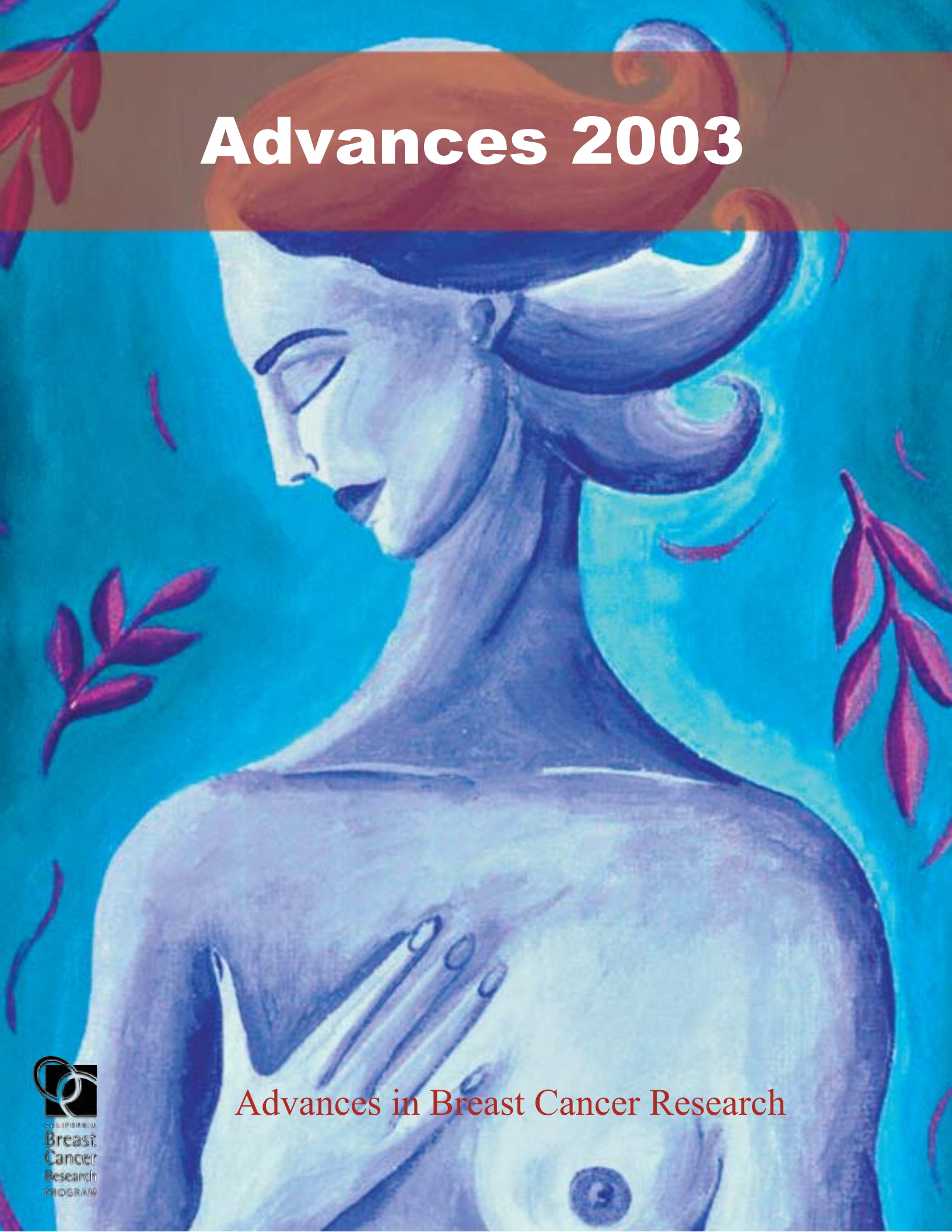
Advances 2003



Advances in Breast Cancer Research

California Breast Cancer Research Program

Research Highlights

Researchers are working to adapt Magnetic Resonance Imaging (MRI) to detect breast cancer earlier than mammograms. See "Measurement of Breast Tissue Viscoelasticity Using MRI," page 54.

Early steps toward a blood test for breast cancer have succeeded. See "Clinical Utility of Breast Cancer DNA Markers in Plasma," page 59.

When women who have survived breast cancer act as volunteer peer counselors for women newly diagnosed with the disease, both groups of women fare better if the survivors get training, supervision, and support. See "Does a Peer Navigator Improve Quality of Life at Diagnosis?" page 70.

Scientists are successfully using computer modeling to hunt for molecules that could be turned into drugs to treat breast cancer. See "Computer-Aided Discovery of Novel Breast Cancer Therapeutics," page 77.

Researchers are testing Chinese herbal extracts as treatments for breast cancer, and one showed promise when tested on mice. See "In Vivo Effects of Chinese Herbal Extracts on Breast Cancer," page 81.

Essiac tea, an herbal remedy some women have used as an alternative breast cancer preventive, promotes the growth of tumors in rats. See "Evaluation of Essiac Tea to Prevent Mammary Tumors," page 110.

Many women at high risk for breast cancer believe their risk is even higher than it actually is. See "Tamoxifen Prevention: Is it Acceptable to Women at Risk?" page 120.

Research is confirming that chemotherapy can cause memory and concentration problems. See "Cognitive Changes After Adjuvant Therapy for Breast Cancer," page 126.

Table of Contents

"The need is urgent. Every two hours, on average, a California woman dies of breast cancer.

"More than 200,000 California women are living with the disease. Every woman is at risk, and every woman who has had breast cancer in the past lives with the knowledge that it can return at any time."

Message from the Director

Welcome to the California Breast Cancer Research Program's 2003 Annual Report, a part of our wide-ranging efforts to make our research available to the public. On these pages, we give brief summaries of the studies we funded this year, along with summaries of studies we funded in previous years that were completed or made progress during 2002. We are one of the few research programs in the world to publish annual summaries of studies while they are still in progress.

During 2002, we awarded $14,809,103 for 67 single- and multiple-year research projects at 22 California institutions. Since 1995, we've provided a total of $130,770,795, for more than 500 grants to over 60 leading research institutions throughout California to investigate ideas that otherwise might not be explored.

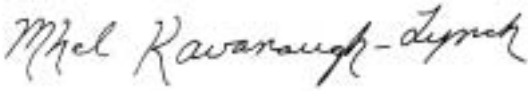
The need is urgent. Every two hours, on average, a California woman dies of breast cancer. More than 200,000 California women are living with the disease. Every woman is at risk, and every woman who has had breast cancer in the past lives with the knowledge that it can return at any time.

However, adequate support for breast cancer research in California is uncertain. Our main source of revenue, a state tax on tobacco products, is steadily declining, because fewer people are using tobacco. This means that every year the amount of research the CBCRP can fund will go down unless we replace that lost revenue.

That's why we launched our Community Partners Program, to open new ways for Californians to support our revolutionary breast cancer research. "The CBCRP Launches Community Partners," on page 12, tells more about how Californians are coming together from the business world, the sports world, and communities to help end breast cancer.

While our top priority is replacing the funds we are losing due to the decline in tobacco tax revenues, we also know there's a lot more research that needs to be done. "Toward More and Faster Progress Against Breast Cancer," page 36, describes what we could do if we could substantially increase the research dollars for breast cancer.

The purpose of all our investment in breast cancer research is to speed the day when we can prevent the majority of breast cancer and cure what we can't prevent. All of our work is dedicated to ending the suffering and fulfilling the hopes of the women who face this deadly disease.



Marion H.E. Kavanaugh-Lynch, M.D., M.P.H.
Director, California Breast Cancer Research Program

Thanks, California Taxpayers!

Every year, thousands of Californians participate in Check It Out! Check It Off!, the public education campaign that encourages voluntary donations on Franchise Tax Board Form 540, Line 56. Donations fund grants to California scientists and community researchers who are searching for more effective ways to prevent, treat, and cure breast cancer.

Last year, for the second year in a row, the CBCRP was #1 in the state for tax check-off donations.

By year's end, 65,374 taxpayers made donations with a total of $736,040.

Thanks, California taxpayers!

About the California Breast Cancer Research Program

Our Key Strategies

1) Support the best, most innovative research

2) Build the research talent pool by training new researchers

3) Encourage creativity by financing collaboration across research fields

4) Widely distribute research results to scientists, health care professionals, and the public

To find a cure for breast cancer, or better yet, to find a way to prevent the disease, we need to approach research in new ways. That's the driving philosophy behind the California Breast Cancer Research Program (CBCRP). We push breast cancer research in new directions.

In 1993, California breast cancer activists, most of them women who had survived or currently had breast cancer, sparked the creation of our program. The activists joined forces with scientists, health care professionals, state legislators, and University of California officials to win passage of statewide legislation establishing the CBCRP.

Californians fund our program through a state tax on tobacco, a voluntary checkoff box on state income tax forms, and individual contributions.

During 2002, we awarded $14,809,103 for 67 single- and multiple-year research projects at 22 California institutions. Since 1995, we've provided a total of $130,770,795, for more than 500 grants to over 60 leading research institutions throughout California to investigate ideas that otherwise might not be explored.

We're honored to be the largest state-funded breast cancer research program in the country. We're also the fourth largest breast cancer research program in the world. Every breast cancer patient around the world benefits from what we do.

We fund exploration and "outside the box" thinking. We've pioneered collaborations where research scientists work side by side with women affected by breast cancer. Above all, we provide resources for the people who sit alone in labs and focus on painstaking, tedious, demanding, trial-and-error science and for people who are working in the community to lessen the impact of the disease. Their work and our support will continue, day after day, until we find a way to end the suffering caused by breast cancer.

CBCRP Structure: Encouraging Public Input

Breast cancer activists play a leading role in every aspect of our work, from setting research priorities to awarding grants to getting out the word about research results.

The California Breast Cancer Research Program's structure has set a standard for community involvement that has inspired similar changes in other research funding agencies around the nation. Breast cancer activists play a leading role in every aspect of our work, from setting research priorities to awarding grants to getting out the word about research results.

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

Our 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 we invest our funds in research. It also conducts one of two reviews every proposal must pass to receive funding. The Council reviews research proposals for their responsiveness to the CBCRP's mission. Simultaneously, some of the nation's top research scientists, health care professionals, and breast cancer advocates from outside California judge all proposals for scientific merit.

In addition, all Californians concerned about breast cancer have opportunities to help set the research agenda via the CBCRP's statewide advisory meetings, open to the public. Our biennial research symposia, held during odd-numbered years to review the CBCRP's research results, bring the scientific and treatment communities into dialog with a broader range of the public than is common at such conferences. We also encourage public review of CBCRP-funded research through our Web site (www.cbcrp.org) and this Annual Report.

Our structure allows us to bring the research, treatment, and advocacy communities into closer cooperation—to work toward an end to breast cancer.

"The CBCRP has supported numerous critical projects that have made major contributions to our understanding of cancer initiation and progression and has also helped fund projects that have led to significant changes in our treatment and diagnostic approaches."

What They're Saying About the CBCRP

Science for Humanity

"My sister died of breast cancer at age 47. It shook me to the core. I asked myself, what is my science doing for humanity? I had been doing pure basic science for many years and I decided that I want to expand my research program into breast cancer research. To get started in a new research area is not that easy. You have to re-gear your tools, and you have to start establishing a track record. I am very grateful to the CBCRP for helping me to explore a new research direction. Now I can apply my skills against this ferocious disease that is killing young women."

—Amy Lee, Ph.D.
Professor of Biochemistry and Molecular Biology, Keck School of Medicine
Associate Director for Basic Research, Norris Cancer Center
University of Southern California
Los Angeles, CA

Groundbreaking

"Whenever I am involved in discussion about medical research programs, someone brings up as a model the California Breast Cancer Research Program. When I spoke at the CBCRP symposium, I, too, was overwhelmed by the breadth of this groundbreaking state-funded program."

