2007, the CBCRP received donations from the United Way of the

Bay Area, United Way of the Capitol Region, United Way Silicon Valley, United Way Southeastern Philadelphia, and the United Way State Employees Charitable Campaign.

This year, the public demonstrated continued enthusiasm for the CBCRP's research. Businesses, community groups, and individuals initiated their own efforts to provide funds for the Program's research, without being solicited to do so. The Just Darling Fashion Boutique in Oakland held a fashion show dedicated to many of the boutique's customers who have been affected by breast cancer, and chose the CBCRP as the beneficiary of the event. Runners participating in the San Francisco Marathon came close to doubling their goal of raising $10,000 for the CBCRP, raising $19,536.50. The top fundraisier was runner Molly O'Mara, who brought in $8,891, second was Scott Harrison, with $5,079, and third was Donna Vazfidar, with $2,650. America's Charities and Community Health Charities also made contributions to the CBCRP.

Businesses that made the CBCRP the beneficiary of their community or employee fundraising efforts included: AT&T Employee Giving Program, Amgen Corporation Matching Gift Program, Honey From the Bee, and Wells Fargo Community Support Campaign. In addition, the CBCRP received contributions from the Kaiser Permanente Community Giving Campaign, and the Superior Court of California - County of San Bernardino.

The public has also responded to the opportunity to make donations via the Program's Web site, www.CABreastCancer.org.

Community Partners Program: Increasing Awareness of the CBCRP

During 2007, the CBCRP's outreach campaign focused on raising awareness of both the Program's work and on increasing citizen contributions via their state income tax forms.

The CBCRP has a five-minute video that showcases the Program. This video—narrated by TV host, breast cancer survivor, and former Olympic figure skater Peggy Fleming—is shown at exhibits and outreach events. A CD or DVD of the video is sent to anyone who requests it, free of charge.

With the assistance and participation of Community Partners, individual donors to CBCRP, and breast cancer advocacy organizations, the CBCRP held public exhibits over the past year calling attention to the opportunity to donate to the CBCRP on state tax returns. During 2007, in addition, the CBCRP conducted a combined outreach effort with other California nonprofit organizations who receive state tax return contributions. Together, the CBCRP and these nonprofit organizations created a radio and Internet marketing campaign to alert the public to the income tax check-off program. The campaign was conducted in partnership with the tax preparation firm Jackson Hewitt and California radio stations. It included radio public service announcements in English and Spanish, along with a Web site highlighting all nonprofit organizations included in the income tax check-off program. To augment this campaign, the CBCRP conducted its own on-air and Internet-based campaign alerting the public to the opportunity to make donations to the CBCRP via the income tax check-off. The campaign included radio spots on Bay Area stations KDFC, KOIT, and KMAX. Targeted advertising was mailed to CBCRP and University of California contacts, and to California female certified public accountants. Governor Arnold Schwarzenegger further boosted California's awareness of the opportunity to make donations through the tax check-off by issuing an official proclamation declaring April 5, 2007, as Checkoff California Day.

The CBCRP made its special Web site dedicated to the income tax check-off, www.endbreastcancer.org, more user friendly during 2007. Over the coming year, the site will inform stakeholders about fundraising progress and also about progress researchers are making with the grants funded via contributions made on state income tax returns.

The CBCRP gained exposure in a variety of media over 2007. CBCRP Director Dr. Marion H. E. Kavanaugh-Lynch appeared on the radio program *It's Your Call* on San Francisco radio station KALW and also on the Bay Area's KPIX TV. In addition, Dr. Kavanaugh-Lynch's comments appeared in a story in the *Sacramento Bee,* which also appeared in the *Seattle Times.* CBCRP-funded research projects were covered over KGO Channel 7 San Francisco, and on the Web sites ScienceDaily.com, ConsumerAffairs.com, and MedPageToday.com.

Unmet Need

Ensuring the CBCRP's present funding sources and increasing funds from new sources are both necessary. Current funds are not sufficient to do all that needs to be done. The CBCRP is unable to make grants to meet the following needs:

- **Clinical Trials.** In a clinical trial, some patients receive a promising new therapy and the outcome is compared to a group receiving standard therapy. Clinical trials are the way science discovers which treatments work. Currently, almost every child with cancer in the U.S. is treated through a clinical trial, compared to 3 percent of women with breast cancer. With California's diverse population, statewide clinical trials here could lead to the discovery of information that could be discovered nowhere else.