—Gwen Darien
Editor in Chief
MAMM Magazine
New York, NY

National and International Impact

"Clearly, the statewide California Breast Cancer Research Program has national and international impact."

—H. Kim Lyerly, M.D., FACS
Professor of Surgery
Duke University Comprehensive Cancer Center
Durham, NC

Wonderful

"The CBCRP's New Investigator Award is wonderful. It allowed me to pursue research when I had a new idea but very limited data, just some computer modeling analysis to support my theory. I was too new to the field to get a grant from the larger research funding agencies, but the CBCRP's New Investigator Award gave me a start in breast cancer research. Now the compound I created with CBCRP funding—a modification of a cancer-preventing molecule found in broccoli—may become a drug to prevent and treat cancer."

—Ling Jong, Ph.D.
Senior Organic Chemist
SRI International
Menlo Park, CA

Numerous Critical Projects

"The CBCRP has supported numerous critical projects that have made major contributions to our understanding of cancer initiation and progression and has also helped fund projects that have led to significant changes in our treatment and diagnostic approaches. The community collaborations in particular are a unique feature of the program and should be preserved."

—Laura Jean Esserman, M.D., M.B.A.
Associate Professor, Department of Surgery and Radiology
Director, Carol Franc Buck Breast Care Center
University of California, San Francisco/Mount Zion
San Francisco, CA

Gratitude

"CBCRP funding for the research I conducted allowed 451 women to voice their concerns about breast cancer. Many of these women have expressed gratitude for the study and for the CBCRP."

—Deborah J. MacDonald, R.N., M.S., A.P.N.G.
Assistant Director
Cancer Screening & Prevention Program
Department of Clinical Cancer Genetics
City of Hope Comprehensive Cancer Center
Duarte, CA

The Best Science

"The CBCRP makes a difference in making sure the best science moves forward quickly to be translated into innovative treatments for breast cancer patients."

—Nora Disis, M.D.
Associate Professor
University of Washington
Seattle, WA

California is Fortunate

"The CBCRP is an outstanding program at several levels. I have had the privilege of serving as a reviewer. The quality of the proposals and the innovation are always striking. California is fortunate to have such a fine cadre of researchers attacking the breast cancer problem. Californians are also lucky to have a funding mechanism that supports the research that will benefit women with breast cancer both today and in the future."

—Danny R. Welch, Ph.D.
Leonard H. Robinson Professor of Pathology
Senior Member - Comprehensive Cancer Center
University of Alabama at Birmingham
Birmingham, AL

CBCRP and CBCRP-Funded Research in the Media

An Oakland non-profit group this week announced $15 million in grants to scientists seeking innovative approaches to preventing, treating and curing breast cancer.

"Revolutionary research is critical" in the quest to reduce the incidence of the disease...

Online Groups Offer Support

BAY AREA (KRON)—Millions of American regularly use the Internet to search for medical information. But now going online could have another medical application, offering support to people battling deadly diseases.

Researchers wanted to see if online support could help women with breast cancer. A small pilot study found it could.

"They found that taking part in the group, women showed a significant decrease in depression, their reactions to pain were lessened, and they saw increases in well-being," says Dr. Marion Kavanaugh-Lynch of the California Breast Cancer Research Program.

—From a September 27, 2002 segment of the evening news, KRON 4 TV, San Francisco. The study of online support groups was conducted in collaboration between The Wellness Community; the University of California, San Francisco; and Stanford University. It was also profiled in a March 21, 2002, article in the *Pasadena/San Gabriel Valley Journal*.

Revolutionary Research is Critical

OAKLAND—An Oakland nonprofit group this week announced $15 million in grants to scientists seeking innovative approaches to preventing, treating and curing breast cancer.

Among the recipients are five Bay Area researchers, who received $1.2 million among them from the California Breast Cancer Research Program.

"Revolutionary research is critical" in the quest to reduce the incidence of the disease, said Dr. Marion Kavanaugh-Lynch, director of the program.

—From an August 22, 2002 article in *The Oakland Tribune*.

Higher Breast Cancer Risk for Lesbians Not Borne Out

SAN FRANCISCO—Almost 10 years ago, a National Cancer Institute researcher said a new study showed that lesbians had a 1-in-3 lifetime risk of developing breast cancer. "It sent shock waves through the lesbian community," said Suzanne Dibble, Professor of nursing at the University of California's Institute for Health and Aging in San Francisco.

The study took known risk factors for breast cancer and looked to see whether they occurred more often in the lesbian population. They most certainly did. But did this really mean there was an epidemic of breast cancer among lesbians? Dibble decided to find out.

With a grant from the California Breast Cancer Research Fund, "We found about a 1 percent added risk for lesbians," she said. In other words, if 10 straight women out of 100 were likely to get breast cancer during their lifetime, the number would be 11 out of 100 for lesbians.

—From an April 28, 2002, article in the *San Francisco Chronicle*.

Californians Lead Tax Checkoff Donations

SACRAMENTO—Few welcome the annual chore of filling out tax returns and sending the government money.

So it may come as a surprise to learn that while Californians are wrangling over their taxes and cursing what they owe, they are increasingly contributing to medical research or other charitable organizations.

The state's "check-off program," in which taxpayers can designate a portion of their refund or even boost their tax payment for a particular cause, has steadily grown since its creation in 1982. Last year $3.8 million in donations checked off on tax returns went to 15 groups ranging from the California Breast Cancer Research Program to the National World War II Veterans Memorial Fund.

—From a March 21, 2002, *Associated Press* article in the *Contra Costa Times, Sacramento Bee, San Jose Mercury News,* and seven other California newspapers.

A Stronger Sense of Self

OAKLAND—Something many survivors of breast cancer say they've gleaned through this arduous physical journey is a stronger sense of self, of individuality, and even spirituality, moving beyond bodies.

Some women have expressed this inspiration through thoughtful pieces of wearable art, each with its own personal meaning.

A "fashion show" of these works was a visual and emotional highlight of Saturday's session of the California Breast Cancer Research Symposium.

—From a March 10, 2002, article in *The Oakland Tribune*.

Art, Close to the Heart

OAKLAND—Kelli Towns wore the plaster breastplate like a soldier's arms to symbolize the war she fought against breast cancer.

She first wore the piece three years ago, at age 28, soon after a doctor told her she was the fourth pre-menopausal woman in her family to be diagnosed with the disease.

On Saturday, Towns donned the wearable art once again, this time to strut across the stage before hundreds of the state's top cancer doctors and researchers.

"Just because you're diagnosed with breast cancer, doesn't mean you can't be beautiful," Towns told the audience at the 2002 California Breast Cancer Research Symposium.

—From a March 10, 2002, *Associated Press* article than ran in the *Marin Independent-Journal, Monterey County Herald, The San Bernadino Sun, the San Luis Obispo Tribune,* and six other California newspapers.

Breast Cancer Patients Help in Study

SANTA CRUZ—A county breast-cancer counseling program was honored this week in Oakland.

The Peer Navigator program has received $600,000 from the California Breast Cancer Research Program since 2000. Women recently diagnosed with cancer, called sojourners, are helping to find out if counseling from a breast-cancer survivor, called a navigator, will improve their quality of life.

"Almost every breast-cancer program throughout the country has some kind of buddy system, but nobody has very much research about their effectiveness," said Caroline Bliss-Isberg, director of the board of WomenCARE, which manages the program along with Stanford researchers.

—From a March 8, 2002, article in the *Santa Cruz Sentinel*.

Check it Out, Check it Off

Fund Breast Cancer Research

Make an entry on **line 56 of the state income tax form 540** for the voluntary Tax Check-Off Program.

Support grants to prevent, treat, and cure breast cancer.

Today's research could lead to discoveries that help save the lives of the 4,200 California women who die of breast cancer each year.

CALIFORNIA
Breast
Cancer
Research
PROGRAM

Become a Community Partner

There are many ways you can become a CBCRP Community Partner. Here are some of them:

- *Make a financial contribution to the CBCRP, either online or by sending a check.*
- *Use the Voluntary Tax Check-Off Program on Line 56, Form 540 of your state income tax return to contribute to the CBCRP. Then let us know you did at www.cbcrp.org/tax/.*
- *If you work for a large employer, find out if your employer would be interested in supporting the CBCRP's research efforts. Employers can provide support through activities such as having a CBCRP leader give a presentation to employees, including information about the CBCRP in internal email messages or paycheck envelopes, and making employees aware of the CBCRP during the United Way Campaign.*
- *Contact us with your idea for increasing our visibility and financial support.*

The CBCRP Launches Community Partners

Individuals and groups from the public and private sector are coming together to provide new sources of funds for our ground-breaking breast cancer research.

California citizens now have a new way to get involved in breast cancer research—the CBCRP's Community Partners program. Community Partners help us raise public awareness about the CBCRP's ground-breaking research and inspire more Californians to support our work with voluntary financial contributions.

The need is great and growing. Our research is primarily funded by a tax on tobacco. Because fewer people are using tobacco products, this source of revenue shrinks every year. California taxpayers make up some of the shortfall, with contributions via their state income tax returns. Even though we receive more contributions than any other non-profit organization in the tax-check-off program, this support does not cover the drop in tobacco tax funds.

That's why we decided to involve individuals and groups from the public and private sectors. The choices for ways to get involved are many—from contributing online, via mail, through state tax returns, to sponsoring events and enlisting others to support the CBCRP.

A Strong Public Response

In early April, CBCRP staff members and community volunteers organized a morning Tax Check-Off Rally in the lobby of a downtown San Francisco office building. The rally was supported by a major law firm in the building, Heller, Ehrman, White and McAuliffe. We invited hundreds of people who passed through the lobby to find out more about breast cancer research and to consider making contributions using their state income tax returns.

Other employers are getting on board. Macy's California is encouraging its 30,000 employees to consider becoming Community Partners. California physicians are getting involved, too, making information about becoming a CBCRP Community Partner available to their patients.

Sports teams in California are joining our effort. The Golden State Warriors basketball team and the University of California, Berkeley, Men's and Women's basketball teams are all dedicating games to raising community awareness about the CBCRP.

To let the public know more about our innovative research, we're reaching out to the media with news of noteworthy

You May Already Be a Community Partner

Thousands of Californians are already Community Partners, but we don't know who you are. Everyone who makes a contribution to the CBCRP through their state income tax return is eligible to be a Community Partner, if they choose.

The state government keeps the names of our tax-return donors confidential. If you are one of these donors, you can be part of Community Partner activities, stay informed about our Community Partner events, and receive special Community Partner communications. Just use the contact information at www.cbcrp.org/tax/ to let us know you've already made your contribution.

studies and CBCRP events.

To develop new funding sources, we're reaching out to foundations in California and across the nation.

An outstanding group of accomplished Californians have come together to provide leadership as the Community Partners Executive Team. These leaders share a passion for supporting research to prevent, treat, and cure breast cancer. Over the coming year, the Community Partners Executive Team will spearhead new outreach and fundraising efforts.

Community Partners Executive Team

Sherry L. Lansing, Chair, Chairman and CEO, Paramount Motion Pictures Group, Los Angeles

Ron Burkle, Managing Partner, Yucaipa Companies, Los Angeles

Sharon Davis, First Lady of California, Sacramento

Gary Erickson, President and CEO, The Erickson Group, Los Angeles

Faith Fancher, Journalist, KTVU FOX TV, Oakland

Linda Griego, President & CEO, Griego Enterprises, Inc., Los Angeles

Judith H. Guggenheime, Philanthropist and Volunteer, San Francisco

Barbara Hopper, Realtor, Prudential California Realty, Berkeley

Dr. Cornelius Hopper, Vice President, Health Affairs, Emeritus, University of California

Dr. Susan Love, President, Susan Love MD Foundation, Pacific Palisades

Lucy McCoy, Partner, Garcia McCoy & Lee Consulting, Los Angeles

Dr. Maria C. Pellegrini, Program Director, W. M. Keck Foundation, Los Angeles

Dr. Marilyn Rosenwein, Breast Cancer Survivor and Physician, San Mateo

Steve Soboroff, President, Playa Vista, Los Angeles

Benefits of Being a Community Partner

In recognition of their support, CBCRP Community Partners receive:

- *Our quarterly newsletter, The CBCRP* Bulletin
- *Special invitations to the CBCRP's biennial Symposium*
- *Special invitations to meet the scientists and learn directly from those who are working around the clock to end breast cancer*

Community Partners Contact Information

To become a Community Partner, share your ideas, or get more information, please contact Laura Talmus by mail at the CBCRP, 300 Lakeside Drive, 6th Floor, Oakland, CA 94612-3550; by phone at 1-888-313-BCRP, by email at cbcrp@ucop.edu, or visit our Web site at www.cbcrp.org

Breast Cancer in California

Our Strategy for Funding Research

What use of our research dollars will do the most to end the human suffering caused by breast cancer? This question guides us when we decide which research to fund. Every three years, the Breast Cancer Research Council sets the priorities for research funding. These priorities, which are reviewed yearly and re-set every three years, are based on the Council's expert judgment of what critical research we can add to move most rapidly to the prevention and cure of breast cancer.'

What use of our research dollars will do the most to end the human suffering caused by breast cancer? This question guides us when we decide which research to fund.

Funding Creative New Research Ideas

We encourage research in new directions by carefully collecting data; soliciting input from advocates, scientists, and clinicians; reviewing progress of research funded in the past and identifying priority topics that need more research. We fund priority topics first. During 2002, our priority topics were Health Policy and Health Services; Racial and Ethnic Differences in Breast Cancer; Sociocultural, Behavioral, and Psychological Issues Relevant to Breast Cancer; Prevention and Risk Reduction; and the Biology of the Normal Breast. After we funded all the research proposals meeting our high standards for scientific merit and innovation in these areas, we used the remaining funds to make grants for studies in more established research areas. These include Etiology, Earlier Detection, Innovative Treatments, and Pathogenesis.

One of our high-priority research areas—Racial and Ethnic Differences in Breast Cancer—was new in 2001. We added this new category of research funding to meet an urgent need. Women from different ethnic groups have different rates of breast cancer, different results from treatment, and different death rates. There may be important differences in the biology of the disease. Research into these questions can help reduce inequality among women with breast cancer and among those at risk for the disease in the future. It may also uncover important information about the disease itself, pointing toward new methods of prevention and treatment, or even cure. Yet insufficient research is being done on these questions. California, with its many diverse ethnic groups, provides one of the best resources in the nation, or the world, for this type of research. The CBCRP is therefore in an ideal position to push this area of scientific inquiry forward.

Outreach Efforts to Expand Underserved Research Areas

Even when we make under-researched areas a priority, scientists may not submit enough promising proposals for

research in these areas. That's why we make extra efforts to build up new areas of research. For example, we have encouraged the women most affected by breast cancer to become more active in doing research.

In 1997, we launched a new grant—our Community Research Collaboration Award. It funds research by teams composed of research scientists and members of communities affected by breast cancer. The members of communities have typically been women involved in breast cancer advocacy organizations, community clinics, or organizations serving minority women. The research teams pursue research questions of interest to both the scientists and the community members.

The first year we funded the Community Research Collaborations, we received few proposals. The second and third years, we received a healthy number of proposals, but in the fourth year, the number of proposals dropped. Was it possible that we had funded all researchers who were ready to do this type of community research? We could have just stopped there, but we wanted to encourage the women most affected by breast cancer to do more research, so we took further action.

The CBCRP did outreach to find more potential researchers. We gave feedback and advice to research teams whose proposals hadn't been strong enough and helped them improve the design of their studies so we could fund them in the future. We interviewed research teams we'd already funded and used their suggestions to make the Community Research Collaboration Award process more user-friendly. We also created a supplement award for CBCRP-funded Community Research Collaboration teams to mentor either new scientific researchers or community groups in community-based research.

During this outreach process, we discovered a barrier that kept some scientists from doing research in collaboration with women affected by breast cancer. Collaborating with a community organization isn't always a career-enhancing move for a research scientist. Sharing decision-making with members of a community organization takes a lot of time, and the resulting research is less likely to get published in a scientific journal. Fewer publications can mean the research scientist has less chance of getting promotions or tenure.

To change this situation, we seek out opportunities to publish articles about community-based research, and make the researchers we fund aware of these opportunities. During 2002, the *Journal of General Internal Medicine* announced a special issue on research done by collaborations of community organizations and scientists. We alerted our Community Research Collaboration teams, making sure the teams had access to the editors and were encouraged to submit articles. Publication of this research could inspire the larger research world and community organizations to think seriously about making it possible for the women most affected by breast cancer to actively do research on the disease. Our goal is to move other breast cancer funding agencies toward this innovative area of research.

Influencing the Research System Nationwide

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

An example is our funding for 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 the mid 1990s, less than 10% of research proposals submitted to the nation's funding agencies were getting funded. 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.

That's why we started our Innovative Development and Exploratory Awards (IDEA), grants specifically designed to encourage scientists to investigate high-risk questions. If the research succeeds, the researcher may well be able to get another research funding agency to fund the next step. For example, the CBCRP gave Robert Debs, M.D., an IDEA in 1997 to investigate gene therapy for breast cancer. When the idea showed promise, he was able to get funding from the federal government's National Institutes of Health (NIH) to pursue the research on a much larger scale. Alex Strongin, Ph.D., received a grant from the CBCRP in 1996 to study the role enzymes play in the spread of breast tumors to other parts of the body. Our funding led to grants from the NIH, the Susan Komen Foundation, and funding from private industry to develop this line of research.

To get creative new research going through our IDEAs, we also encourage and train researchers in California to submit exciting new ideas. In addition, we train scientific experts from outside California, who review research proposals submitted to the program for scientific merit, to use criteria that result in funding for promising new research concepts. We developed a new scoring system to help reviewers read proposals with a perspective toward rewarding high-risk, high-reward research.

Enlarging the Pool of Breast Cancer Researchers

Another of our major goals is to increase the number of talented scientists engaged in breast cancer research. Prior to 2002, we had several awards to meet this goal, including Postdoctoral Awards, New Investigator Awards, and Training Program Awards. Recent evaluations of the Postdoctoral and New Investigator Awards yielded the suggestion that we make grants to talented scientists earlier in their careers. This led us, during 2002, to develop three new types of awards. Dissertation awards fund masters' and doctoral students' dissertation research into breast cancer. Diversity Supplements allow scientists we fund to hire and mentor promising graduate or undergraduate students who face economic or social barriers to pursuing a career in breast cancer research. Mentored Scholar Awards fund new researchers who are not yet ready to become independent investigators for work under an experienced mentor. Career Enrichment awards allow established researchers to gain valuable training in a new breast-cancer-focused research discipline, and Community Supplements enable community members to better understand how they would engage in participatory research with scientists

Two Criteria: Priority Issues and Award Types

Every research project funded by the CBCRP must fit into two separate sets of categories, the Priority Issues and the Award Types. The CBCRP's Priority Issues are broad, to allow us to have an impact across a wide spectrum of breast cancer research. Our

Award Types , which include the IDEA and Community Research Collaborations discussed above, are narrowly targeted. The narrow targeting is designed to jump-start under-funded areas of research, encourage creative new thinking, and bring new investigators into the fight against breast cancer.

CBCRP Priority Issues:

—The Biology of the Normal Breast: The Starting Point

—Earlier Detection: Improving Chances for a Cure

—Etiology: Finding the Causes

—Health Policy and Health Services: Better Serving Women's Needs

—Innovative Treatments: Search for a Cure

—Pathogenesis: Understanding the Disease

—Prevention and Risk Reduction: Ending the Danger of Breast Cancer

—Racial and Ethnic Differences in Breast Cancer: Eliminating Disparity

—Sociocultural, Behavioral, and Psychological Issues: The Human Side

Award Types:

—Collaboration Awards

- Scientific Perspectives Research Collaboration (SPRC) Awards
- Community Research Collaboration (CRC) Awards
- Translational Research Collaboration (TRC) Awards
- Joining Forces Conference Award

—Topic-Targeted Awards

- Request for application (RFAs) awards are available only for primary priority issues

—Career Development Awards

- New Investigator Awards
- Postdoctoral Fellowship Awards
- Mentored Scholar Awards
- Dissertation Awards
- Training Program Awards
- Career Enrichment Awards

—Innovative Research Awards

- Innovative Developmental and Exploratory Awards (IDEAs)
- STEP Awards

—Diversity Supplements and Community Research Collaboration Award Supplements

On the following pages, we explain our nine Priority Issues and provide statistics on the 67 projects funded in 2002 by Priority Issue. Then we explain our Award Types, and again, provide statistics on the 67 newly-funded projects, this time by Award Type.

Priority Issues

The Starting Point

Biology of the Normal Breast

Understanding the biology of the normal breast may provide important clues about how tumors develop, and point to ways to prevent or stop breast cancer. Yet relatively little research has been done on normal breast structure and physiology. So the CBCRP makes it a priority to expand knowledge in this area. We encourage investigations that include normal breast development, how different types of breast cells interact, and the process of normal breast cells becoming precancerous. We also encourage the development of cell lines and animal models that reflect human breast development more closely than those currently in use.

Biology of the Normal Breast

Number of projects funded in 2002: 11

Funds awarded: **$3,076,254**

Percentage of total projects funded: 16%

Percentage of total funds awarded: 21%

Types of awards: 1 Translational Research Collaboration, 2 Targeted Awards, 1 New Investigator Award, 3 Postdoctoral Fellowship Awards, 1 Dissertation Award, 1 IDEA, 2 STEP Awards.

Improving Chances for a Cure

Earlier Detection

Since there is still no effective way to prevent breast cancer, early detection remains the best line of defense. Present methods of detection are far from perfect. Mammograms miss some tumors, falsely indicate cancer in some cases, and expose women to ionizing radiation. Low-income and minority women are also less likely to have their cancer detected early, when treatment is most likely to succeed. The CBCRP concentrates funding for detection in areas not well addressed by other funding agencies. These include new detection technology, potential new detection methods (such as blood or urine tests) that may detect cancer earlier than methods now in use, and methods for identifying women at high risk for breast cancer.

Earlier Detection

Number of projects funded in 2002: 2

Funds awarded: **$855,959**

Percentage of total projects funded: 3%

Percentage of total funds awarded: 6%

Types of Awards 2 Translational Research Collaborations.

Finding the Causes

Etiology

Discovering the causes of breast cancer can lead to strategies to prevent, treat, or cure it. The CBCRP emphasizes research in areas that haven't received enough study, including possible environmental causes, environment-gene interactions, as-yet-undiscovered genes that affect breast cancer risk, and finding the biological basis behind factors—such as early pregnancy or socioeconomic status—that affect risk.

Etiology

Number of projects funded in 2002: 3

Funds awarded: **$389,696**

Percentage of total projects funded: 4%

Percentage of total funds awarded: 3%

Types of awards: 1 Training Program Award, 2 Dissertation Awards.

Better Serving Women's Needs

Health Policy and Health Services

How can breast cancer treatment, prevention, and detection be organized to better serve women? The CBCRP funds investigations into this under-researched question. We encourage research on methods for improving the health and quality of life for women with breast cancer, on more effective and efficient ways to organize care, on issues facing women who survive the disease, and issues confronting women at the end of life. We encourage more work on ethical and legal issues surrounding breast cancer. In addition, we encourage investigations into the cost and efficiency of breast cancer care, into the economic and social costs of the disease in California, and into ways to reduce unequal access to prevention and care.

Health Policy and Health Services

Number of projects funded in 2002: 2

Funds awarded: **$432,055**

Percentage of total projects funded: 3%

Percentage of total funds awarded: 3%

Types of awards: 1 Community Research Collaboration Award, 1 New Investigator Award.