- **Drug Development.** Developing a new drug can take 10–15 years and cost hundreds of millions of dollars. Pharmaceutical companies select potential drugs most likely to be profitable; discoveries that are too risky or only have the potential to help a small population may never become treatments.

- **Long-term Studies.** A 20- or 30-year study of California women and girls could reveal a lot about risk factors that lead to breast cancer and point to ways to prevent the disease.

- **Tissue Banks**. Samples of tumors from California women, along with the women's medical history, could provide answers to research questions now and in the future.

- **Services.** The CBCRP provides funding for community-based organizations to test services for women with cancer, but once those services have been shown to help women with breast cancer cope or survive, the Program is unable to ensure that those services will be provided.

- **Collaborative Consortium with Biotechnology.** One of the most promising areas to support new therapies and drug discovery is the potential collaboration between the CBCRP and biotechnology leaders in academia, industry, and government. Agenda-setting conferences could propel research into development.

- **National Priority-Setting Conferences.** As the largest state-funded research organization in the nation, the CBCRP carries a leadership role. The Program has the opportunity to attract experts from medicine, research, and science to take part in a series of "think tank" conferences to support new directions in breast cancer research. The conferences would also draw new researchers into this field.

- **Grant Proposals the CBCRP Does Not Fund**. During 2007, the CBCRP turned down grant applications requesting a total of $10,647,003 that were rated by expert reviewers as having sufficient scientific merit for funding.

Since the CBCRP's major source of funding, the state tobacco tax, is decreasing every year, the Program will not be able to meet these critical needs or continue to fund the broad range of projects it has funded in the past.

Types of Research Funded by the CBCRP: Fulfilling our Mandate

One of the CBCRP's mandates is to "fund innovative and creative research, with a special emphasis on research that complements, rather than duplicates, the research funded by the federal government." The CBCRP fulfills this mandate in three ways:

1. By identifying gaps in the research funded by the federal government, and providing funding to fill those gaps
2. By having expert reviewers from across the U.S. review grant applications for their innovation and impact
3. Before funding a grant application, reviewing it for overlap with current and pending funding from other agencies

Filling Research Gaps

The federal government funds most health-related research through the National Institutes of Health (NIH). The NIH view is on "capitalizing…investigator-initiated research." The primary basis on which the NIH chooses grants for funding is their scientific merit, not their relevance to a particular disease. As a result, most research proposals submitted to the NIH address scientific questions in which the investigators have theoretical and empirical interest, even though there may be no clear relevance to particular diseases.

Only a small percentage of NIH funds go to research in issues the NIH has identified as particularly important to specified diseases (i.e., Requests for Applications). The majority of NIH funds support the most scientifically meritorious research regardless of the applicability of the research to particular diseases.

In contrast, a fundamental priority for the CBCRP is to fund research that will speed progress in preventing and curing breast cancer. The CBCRP's advisory Breast Cancer Research Council sets the Program's funding priorities, taking into account:

- Opinions from national breast cancer experts;

- Opinions from California advocates and activists, healthcare providers, public health practitioners, community leaders, biotechnology scientists, and academic researchers;
- Current literature on breast cancer and current gaps in knowledge.

The council attempts to identify and fill important gaps in knowledge about breast cancer, and reviews priorities yearly in light of changes in the research field, successes and failures of previous funding initiatives, and the results of previous funding.

The CBCRP is conducting a five-year program initiative, begun in 2005, to fill a significant gap in breast cancer research. This initiative addresses two overlapping research questions that California is uniquely positioned to address. They are the relationship between breast cancer and the environment, and the reasons for the unequal burden of breast cancer among various populations of women. More information on this initiative may be found in a previous section of this report, "The CBCRP Strategy for Funding Research."

Choosing Research for Innovation and Impact

The CBCRP created its own scoring system to allow the Program's expert reviewers to differentiate applications that are especially innovative and that have the most potential impact on breast cancer. The scoring system has improved the Program's ability to choose the most innovative and creative research for funding.

In the past, the majority of research funding agencies, including the CBCRP and the National Institutes of Health, scored funding proposals with a single score based solely on scientific merit. With this method, an application with an excellent research plan to test an idea that wasn't particularly novel could receive the same score as an application with a flawed research plan to test a novel idea. The CBCRP's scoring method, based on the recommendations of an NIH Advisory Committee, can distinguish these two applications. The CBCRP scores applications separately for innovation, impact, approach, and feasibility. The CBCRP's advisory Breast Cancer Research Council uses these separate scores to inform their funding recommendations. Under the CBCRP's "impact" criterion, researchers are required to describe the steps necessary to turn their research into products, technologies, or interventions that will have an impact on breast cancer, and describe where their study fits into this critical path.