Search for a Cure

Innovative Treatments

Rather than fund more studies on new combinations of standard chemotherapy, the CBCRP puts our research dollars into novel medical approaches that hold potential to improve treatment or even point toward a cure. These include methods for tailoring drug treatment to individuals, investigations of alternative medicine and nutrition, and new ways to evaluate a tumor's danger. We also encourage research that evaluates new, unconventional treatments and develops methods to better manage the side effects of current treatments.

Innovative Treatments

Number of projects funded in 2002: 10

Funds awarded: **$2,293,421**

Percentage of total projects funded: 15%

Percentage of total funds awarded: 15%

Types of awards: 1 Community Research Collaboration, 2 IDEAs, 5 STEP Awards, 2 Dissertation Awards.

Understanding the Disease

Pathogenesis

Using the tools of molecular biology, scientists can discover the gene and protein interactions that make breast cancer cells grow and spread. These discoveries may lead to new treatments, they may be dead ends, or their implications for breast cancer may only become apparent after further discoveries. The process of turning a discovery on the molecular, gene, or cell level into a treatment can take 10–15 years and hundreds of millions of dollars, with hundreds of promising leads discarded. Other funding agencies adequately support this type of large scale research. To encourage scientists to try for breakthroughs, the CBCRP is willing to fund completely new paradigms and novel approaches.

Pathogenesis

Number of projects funded in 2002: 30

Funds awarded: **$6,079,554**

Percentage of total projects funded: 45%

Percentage of total funds awarded: 41%

Types of awards: 1 Translational Research Collaboration, 3 New Investigator Awards, 9 Postdoctoral Fellowship Awards, 4 Dissertation Awards, 3 IDEAs, 10 STEP Awards.

Ending the Danger of Breast Cancer

Prevention

According to current science, only about one in ten cases of breast cancer is due to inherited abnormal genes. The other nine are caused by environment and lifestyle, or by interactions between genes and environment and lifestyle, so changing women's environment or lifestyle has great potential to prevent cancer. However the question is: which changes? The CBCRP funds research into promising areas, including diet, potential vaccines, and ways to monitor substances in the environment that may cause breast cancer. We also encourage studies on tests that can predict the likelihood of a woman getting breast cancer or measure if attempts at prevention are reducing her risk.

Prevention

Number of projects funded in 2002: 5

Funds awarded: **$1,187,573**

Percentage of total projects funded: 7%

Percentage of total funds awarded: 8%

Type of award: 1 Scientific Perspectives Research Collaboration, 1 Targeted Award, 1 Postdoctoral Fellowship Award, 1 Dissertation Award, 1 STEP Award.

Eliminating Disparity

Racial and Ethnic Differences

Women from different ethnic groups have different rates of breast cancer, different results from treatment, and different death rates. There may be important differences in the biology of the disease. Research into these questions can help reduce inequality among women with breast cancer and among those at risk for the disease in the future. It may also uncover important information about breast cancer that could point to new methods of prevention and treatment, or even a cure. California, with its many diverse ethnic groups, provides one of the best resources in the nation, or the world, for this type of research. This Priority Issue is new for 2002.

Racial and Ethnic Differences

Number of projects funded in 2002: 2

Funds awarded: **$289,563**

Percentage of total projects funded: 3%

Percentage of total funds awarded: 2%

Types of awards: 1 IDEA, 1 STEP Award.

Sociocultural, Behavioral, and Psychological Issues

California women with breast cancer, and those at high risk, get treatment or don't get treatment, make decisions or miss their chance to make them, and cope with the disease—all in a social and cultural context. This context has great impact on well-being and even survival. The CBCRP encourages research on the human side of the disease, including studies on enhancing quality of life for women with breast cancer, on improving doctor-patient interaction, and on public perceptions of the disease. We also fund studies on how to increase the number of women with breast cancer taking part in the testing of promising treatments, and on issues women face when they survive breast cancer, or as it ends their lives.

Sociocultural, Behavioral, and Psychological Issues

Number of projects funded in 2002: 2

Funds awarded: **$205,028**

Percentage of total projects funded: 3%

Percentage of total funds awarded: 1%

Types of awards: 1 Dissertation Award, 1 IDEA.

Award Types

Collaboration Awards

To encourage thinking outside traditional research modes, we offer four types of award to bring together new combinations of researchers. Two awards—the Scientific Perspectives Research Collaboration (SPRC) Award and the Joining Forces Conference Award—are designed to bring talented researchers from other scientific disciplines into breast cancer research. All collaboration awards except the Conference Award offer one-year grants to explore innovative ideas and grants for up to three years to pursue promising full projects.

Scientific Perspectives Research Collaboration (SPRC) Awards

To spark creative new approaches to overcoming breast cancer, this award encourages researchers from other disciplines to team up with breast cancer researchers. The projects apply tools, insights, and ideas from another field of study to breast cancer.

Scientific Perspectives Research Collaboration (SPRC) Awards

Number of projects funded in 2002: 1

Funds awarded: **$100,000**

Percentage of total projects funded: 1%

Percentage of total funds awarded: 1%

Priority Issue: Prevention and Risk Reduction.

Community Research Collaboration (CRC) Awards

We believe communities should take an active part in research about themselves. This award brings community organizations—such as breast cancer advocacy organizations, community clinics, or organizations serving minority women—together with experienced scientists. The teams investigate breast cancer problems that are important to that community, using culturally-appropriate research methods. This award allows women most affected by breast cancer to enrich the breast cancer research process with new expertise and ideas.

Community Research Collaboration (CRC) Awards

Number of projects funded in 2002: 2

Funds awarded: **$266,889**

Percentage of total projects funded: 3%

Percentage of total funds awarded: 2%

Priority Issues: 1 Health Policy and Health Services, 1 Innovative Treatments.

Translational Research Collaboration (TRC) Awards

Lab scientists may have already discovered the key to curing breast cancer and not even know it. That's a paradox of research. Basic scientists who make the discoveries need a laser-like focus on a specialty. They may not see the potential of their discovery, and they may not have the interest or knowledge to apply it. Turning a discovery into a way to detect, treat, or prevent cancer may need insights and expertise from several other fields. The TRC award generates creative research partnerships that might not otherwise occur. The goal is to move scientific discoveries as quickly as possible from the lab to the clinic or comparable health application.

Translational Research Collaboration (TRC) Awards

Number of projects funded in 2002: 4

Funds awarded: **$1,512,755**

Percentage of total projects funded: 6%

Percentage of total funds awarded: 10%

Priority Issues: 1 Biology of the Normal Breast, 2 Earlier Detection, 1 Pathogenesis.

Joining Forces Conference Award

Creative thinkers working in fields far removed from breast cancer research may have concepts, methods, and discoveries that could lead to breakthroughs. By bringing breast cancer researchers into dialog with experts from other fields, the Conference Award is aimed at kindling new research across disciplines.

Joining Forces Conference Award

Number of awards made in 2002: None, but the CBCRP hopes to fund more conferences of this type and is actively encouraging the submission of proposals for 2003.

Topic-Targeted Awards

Each year, the CBCRP selects under-researched areas that are crucial to progress against breast cancer and makes a special effort to encourage more research in these areas. In 2002, $1.5 million was set aside to encourage creative research in each of the following areas:

- Biology of the Normal Breast
- Prevention and Risk Reduction
- Racial and Ethnic Differences in Breast Cancer
- Health Policy and Health Services
- Sociocultural, Behavioral, and Psychological Issues

Topic-Targeted Awards (RFAs)

Number of projects funded in 2002: 3

Funds awarded: **$2,282,399**

Percentage of total projects funded: 4%

Percentage of total funds awarded: 15%

Priority Issues: 2 Biology of the Normal Breast, 1 Prevention and Risk Reduction.

Career Development Awards

By investing in training for researchers early in their careers, we increase the pool of scientific talent working to end breast cancer. This year, we added two new types of awards, Dissertation Awards and Mentored Scholar Awards. Both awards are designed to encourage promising future scientists to enter the breast cancer field early in their careers.

New Investigator Awards

To launch careers in breast cancer research, we provide funding for new M.D.s, Ph.D.s, and other entry-level scientists to set up their own research programs.

New Investigator Awards

Number of projects funded in 2002: 5

Funds awarded: **$2,028,655**

Percentage of total projects funded: 7%

Percentage of total funds awarded: 14%

Priority Issues: 1 Biology of the Normal Breast, 1 Health Policy and Health Services, 3 Pathogenesis.

Postdoctoral Fellowship Awards

To encourage new talent to enter the field, we fund advanced training for Ph.D.s under a breast cancer research mentor.

Postdoctoral Fellowship Awards

Number of projects funded in 2002: 13

Funds awarded: **$1,092,544**

Percentage of total projects funded: 19%

Percentage of total funds awarded: 7%

Priority Issues: 3 Biology of the Normal Breast, 9 Pathogenesis, 1 Prevention and Risk Reduction.

Mentored Scholar Awards

To encourage new researchers who are not yet ready to become independent investigators to work in breast cancer research, we fund research under a mentor. This type of award is new for 2002.

Mentored Scholar Awards

Number of projects funded in 2002: None, but the CBCRP is actively encouraging scientists to apply for this type of award in the future.

Dissertation Awards

To encourage talented students to pursue careers in breast cancer research, we fund dissertation research conducted by masters or doctoral candidates. The students work under a breast cancer research mentor. This Award is new for 2002.

Dissertation Awards

Number of projects funded in 2002: 11

Funds awarded: **$551,729**

Percentage of total projects funded: 16%

Percentage of total funds awarded: 4%

Priority Issues: 1 Biology of the Normal Breast, 2 Etiology, 2 Innovative Treatments, 4 Pathogenesis, 1 Prevention and Risk Reduction, 1 Sociocultural, Behavioral, and Psychological Issues.

Training Program Awards

To increase the pool of excellent researchers working on breast cancer, we fund educational programs that train undergraduate or graduate students in disciplines important to breast cancer research.

Training Program Awards

Number of projects funded in 2002: 1%

Funds awarded: **$269,698**

Percentage of total projects funded: 2%

Percentage of total funds awarded: 2%

Priority Issue: 1 Etiology.

Career Enrichment Awards

To encourage established scientists to pursue innovation, the CBCRP funds up to one year of research in a field important to breast cancer that is new to the researcher.

Career Enrichment Awards

Number of projects funded in 2002: None, but the CBCRP is actively encouraging scientists to apply for this type of award in the future.

Innovative Research Awards

Innovative Developmental and Exploratory Awards (IDEAs)

Our IDEAs fund research with a high potential for scientific payoff, understanding that trying out new concepts also means a high risk of failure. IDEAs open new research channels in the wider world of breast cancer research, because researchers who receive start-up IDEAs from the CBCRP can leverage them into larger grants from mainstream research funding agencies.

Innovative Developmental and Exploratory Awards (IDEAs)

Number of projects funded in 2002: 8

Funds awarded: **$1,085,670**

Percentage of total projects funded: 12%

Percentage of total funds awarded: 7%

Priority Issues: 1 Biology of the Normal Breast, 2 Innovative Treatments, 3 Pathogenesis, 1 Racial and Ethnic Differences in Breast Cancer, 1 Sociocultural, Behavioral, and Psychological Issues.

STEP Awards

STEP Awards fund innovative developmental research into exceptionally promising topics. This allows research teams with some preliminary data to develop their research further, as a step toward getting funding from a major research agency for a full-scale study.

STEP Awards

Number of projects funded in 2002: 19

Funds awarded: **$5,618,764**

Percentage of total projects funded: 28%

Percentage of total funds awarded: 38%

Priority Issues: 2 Biology of the Normal Breast, 5 Innovative Treatments, 10 Pathogenesis, 1 Prevention and Risk Reduction, 1 Racial and Ethnic Differences in Breast Cancer.

Diversity Supplement and Community Research Collaboration Supplement Awards

To bring students who face economic or social barriers to entering a career in breast cancer research into the field, we offer Diversity Supplement Awards. These awards go to a scientist whose research project is already funded by the CBCRP to hire a promising student who might otherwise not have the opportunity. We also make Diversity Supplement Awards to CBCRP-funded collaborations between community organizations and scientific researchers, to allow them to bring new scientists and new community groups into their projects. Funding for both supplement awards comes from a portion of the donations made by California taxpayers on their state income tax returns.

Diversity Supplement Awards

Number of supplements funded in 2002: 6

Funds awarded: **$199,900**

Priority Issues: 1 Earlier Detection, 3 Health Policy and Health Services, 1 Pathogenesis, 1 Racial and Ethnic Differences in Breast Cancer.

Award Types: 2 Community Research Collaborations, 1 New Investigator Award, 3 Targeted Awards.

Sharing Our Research With Scientists and the Public

Research scientists presented their findings to a concerned public. Equally important, women whose lives have been affected by breast cancer shared their priorities and hopes with researchers.

Our new Web site (www.cbcrp.org) allows visitors easier ways to find the information they want about the research we fund.

Funding good research isn't enough. If the research is going to be effective in reducing or ending the suffering caused by breast cancer, 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. Women with breast cancer need the opportunity to learn about new treatment options. Breast cancer activists need information about research results to help them decide which changes they want to push for. 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 we fund publish their results in peer-reviewed scientific journals and present them at scientific conferences. However, the California Breast Cancer Research Program is committed to making the research we fund available to a much wider public. We publish and distribute summaries of our research widely, in print and over the Internet. We are one of the few research funding programs in the world to publish annual summaries of research while the studies are still in progress. The CBCRP does this so scientists and other interested people can make use of the information as soon as possible. We get out the word about our research results and research in progress in a variety of ways:

Research Symposia:

Seven hundred people with a stake in breast cancer research exchanged ideas at the California Breast Cancer Research Program's third Symposium, held March 8–10, 2002, in Oakland. The event brought together the researchers who are working hard to end the disease and those with the most to gain from research progress: women who have, had, or are at risk for breast cancer.

The Symposium, postponed from the previous fall because the events of September 11 made travel difficult, provided a forum where research scientists presented their findings to a concerned public. Equally important, women whose lives have been affected by the disease shared their priorities and hopes with researchers.

At a plenary panel, experts discussed the process of transforming research discoveries into effective treatments. A crucial step is testing the new treatment on humans, known as a clinical trial. The panel discussed the paradox that treatment progress depends on clinical trials, yet any individual woman

Our new Web site allows visitors easier ways to find the information they want about the research we fund.

taking part in a trial may—or may not—benefit. Speakers also explained why trials take so long, gave advice to women on how to find out about opportunities to take part in testing new treatments, and talked about the media's sometimes-distorting role in interpreting the results of trials.

Researchers funded by the CBCRP presented their findings in meetings that included time for questions and comments from the audience. Symposium-goers could also find out about research results by viewing over 100 colorful posters. The posters ran the gamut from images of microscopic parts of cells to data on how participating in a support program helped a community of women. Scientific experts and breast cancer advocates were on hand to discuss the posters.

An art exhibition, ongoing throughout the weekend, used painting, photography, sculpture, and mixed media to depict the many faces of breast cancer. Some of the art pieces were designed to be worn. They were modeled in a fashion show by survivors of breast cancer and women affected by breast cancer who ranged from a 22-year-old to a grandmother.

The hallway connecting the meeting spaces showcased tables staffed by representatives of community-based organizations that advocate for and serve women with breast cancer. The three-day event also included an additional day of training for members of community-based organizations and research scientists interested in teaming up to conduct research with funding from the CBCRP's innovative Community Research Collaboration grants.

At a luncheon for all participants on Saturday, Faith Fancher, news reporter on the Bay Area's KTVU/Fox Channel 2, told the story that followed her courageous decision, after she was diagnosed with breast cancer in 1997, to share her journey through treatment with her viewers.

A moment at the luncheon captured the spirit of the Symposium. Emcee Holly J. Mitchell motioned for everyone to stand and said, "Let's have a moment of noise in honor of survivors and warriors!" Scientists stood beside women living with breast cancer. Survivors of the disease stood with policy makers. They waved their napkins above the tables like a sea of flags, and a mighty roar filled the hall.

We hold a research symposium every other year. The next symposium is scheduled for September 12–14, 2003, in San Diego.

Web site:
During 2002, we redesigned our Web site (www.cbcrp.org) to make it more user-friendly. Now, visitors to our Web site

A moment at the luncheon captured the spirit of the Symposium. Emcee Holly J. Mitchell motioned for everyone to stand and said, "Let's have a moment of noise in honor of survivors and warriors!" Scientists stood beside women living with breast cancer. Survivors of the disease stood with policy makers. They waved their napkins above the tables like a sea of flags, and a mighty roar filled the hall.

can more easily find the information they want about past and present CBCRP-funded research. We also offer a lot more online information for members of California communities who would like to team up with a scientist to conduct breast cancer research. Visitors to the Web site can to join the CBCRP Community Partners and make online donations.

Our new Web site retains the best features from our old one. It has summaries of all completed research projects and annual progress reports for ongoing projects, all in language accessible to the general reader. For anyone who wants a more detailed description, our summaries are linked to PubMed, a public access Web site for abstracts of published scientific studies. Our Web site also contains a list of each year's awards and information on applying for grants.

Annual Reports:

Our Annual Report, available free of charge to the public, contains summaries of all ongoing and completed research for the year. Multiple copies of our Annual Reports are available free of charge to organizations.

Summary of Awards:

To make it easy for scientists and the public to track CBCRP-funded research from the beginning, we publish a summary of new projects funded for the year. The summary is free to the public and posted on our Web site.

Newsletter:

Our newsletter, also available free to the public and posted on our Web site, reports on new awards, research results, and other program news.

Serving the Media:

We do regular outreach to the media about our program and about research projects we fund 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 appropriate experts.

Speakers and Educational Bureau:

When community organizations want speakers on breast cancer research for meetings and public events, we provide referrals from our network of researchers and advocates. We also refer research experts to teach continuing education classes for health care professionals.

Collaborating with Breast Cancer Activists and California Communities

Lay advocates have played a leadership role in our program right from the start.

Women with breast cancer and survivors of the disease are involved in every level of the California Breast Cancer Research Program, from deciding which research we fund to actually carrying out some of our research. Lay advocates have played a leadership role in our program right from the start. We've been in the forefront of a nationwide trend among research funding agencies toward a greater voice for the people breast cancer affects most, and we still set the standard for having advocates at all levels of involvement and participation.

Breast Cancer Advocates in Leadership

Breast cancer advocates are one-third of our highest leadership body, the advisory Council. The Council recommends the research proposals that best fit our funding strategy. Throughout our nine-year history, an advocate has also always served as the Council's Chair or Vice-Chair. In addition, out-of-state breast cancer advocates are full voting members of our scientific review panels and a California advocate observes each panel.

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

Advocates Doing Research

Breast cancer advocates are also investigators on a rising number of the CBCRP's research projects. In 1997, we pioneered a new type of research grant that allows breast cancer advocacy organizations to team up with experienced scientists for a research project. These Community Research Collaboration Awards are open to nonprofit organizations or ad-hoc community groups in any California community affected by breast cancer. The majority of community collaborators we've funded to date have been breast cancer survivors.

Projects we've funded over the years include:

- Investigation of problems women face returning to work after breast cancer surgery
- Pioneering research into breast health and breast cancer programs for deaf and hard-of-hearing women
- A community-based workbook for helping rural cancer patients

We're in the midst of a multi-year process to increase the participation of women affected by breast cancer in research into the disease.

- 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 help newly-diagnosed women make decisions about treatment and cope with the disease.

Fostering Community-Based Research

We're in the midst of a multi-year process to increase the participation of women affected by breast cancer in research into the disease. During 2000, we conducted a formal evaluation of the Community Research Collaboration Awards. As a result of the evaluation, we increased our outreach efforts to let potential researchers know about this opportunity. We also improved the grants in several ways. These improvements inspired members of more California communities to team up with scientists and send the CBCRP well-designed and scientifically-sound research proposals. As a result, we increased the amount of community research we funded, with 15% of our research funds going for Community Research Collaborations during 2001, compared to 1% the year before.

During 2002, we added another improvement designed to increase the pool of researchers and community groups capable of doing research that empowers California communities of women to investigate breast cancer. CBCRP-funded Community Research Partnerships can receive a supplement to their grant to mentor a student, a new researcher, or a community group interested in doing this type of collaborative research. Next year, we will conduct training at sites throughout California to encourage and educate community groups to get involved in breast cancer research.

Toward More and Faster Progress Against Breast Cancer

Although the California Breast Cancer Research Program concentrates on research to speed progress against the disease, we don't have enough funds to do all that needs to be done. This year, we established our Community Partners Program, a way for Californians to come together to provide more funding for breast cancer research. Our Community Partners' first priority is to generate funds to replace the drop in our revenue from the state tax on tobacco, which is going down every year. But if we could also increase the funds available, we could make faster progress against the disease by initiating the following research:

♦ 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 US is treated through a clinical trial, compared to 3% 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

Our first priority for Community Partners is to generate funds to replace the drop in our revenue from the state tax on tobacco, which is going down every year. But if we could also increase the funds available, we could make more and faster progress against the disease...

with breast cancer cope or survive, we are unable to provide continued funding.

♦ 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.

♦ Staff Scientist at the CBCRP. The CBCRP's funding is devoted to research grants. The addition of a staff scientist would enable us to significantly increase the potential to efficiently coordinate programs with scientific and medical communities, and to pursue new research opportunities on both a short and long-term basis.

♦ National Priority-Setting Conferences. As the largest state-funded research organization in the nation, the CBCRP carries a leadership role. We have 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 2002, the CBCRP turned down 131 grant applications requesting a total of $38,377,572. While some of these applications lacked merit, the majority contained good ideas. With technical assistance from the CBCRP, the majority of these applications could become good, creative projects that could help enlarge the scope of breast cancer research.

As Californians become involved in the CBCRP's Community Partners Program, we hope that increased financial support will allow us to move into these new research directions and also to continue to fund the broad range of studies we have funded in the past.

Improving Our Program Through Evaluation

95% of our New Investigators got a chance to do breast cancer research that they would otherwise not have been able to do.

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 our entire program. Evaluation helps us target research dollars where they will do the most good.

During 2002, we evaluated two of our ground-breaking grant programs: our New Investigator Awards and our Innovative, Developmental, and Exploratory Awards (IDEAs).

New Investigator Awards

Our New Investigator Awards go to entry-level scientists to carry out their own breast cancer research projects. The grants are designed to recruit high-quality new researchers into the breast cancer field. Since 1995, we've invested over $13 million in New Investigator grants.

During 2002, we conducted a survey among researchers who received New Investigator Awards between 1995 and 1999.

We learned that 95% of the new investigators we funded felt they got a chance to do breast cancer research that they would otherwise not have been able to do. In addition, 85% said the New Investigator Award allowed them to stay in breast cancer research after the award ended. While some of the scientists were already working in breast cancer research when they received their New Investigator grant, 35% were recruited from other fields.

One goal of these grants is to help new researchers develop their careers. Our new investigators reported that the grant did help them do this. New Investigator awards allowed some scientists who had been assisting other more senior researchers to conduct their own research for the first time. Others received job advancement, or learned enough about breast cancer to be able to pursue further research.

Our grants also gave some of these scientists the opportunity to launch significant research that was later funded by other agencies. Another measure of the research's significance is that peer-reviewed scientific journals published papers about the CBCRP-funded work of 65% of our new investigators.