Reviewing Grant Proposals for Overlap with Federal Funding

As a final step to ensure that CBCRP-funded research doesn't duplicate federally-funded research, breast cancer science experts in other states and Program staff scientists review all grants recommended for funding for overlap with current and pending federal grants. If overlap with federal funding is found, the overlapping grant (or portion of the grant) is not funded.

Taking Leadership to Coordinate Federal, State, and International Funding

During 2007, the CBCRP participated in the start of a nationwide effort to reduce barriers and waste in research toward the goal of ending breast cancer. Along with other U.S. breast cancer research funding agencies, industry representatives, regulators, advocates, and social scientists, the CBCRP took part in the Collaborative Summit on Breast Cancer Research. Participants in the summit formed the National Breast Cancer Planning Committee, which will review the national breast cancer research agenda and assist U.S. breast cancer organizations in identifying gaps, opportunities and overlaps in research into the disease. The committee will also produce a report to the general public on how key breast cancer organizations use donations to fund research.

In addition, the CBCRP is working to make it easier to avoid duplication among research funding agencies and to speed progress in breast cancer research by increasing communication among agencies that fund breast cancer research. One way the Program pursues these goals is by taking part in developing a research classification system to encourage agencies to report their funding in a way that is more accessible and meaningful to other agencies and the public.

The CBCRP joined with six other cancer research funding organizations in the U.S., 15 of the largest government and charitable cancer research funders in the United Kingdom, and the key government and non-government cancer research funders in Canada to launch the International Cancer Research Portfolio (ICRP) Web site (www.cancerportfolio.org). This Web site includes research abstracts from more than 14,000 current and past research projects. The online database is searchable by cancer type, scientific area, funding organization, and other selected criteria. The Web site allows scientists to identify possible collaborators, plan their research based on current research, and facilitate dialogues among cancer researchers. Access to this information about ongoing research also aids research funding organizations in strategic planning for future spending. In addition, the Web site is a useful tool for other groups. Policy makers may use the database during the formulation of new health care and service delivery policies. Healthcare professionals, patients, survivors, and advocates may review the current status of funded research.

The partners in this effort are dedicated to making current research information available to funding agencies and the public, and to promoting scientific collaboration. To extend coordination further, the ICRP partners invite representatives from the other organizations to attend their scientific meetings and review in person their funded research. During 2008, the ICRP will take international coordination to a higher level by completing a review of all funded cancer research grants in the U.S., U.K., and Canada that will point to gaps in research and make recommendations for research priorities to fill those gaps.

Research on Women and Minorities

Thirty-four percent (12 of 35) of the grants that the CBCRP awarded in 2007 studied either women or tissues from women, while the remaining 66 percent were laboratory studies that did not directly involve women or tissues from women.

Of the 12 grants that involved women or tissues from women, 100 percent (12) had women as participants in the study.

Thirty-one percent (11) of these studies included minority women in the study.

- Twenty percent (7) are focused on underserved women.
- Fourteen percent (5) are focused on minority women.

A total of (7) grants were funded with a primary emphasis on minority and/or underserved women:

Sister Survivor: African American Breast Cancer Coalition
Kimlin Ashing-Giwa, Ph.D., Beckman Research Institute of the City of Hope
Gloria Harmon, B.A., Women of Essence

Breast Health Behaviors of Immigrant Afghan Women
Joan Bloom, Ph.D., University of California, Berkeley
Aida Shirazi, Afghan Coalition

Science Literacy & Breast Cancer Clinical Trials Education
Georgia Sadler, Ph.D., M.B.A., University of California, San Diego
Natasha Riley, M.A., Vista Community Clinic

Underserved Women with Breast Cancer at End of Life
Shelley Adler, Ph.D., University of California, San Francisco
Denise Wells, Charlotte Maxwell Complementary Clinic

Breast Cancer Risks in California Nail Salon Workers
Peggy Reynolds, Ph.D., Northern California Cancer Center
Linda Okahara, Asian Health Services

Circuit Training to Lower Breast Cancer Risk in Latina Teens
Jaimie Davis, Ph.D., University of Southern California