We drew three recommendations from this evaluation. First, our former new investigators suggested that we host an

Almost half of the researchers we funded with IDEAs made a new discovery or developed a new tool.

annual gathering where they can exchange ideas with each other, and also with senior researchers and breast cancer experts. Second, we should provide more consultation to new investigators to help them better manage their grants and employees. Finally, we plan to evaluate this program again in four or five years, when we'll have a larger group of former new investigators to survey and we'll be likely to learn more.

IDEAs

This year we also evaluated our Innovative, Developmental, and Exploratory Awards (IDEAs). These grants are designed to push breast cancer research in promising new directions. They provide seed money to test new ideas that have a high potential for scientific payoff, but also a risk for failure.

In interviews with 35 scientists who have received IDEAs since 1995, we learned that we are meeting many of our goals.

Almost half of the scientists we funded said the results of their research confirmed their original hypothesis. Some of the projects failed, but we expected this to happen with high-risk research. Almost half of the researchers who received IDEAs also made a new discovery or developed a new tool. One study led to two new patents. Some studies have led to increased scientific interest in a new area of breast cancer research.

One of our goals for the IDEAs was to jump-start new research that other funding agencies—which generally have larger budgets—would then continue to fund. We have had some success. Our past IDEA researchers have received $16.7 million in additional funding for breast cancer research that is at least partially based on the project we funded—five times the total amount we invested in these grants.

However, the IDEAs have not done what the CBCRP hoped for most—created a major breakthrough to prevent, treat, or cure breast cancer. Perhaps time is a factor, and one of these studies will be seen in the future to have led to a breakthrough. But we also want to learn if we can improve these grants to make breakthroughs more likely. Over the coming year, we plan to ask deeper questions in our continued evaluation of our IDEAs.

Evaluation Spurs Improvement

We use formal evaluations like those we conducted this year to improve the CBCRP. Here are some of the ways we've changed our grant-making as a result of evaluations:

- During 2000, we evaluated our Community Research Collaborations. As a result, we've engaged in a successful, ongoing, multi-year effort to increase the number of community organizations and scientific researchers collaborating on breast cancer research. These researchers investigate questions of

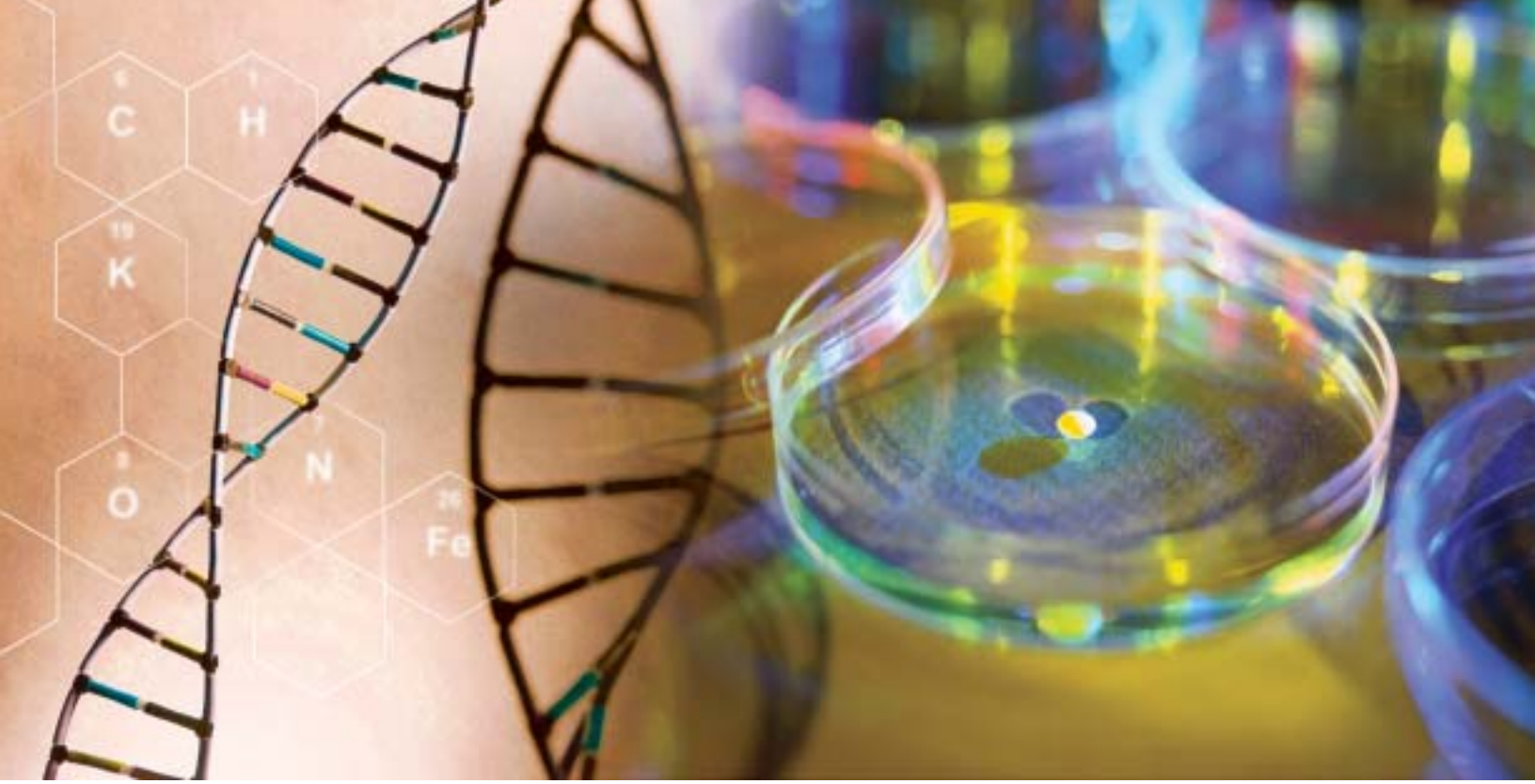
interest to communities of California women. We've changed the awards to make them more user-friendly to people new to the research world. We've done extensive outreach to community organizations and to researchers. We've also held special training workshops to prepare interested scientists and members of community groups to embark on research collaborations.

♦ This year's evaluation of the CBCRP's New Investigator Awards, combined with a 2001 evaluation of the program's postdoctoral awards, led us to develop a new award. During the evaluation, scientists who had received these grants, which are designed to increase California's pool of talented breast cancer researchers, told us, "You need to encourage people to start doing breast cancer research even earlier in their careers." Responding to this suggestion, the CBCRP now makes two new awards, Diversity Supplements and Dissertation Awards. Diversity Supplements go to promising graduate or undergraduate students who face economic or social barriers to embarking on a career in breast cancer research. The students work under a CBCRP-funded scientific investigator. Dissertation Awards fund dissertation research conducted by masters or doctoral candidates working under breast cancer research mentors.

Responding to evaluations and suggestions, the CBCRP now makes two new types of awards, Diversity supplements and Dissertation Awards.

More Evaluations in the Future

We plan to continue evaluating our program and to keep making improvements as a result of these evaluations.



Research Progress and Results

On the following pages, we present the results of research funded by the California Breast Cancer Research Program that was completed during 2002. We also present summaries of research in progress and of new research started this year.

We have organized the Research Progress and Results section by the CBCRP's nine Priority Issues:

- Biology of the Normal Breast: The Starting Point
- Earlier Detection: Improving Chances for a Cure
- Etiology: Finding the Causes
- Health Policy and Health Services: Better Serving Women's Needs
- Innovative Treatments: Search for a Cure
- Pathogenesis: Understanding the Disease
- Prevention and Risk Reduction: Ending the Danger of Breast Cancer
- Racial and Ethnic Differences in Breast Cancer: Eliminating Disparity
- Sociocultural, Behavioral, and Psychological Issues: The Human Side

Biology of the Normal Breast: The Starting Point

As any woman who performs breast self-exams knows, the normal breast is a constantly changing organ. The breast's normal changes can obscure the more ominous changes associated with cancer. Researchers have worked hard to determine what constitutes a cancerous change in the breast, but the lack of a thorough understanding of the normal breast makes this work more difficult.

Because a relatively small amount of research is being done in this area, the California Breast Cancer Research Program earmarks funds especially for it. We hope these studies will provide a strong foundation for distinguishing the difference between benign and malignant breast changes.

Research Conclusions

Receptors

Several studies in this section mention receptors. Receptors are usually proteins. They are found on or in cells. Receptors bind with another substance, such as a protein, hormone, or drug that comes from outside the cell. Once the receptor has bound to the other substance, it changes chemically and triggers changes within the cell. Receptors initiate a wide variety of cell changes. In breast cells, these can include changes that make the cell produce milk, divide, or go through the normal process of cell death.

Breast Development

Hormonal Regulation of TGF-ß-1 During Mammary Development.

The reproductive organs of female mice go through the estrus cycle, where fertile periods (when pregnancy is possible) alternate with infertile periods (when it isn't). Levels of the hormones estrogen and progesterone rise and fall in a pattern during the mouse estrus cycle, as they do during the human menstrual cycle. ***Mary Helen Barcellos-Hoff, Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, investigated how changes in hormone levels interact with a protein, transforming growth factor ß-1 (TGF-ß-1), found in some human breast (and mouse mammary) cells. There is evidence that TGF-ß-1 can both promote and suppress human breast tumors and that it plays a role in the formation of new cells during breast development. TGF-ß-1 is chemically locked up in cells, and has to be released in order to be active in the cell processes. The research team found that the hormones estrogen and progesterone play a role in activating TGF-ß-1. They also found that TGF-ß-1 is present in all cells that produce a protein called the estrogen receptor, which allows cells to combine with, and be affected by, the hormone estrogen, and that TGF-ß-1 is also in most of the cells that produce the progesterone receptor. Depriving mice of TGF-ß-1 makes these cells multiply faster than normal during puberty, pregnancy and estrus. TFG-ß-1 prevents cells from multiplying in response to estrogen and progesterone. Based on this research, the team hypothesizes that disruption of the action of TGF-ß-1 is involved in breast cancer in cells that produce the estrogen receptor, a finding that could lead to new treatments for this type of the disease.

Breast Function

Breast Cancer Chemoprevention by Retinoids.

Xiaokun Zhang, Ph.D., at ***The Burnham Institute***º La Jolla, investigated how Vitamin A inhibits breast cell growth. Vitamin A and its natural and synthetic derivatives, retinoids, are promising preventive agents for women at risk for breast cancer. Most of the retinoids investigated so far do not prevent the most malignant breast cancers, or they must be given at such high doses that they are toxic to patients. Dr. Zhang investigated the molecule-level interactions between retinoids and the retinoid receptor proteins that allow cells to take them in. The team found that one retinoid receptor protein inhibits two cancer genes and also causes breast cancer cell death. They identified two proteins that interfere with retinoid receptor

proteins. Another protein, TR3, is necessary for a new group of retinoids to cause breast cancer cells to die. This research could contribute to the development of a more effective breast cancer-preventive drug based on Vitamin A. Results from this study have been published in *Molecular and Cell Biology* (2000;20(3):957-970) and *Cancer Research* (2000;60(12):3271-80).

Mechanisms of Fluid Transport in Human Mammary Epithelium.

Fluid accumulates in the breasts of many women who have not yet reached menopause. This condition causes breast tenderness and pain; it also leads to increased cancer risk. ***Sheldon Miller, Ph.D.***, at ***University of California, Berkeley***, investigated proteins and chemical reactions involved in fluid moving through epithelial cells, the cells where most breast cancers arise. The research team identified several "transport proteins" involved in the movement of fluids in and out of mouse mammary epithelial cells (the mouse equivalent of human breast cells). The team also identified a number of chains of chemical reactions, known as signaling pathways, within these cells. These signaling pathways are involved in the movement of fluids and also of ions—substances that include sodium, potassium and calcium—into and out of these cells. The team plans to continue this research toward the goal of a medication to prevent abnormal fluid accumulation in the breast. Such a medication could reduce breast cancer scares and unnecessary tests caused by abnormal fluid buildup being misdiagnosed as possible breast cancer, and could also reduce breast cancer risk.

Method for Measuring Breast Epithelial Turnover in Humans.

Epithelial cells in the breast produce milk and deliver it to the nipple, and are also the source of most breast cancers. Breast cancer cells divide more rapidly than normal cells. Each time a normal cell divides, the chance of a genetic mutation goes up, and so does the risk that the mutation will lead to cancer. Therefore, it is important to have a reliable way to measure the division rate of cells in the breast. ***Marc Hellerstein, M.D., Ph.D.***, at the ***University of California, Berkeley***, developed a method to measure cell division rates directly, without using radioactivity or toxic substances, using breast tissues from core biopsies. The research team found that the cell division rate varies in samples of tissue taken from different parts of a woman's breast. Postmenopausal women tend to have lower rates of cell division than women who are still menstruating. The

research team also found that exposing rats to genistein, a substance found in soybeans, both before and after the rats are sexually mature, decreases their cell division rate by 28%.

Pregnancy and Breast Cancer: an Immunological Connection?

A full term pregnancy at an early age protects a woman against developing breast cancer. But what changes occur in the breast to explain it? Many theories concentrate on hormones. ***Michael Campbell, Ph.D.***, of the ***University of California, San Francisco***, investigated whether the immune system plays a part. Dr. Campbell examined the sera (a part of blood) from women who had multiple pregnancies and compared it to the sera of women who had never had a baby. He looked for antibodies that recognize breast tumors. Using several increasingly sensitive screening methods, the research team at first found no antibodies, then found possible evidence of antibodies. The team plans to continue this research, using sera from women whose last pregnancy was one year earlier, compared to four years earlier for these experiments, because these antibody levels may drop over time. Success with this approach could provide the basis for vaccines to prevent breast cancer.

The Role of Nitric Oxide and Arginine in the Breast.

The breast cells responsible for milk production, the epithelial cells, are where most breast cancer starts. When these cells grow too much and develop the ability to invade other tissues, it leads to cancer. However, these cells also often grow too much in a way that does not lead to cancer. ***Carol MacLeod, Ph.D.***, at the ***University of California, San Diego***, systematically investigated the biology and genetics of these cells, looking for ways to distinguish truly precancerous cells from harmless ones. The team made progress with genes, developing a method to assess the role of one gene in the progression from normal cells, to cells that grow too much, to cells that later become cancer. They also developed a method for determining biological properties of these cells. This method will be used in future research to assess the potential of these cells to turn cancerous in the presence of various substances that do, or can, circulate in the body. Funding from the CBCRP led to a grant from another funding agency to pursue this research. The team is currently testing a substance derived from soy beans for its ability to halt the early changes cells go through on the way to becoming cancerous. The CBCRP-funded research was published in *Cancer Res.* 2001 61:8298-305.

Epithelial Cells

Several studies in this section deal with epithelial cells. In the bodies of humans and animals, epithelial cells cover most surfaces, form glands and line most cavities. The breast (or the mammary gland in mice, rats, and other mammals) is composed of several types of epithelial cells that are responsible for producing milk and delivering it to the nipple. These cells are also the source of most breast cancers.

Genetic Repair of Oxidative Damage: Effect of Estrogen.

Nicholas J. Rampino, Ph.D., at ***The Burnham Institute***, La Jolla, investigated how three breast cancer prevention medications work in cells on the biochemical level. The three medications are raloxifene, tamoxifen, and ICI 182,780. The team tested how well each worked at protecting genes from the kinds of mutation that lead to cancer. Raloxifene did the best at stimulating the normal DNA repair process in cells. This process repairs mutations in DNA that lead to cancer. Raloxifene was also most effective at stopping a number of other molecule-level gene-related processes in cells that can lead to cancer, and stimulating others that allow cells to overcome cancer. These differences help to explain, at least in part, raloxifene's superior ability to prevent breast cancer. This research helps explain how these medications prevent breast cancer and could, in addition, provide the basis for developing more potent medications of this type.

Role of the POP1 Gene in Breast Cancer Genomic Stability.

Peter K. Jackson, Ph.D., at ***Stanford University***, investigated the human POP1 gene for its role in breast cancer, but found no clear evidence that it plays one. The team then shifted its focus to another gene, Fbx5. They found that the Fbx5 gene controls the entry of cells into the phase where they prepare to divide. This gene is more active in 30–40% of breast tumors, compared to normal breast cells. The gene is also overactive in several other types of tumors. This research was published in *Nat Cell Biol.* 4(5):E119-20.

Breast Aging

The Role of PAK2 in Breast Cancer Cell Death.

Normally, the body maintains a critical balance between the growth of new cells and the death of the old. When the balance shifts away from normal levels of cell death, then cells multiply abnormally and cancer develops. ***Gary M. Bokoch, Ph.D.***, at ***The Scripps Research Institute***, La Jolla, investigated a protein, p21-activated kinase, or PAK, that plays a role in this balance. PAK interacts chemically with other proteins within cells, probably in the course of both normal and cancerous cell growth and death. The research team found that PAK was necessary but not sufficient for another protein, Jun kinase, to cause cells to die. Surprisingly, PAK could block the action of another cell death protein, called Bad. The team found that PAK was abnormally high in some kinds of breast cancer cells. PAK is

also involved in the ability of cells to migrate in the course of normal development and in cancer cells spreading to other body parts. The team plans to pursue this research further to find out if PAK could be a target for a therapy to treat some types of breast cancer.

Cloning of Senescence Genes in Mammary Epithelial Cells.

Normal cells have only a limited capacity to grow in lab cultures. They soon stop growing, entering a state called replicative senescence. The inability of senescent cells to continue to divide in two and form new cells has led researchers to suggest that replicative senescence may be a tumor suppression mechanism that prevents normal cells from turning into cancer. There is evidence that gene activity determines senescence. ***Hong Zhang, Ph.D.***, at ***Stanford University***, used techniques called random homozygous knock-out, or RHKO, and cDNA microarrays to investigate which genes are active in cells during senescence. Dr. Zhang compared the "genetic fingerprint" of senescent cells with cells in growth arrest. Many changes in the activity of genes previously thought to reflect senescence turned out to also reflect growth arrest. Dr. Zhang is currently investigating two genes that have abnormal activity only during senescence. Dr. Zhang also compared the activity of genes in senescent human breast epithelial cells (the cells where most cancers arise) with the activity of genes in the cells that make up connective tissue in the breast. The genes that were active were very different for the two types of cells, indicating that the process of senescence is different for different types of cells.

Research in Progress

Telomeres and Telomerase

DNA is organized into structures called chromosomes. Chromosomes will unravel if they are not capped by specialized sequences of DNA, called telomeres. Telomeres shorten every time a cell divides, unless their integrity is maintained by an enzyme, called telomerase. Telomerase is present in large amounts in immature cells, such as reproductive cells or stem cells, but most mature normal cells do not have telomerase.

When the telomeres in normal cells become short enough, the cells stop dividing. This is part of the natural cellular aging process.

Many tumor cells have active telomerase, therefore their telomeres do not shorten during cell division and they continue dividing long after normal cells stop. This observation has led many cancer biologists to believe that telomerase activity is one of the reasons that cancer cells are immortal. By investigating this aspect of the cell aging process, researchers hope to find a way to exploit a critical difference between normal and tumor cells.

Genetic Aspects of Physiological Response During Lactation.

Scientists believe that when tissue grows too large for its existing blood vessel network, the level of oxygen in the tissue drops. In response, a protein, HIF-1α, increases and activates genes that control new blood vessel growth. HIF-1α is present in larger than normal amounts in tumors that grow rapidly ***Randall S. Johnson, Ph.D.***, at the ***University of California, San Diego***, is investigating the role of HIF-1a in the development and function of the normal breast. The research team has found that female mice bred with no HIF-1a don't develop enough milk-producing cells. These mice don't produce enough milk to feed their babies, and their babies are 33–50% underweight. Mice bred with too much HIF-1α have a greater than normal number of blood vessels in their milk-producing glands, but these glands don't fully develop, and the milk these glands produce has blood mixed with it. The goal of this research is to generate information that will lead to better therapies to block tumor growth and development of a blood supply.

Telomere Clustering is Lost in Mammary Epithelial Tumors.

Telomeres—structures of DNA and proteins that cap the end of chromosomes—play a role in normal breast development, aging, and cancer. ***Paul Kaminker, Ph.D.***, of ***Lawrence Berkeley National Laboratory***, is investigating whether disrupting the structure of telomeres in cells leads to the formation of breast cell tumors. When a protein called Tin2 is present in larger than normal amounts, cells develop a structure similar to cancer cells and the cell DNA loses telomere clusters. The team has found that as normal cells mature, Tin2 detaches from telomeres, and this causes clusters to form. The team is trying to find out if Tin2 reattaches to telomeres later in the cell developmental process.

Genetic Changes in Normal Epithelium of the Cancerous Breast.

Shanaz Dairkee, Ph.D., of the ***California Pacific Medical Center Research Institute***, San Francisco, is trying to identify genetic changes in normal-appearing breast cells that indicate a propensity to become breast cancer. Some genes, including ATM and the normal version of BRCA2, suppress breast cancer. In inherited cancer, these genes

undergo mutations that make a woman more susceptible to breast cancer. In non-inherited cancer, these genes are frequently turned off because the cell loses this part of the DNA when it reproduces itself. This year the team investigated normal-appearing cell structures (called terminal ductal lobular units, TDLU) in breast tissue samples that also contained cancerous tumors. In four out of eleven tumor samples, the normal-looking cell structures had lost the ATM tumor suppressor gene. In two out of four, the normal-appearing cell structures had lost the BRCA2 gene. This strongly suggests that for a subset of breast tumors, loss of these genes are among the earliest signs that the disease is developing, detectable well before any tumor forms. The team also found that a woman who has a cancerous lump removed where the TDLU have lost DNA in the chromosome 3p24 region has a five times greater than average risk of recurrence. It takes longer than average for the cancer to recur, suggesting that the cancer is arising from normal cells that have lost part of their DNA, rather than from tumor cells that were not removed. This research led to a publication in *Cancer Research* 62:1000, 2002.

Research Initiated in 2002

Breast Development

Role of Epimorphin and Progesterone in Breast Development.

Jamie Bascom, at the ***Lawrence Berkeley National Laboratory***, is investigating epimorphin, a protein that stimulates breast epithelial cells to become specialized milk producing cells. The research team will determine if there is a relationship between epimorphin and the hormone progesterone in this process.

Steroid Receptor Coactivators in Mammary Gland Development.

Shi Huang, Ph.D., at ***The Burnham Institute***, La Jolla, is investigating the RIZ1 gene and the protein this gene produces, to see if it plays a role in the action of the hormone estrogen on normal breast development.

Breast Function

Defining a Role for Endothelial Precursor Cells in Breast.

New blood vessel growth is necessary for both normal tissue expansion and breast cancer. Blood vessels are lined with endothelial cells; new endothelial cells can come from existing blood vessels or from endothelial precursor cells that circulate in the blood. ***Longchuan Chen, Ph.D.***, at the ***La Jolla Institute for Molecular Medicine***, is investigating the significance of endothelial precursor cells in both normal breast development and in breast tumors, and will try to design a way to block these cells to see if this stops tumor growth.

Rac/STAT5 Signaling.

Normal breast function depends on proper interactions of breast epithelial cells with the cells that surround them. These interactions regulate the responses of epithelial cells to hormones and allow them to grow normally. Disruption of these interactions can result in breast cancer. ***Hee Kwang Choi, Ph.D.***, at ***The Burnham Institute,*** La Jolla, is investigating two molecules, called Rac and STAT5, to see if they function together as a master switch that allows breast cells to respond normally to hormones, and the molecules' possible role in breast cancer.