Multinuclear MRI of Breast Tumors
Brian Hargreaves, Ph.D., Stanford University

Advisory Council Members and Staff

Advisory Council (2007)

Chair
Lisa Wanzor (2006-2007)
Angela Lucia Padilla (2007-2008)

Vice-Chairs
Amy Kyle (2006-2007)
Maria Wetzel (2007-2008)

Advocates
Roxanna Bautista, M.P.H, Asian & Pacific Islander American Health Forum (2007-2010)
Angela Lucia Padilla, Esq., Bay Area Young Survivors (BAYS) (2005-2008)
Karren Ganstwig, Los Angeles Breast Cancer Alliance (2007-2010)
Diane Griffiths, The Breast Cancer Fund (2006-2009)
Maria Wetzel, Cancer Resource Center of Mendocino County (2005-2008)
Lisa Wanzor, Breast Cancer Action (2004-2007)

Scientists/Clinicians
Moon Chen, Ph.D., University of California, Davis (2004-2007)
Laura Fenster, Ph.D., California Department of Public Health (2007-2010)
Shelley Hwang, M.D., University of California, San Francisco Comprehensive Cancer Center (2007-2010)
Amy Kyle, Ph.D., University of California, Berkeley (2004-2007)
Jan Schnitzer, M.D., Sidney Kimmel Cancer Center (2007-2010)
Mary Alice Yund, Ph.D., University of California, Berkeley Extension (2007-2010)

Industry Representatives
Chris Bowden , Ph.D., Genentech (2007-2010)
Gordon Parry, Ph.D., Monogram Biosciences (2005-2008)

Non-Profit Health Representatives
Crystal D. Crawford, Esq., California Black Women's Health Project (2006-2009)
Catherine Quinn, California Health Collaborative (2006-2009)

Medical Specialist
Klaus Porzig, M.D., South Bay Oncology Hematology (2006-2009)

Ex Officio Member
Sherie Smalley, M.D., California Department of Public Health (ongoing)

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Katherine McKenzie, Ph.D. - Manager: External Relations; Biomedical Research Administrator
Walter Price, Dr.P.H. - Manager: Community Outreach; Public Health Research Administrator

DeShawn Boyd - External Relations Assistant
Natalie Collins, M.S.W. - Outreach and Technical Assistance Coordinator
Sharon Cooper, M.P.A. - Research Analyst
Janna Cordeiro, M.P.H. - Coordinator of Special Projects
Mary Daughtry - Core Funding Assistant
Elizabeth Day - Program Assistant
Brenda Dixon-Coby - Community Outreach & Special Events Coordinator
Lyn Dunagan - Communications Project Coordinator
Stella Gonzales - Administrative Assistant
Claudia Grossmann, Ph.D. - Program Evaluator
Lisa Minniefield - Assistant to the Director
Eric Noguchi - Senior Designer
Marj Plumb - Community Collaboration Consultant
Joyce Price - Administrative Assistant
Catherine Thomsen, M.P.H. - Project Lead, Special Research Initiatives

Appendix A:
Special Research Initiatives
"Identifying Gaps in Breast Cancer Research"
Science Advisors, Staff, and Consultants

Science Advisors

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Judith Salmon Kaur, MD, Medical Director, Professor of Oncology, Native American Programs, Mayo Comprehensive Cancer Center
Steve Kaye, PhD, Associate Professor, University of California, San Francisco
Charles Land, PhD, Senior Investigator, National Cancer Institute
Robert Millikan, PhD, Professor, University of North Carolina, Chapel Hill
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Mary Wolff, PhD, Professor, Mount Sinai Medical Center

Staff and Consultants

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Judy MacLean, BA, Editorial Consultant
Katherine McKenzie, PhD, Manager-External Relations; Biomedical Research Administrator
Marj Plumb, DrPH, MNA, Senior Consultant, Plumbline Coaching and Consulting, Inc.
Patrice Sutton, MPH, Technical Consultant
Catherine Thomsen, MPH, Project Lead

Appendix B:
Special Research Initiatives Strategy Team

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Vernal Branch, Virginia Breast Cancer Foundation
Barbara Brenner, JD, Breast Cancer Action
Linda Burhansstipanov, MSPH, DrPH, Native American Cancer Research, Corp.
José Escarce, M.D., Ph.D., Rand Corporation and UCLA Medical Center
Harold Freeman, M.D., Ralph Lauren Cancer Center, North General Hospital
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