The Importance of Growth Inhibitory Signals in Normal Breast Cells.

HER-2 is a protein found in larger than normal amounts in about 30% of breast cancer cases. Scientists do not understand what role HER-2 plays in promoting breast cancer. ***Cindy Wilson, Ph.D.***, at the ***University of California, Los Angeles***, is testing the hypothesis that HER-2 promotes breast cancer by inhibiting the action of proteins that are naturally present in the breast and that are the body's first line of defense against breast cancer.

Statistical Techniques for Breast Biology and Cancer Research.

New technologies allow scientists to rapidly and simultaneously measure thousands of genes, proteins and other molecules within cells. However, statistical techniques to identify the significant patterns in this information are not available. ***Saira Mian, Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, will develop a variety of statistical techniques that could help provide more reliable diagnoses, uncover unrecognized categories of breast cancer, and explain why cancer treatments work on some people, but not on others.

Targeting Estrogen Receptors to Mammary Epithelial Cells.

The hormone estrogen causes normal breast growth and also the growth of tumors, but scientists don't know exactly how. Estrogen receptors are proteins that allow cells to take up estrogen. ***Richard H. Price, Jr., Ph.D.***, at the ***University of California, San Francisco***, will engineer mice with more than the usual amount of estrogen receptors in the cells where mammary cancer (the mouse equivalent of breast cancer) usually arises. They will compare the growth of these cells with those in normal mice.

Effect of Breast Cell Environment on Repair of DNA Damage.

Aylin Rizki, Ph.D., at the ***Lawrence Berkeley National Laboratory***, will investigate whether scaffolding cells that support milk-producing cells interact with the milk-producing cells in a way that protects the milk-producing cells from DNA damage.

Breast Aging

Understanding Telomere Dynamics in the Breast.

Telomeres are DNA sequences on the ends of all our chromosomes that cap and protect them from breaking down and joining with other chromosomes. Telomeres shorten in many of our organs as we age, limiting the organs' ability to replace worn-out cells. In the breast, shorter telomeres can also allow cells to become cancerous. ***Steven Artandi, Ph.D.***, at ***Stanford University***, will study how normal breast cells react to telomere shortening as they age.

Understanding Aging Effects in the Breast.

Ana Krtolica, Ph.D., at the ***Lawrence Berkeley National Laboratory***, is investigating a type of breast cell called fibroblasts. Fibroblasts do not usually become cancerous, but they are part of the structure that supports the cells that do. Dr. Krtolica is investigating whether old fibroblasts that have lost the ability to divide into new cells create an environment that allows nearby cells to become cancerous.

Separating Normal from Abnormal Breast Structures

Genetic Alterations in MRI Screen-Detected Breast Lesions.

James Ford, M.D., and ***Sylvia Plevritis, Ph.D.***, at ***Stanford University***, will use Magnetic Resonance Imaging (MRI) screening to detect breast lumps, then see whether analyzing the genes in these tissues can detect genetic changes that could predict whether a benign lump may later become cancerous.

Earlier Detection: Improving Chances for a Cure

Both the mainstream media and research scientists have raised questions about the effectiveness of screening mammography. However, the underlying rationale behind detecting cancers at an earlier stage of progression is strong. As more California women have regular mammograms, examine their own breasts, and receive breast exams from their physicians, breast cancer is detected more frequently at earlier stages. Earlier detection combined with improvements in treatment has led to a 25% drop in the rate of death from breast cancer in the state. However there's still room for a lot of improvement. Women need detection methods that can find smaller tumors and distinguish harmless breast abnormalities from cancer. Mammograms don't provide information about whether a tumor is likely to grow quickly or respond to a particular treatment.

Areas of research that the CBCRP funds include:

- Developing and Improving Imaging Technologies: Technologies such as Magnetic Resonance Imaging (MRI) or optical detection hold promise for finding tumors faster and more easily. We have also funded projects to improve the accuracy of the x-ray technology used for mammograms.
- Improving Women's Access to Screening: California women don't all have equal access to mammograms, so we fund research on how to make current detection methods available to all.
- Novel Screening Approaches: Finding a substance in the body that shows the presence of breast cancer could lead to a blood or urine test as a detection method.

Research Conclusions

Developing and Improving Imaging Technologies

Measurement of Breast Tissue Viscoelasticity Using MRI.

Michael Buonocore, Ph.D., of the ***University of California, Davis***, is adapting Magnetic Resonance Imaging (MRI) to detect breast abnormalities based on differences in the elasticity and viscosity (thickness) of abnormal breast tissue as compared to normal breast tissue. These same mechanical properties enable a health care professional to detect a lump during a clinical examination. Dr. Buonocore has developed the necessary equipment, including the MRI breast coil with a built-in device to generate mechanical waves in breast tissue, gel phantoms, and image reconstruction software. He has tested the method and confirmed that the images are consistent and repeatable. Next, he will test the adapted MRI in human subjects and develop methods for calculating tissue viscoelasticity from the images. Developing this new technology could lead to earlier detection of breast cancer and may also provide data that could improve the accuracy of manual breast exams.

Improved Access to Screening

Does Mobile Mammography Increase Screening in Older Women?

Many older women don't get mammograms to check for breast cancer, despite expert consensus that they should. ***David B. Reuben, M.D.***, and ***Roshan Bastani, Ph.D.***, of the ***University of California, Los Angeles***, recruited women age 60–84 from community sites where older people gather. The team provided health education that included the benefits of mammograms to 247 women; 254 received the health education along with access to a mammogram van at the community site. Older women who had access to on-site mammograms were more likely to have one; 55% of this group had a mammogram within three months, compared to 40% of the group who received health education alone. On-site mammography appears to be especially effective with two groups of women. Among Latina older women, 56% of women who had access to mobile mammograms had one, compared to 35% of those who received only health education. Among Asian and Pacific Islander women, the figures were 70% versus 35%. These findings indicate that mobile mammography does increase breast cancer screening in older women. An article based on this research has been accepted in the *American Journal of Roentgenology.*

Novel Screening Approaches

Molecular Staging of Breast Cancer Progression.

Cheng-Ming Chuong, M.D., Ph.D., of the ***University of Southern California***, Los Angeles, is looking for new ways to accurately diagnose breast cancer and predict whether it is likely to spread. Biological researchers want to understand the molecule-level changes—involving genes and the proteins those genes produce—that occur in cells during different stages of breast cancer. Since tumor cells grow near normal cells, it is impossible with current technology to analyze a pure tumor cell sample. Dr. Chuong's team has developed a method that needs only 100 cells instead of the million cells necessary with other methods. It uses technologies called gene amplification and microarray to provide a snapshot of the genes that were producing proteins at the moment the cells were collected. With CBCRP funding, the team refined the method and showed that it works in cells grown in lab cultures. Next, they will test the method in tissue samples. The goal is a kit that can be used in any hospital to find out how far a breast tumor has advanced in its growth and whether it is likely to spread.

Oncogenes, Progression, and Biomarkers.

Robert Cardiff, M.D., Ph.D., of the ***University of California, Davis***, searched for biomarkers. Biomarkers are characteristics for which breast cells could be tested, with the test yielding information about whether the cells were becoming cancerous, already were cancerous, or were cancerous and likely to spread to other body parts. Dr. Cardiff's hypothesis was that genes that control a breast cell's transition from a normal to a cancerous state produce patterns of proteins that could be used as biomarkers. Using antibodies to probe tumors in genetically-engineered mice, the research team identified several potential biomarkers. One is the protein osteopontin, which is found at very high levels in most tumors but at low levels in healthy tissues. The research team found that the presence of osteopontin may indicate that breast tumors have the ability to spread to other body parts. Dr. Cardiff further found that defects in different genes that are part of the same developmental process within cells result in tumors that resemble each other. Defects in a series of genes known as the Wnt pathway, which are involved in organ development, form tumors with branching shapes. Defects in another series of genes, the erbB2 pathway, which are involved in specialization of cells within the breast, form round tumors with small lobes. This research has led to a better understanding of how cancer genes affect the appearance and biology of tumors, and is a step toward the goal of providing information about a tumor that can predict how it will respond to various possible treatments.

Markers

Several studies in this section deal with various types of markers. Research scientists are looking for characteristics of breast cancer cells, or characteristics of the blood of women with breast cancer, that could be easily detected with a test, distinguish breast cancer from normal cells, and also possibly point toward which treatment would work best.

Biomarkers are characteristics for which breast cells could be tested, with the test yielding information about whether the cells were becoming cancerous, already were cancerous, or were cancerous and likely to spread to other body parts.

DNA tumor markers are portions of the genetic code found inside tumor cells that differ from the genetic code found inside normal cells.

Protein markers are proteins that are chemically active in cancer cells compared to normal cells.

Research in Progress

Developing and Improving Imaging Technologies

UCLA Biomedical Physics Graduate Training in Breast Cancer.

Virgil Cooper, Ph.D., of the ***University of California, Los Angeles***, is training graduate students to design and improve early detection and diagnostic imaging equipment, and to solve medically significant problems involving these technologies. The training emphasizes awareness of the needs of clinicians and patients. This year, one student has been trained, working on improving digital mammography.

Non-Invasive Optical Characterization of Breast Physiology.

Bruce Tromberg, Ph.D., ***Randall Holcombe***, ***M.D.***, and ***John Butler***, ***M.D.***, from the ***University of California***, ***Irvine***, are making excellent progress on developing a Laser Breast Scanner. The portable hand-held scanner uses harmless near-infrared light to measure physical characteristics of breast tissue, such as water content, cell shape, blood volume, and the interaction of oxygen and a component of blood, hemoglobin. In the past year, the team tested the device on two breast cancer patients. The scanner detected changes in the breast tissue of a woman whose tumor was responding to chemotherapy. For another woman whose tumor did not respond to chemotherapy, the scanner showed no changes of the type found in the first woman's tumor. During the coming year, the team will test the scanner on a larger group of women at the University of California, San Francisco. Results from this project have been published in *J Biomed Opt.* 7(1):60-71 (2002).

Breast CT for Much Earlier Detection of Breast Cancer.

Researchers estimate that a woman's first breast tumor exists for about eight years before a mammogram can detect it. A more accurate and sensitive detection method would reduce this latent period and offer better odds at beating the disease. ***John M. Boone***, ***Ph.D.***, and ***Karen K. Lindfors***, ***M.D.***, at the ***University of California, Davis***, are building a prototype computed tomography (CT) breast scanner. CT, also known as "CAT scan", uses special x-ray equipment to obtain image data from different angles around the body. Computer processing is then used to show a cross-section of body tissues and organs. Dr. Boone and colleagues believe their method could detect cancers in the

3–5 mm range. Other advantages include a lack of breast compression and a modest reduction in radiation dose. The rationale for this research was published in *Radiology* 221:657-67 (2001).

Patient-individualized Chemotherapy in Breast Cancer.

Daniel H. Silverman, M.D., Ph.D., at the ***University of California, Los Angeles***, is working on a novel strategy to develop a test that would show, in advance, if a particular chemotherapy will eliminate an individual breast cancer patient's tumor. The research team is using chemotherapy drugs that are chemically combined with fluorine-18 (F-18). The F-18 "lights up" when the tissue is tested with positron emission tomography (PET), to detect whether the tumor is taking up the drug. Dr. Silverman is making rapid advances, because he is collaborating with a group that has solved the difficult step of chemically combining F-18 with the drug paclitaxel. This drug is used for advanced breast cancer and in settings where previous chemotherapy has failed. Dr. Silverman's lab is now studying the distribution of F-18 paclitaxel in mice, and is in a better position to develop other F-18-labeled drugs for comparative studies. Although routine use of PET is expensive, this approach could spare women the exposure to chemotherapy that has no chance of working.

Novel Screening Approaches

Protein Markers in Nipple Aspirates for Breast Cancer.

Helena Chang, M.D., Ph.D., at the ***University of California, Los Angeles***, is using a new technology to compare the proteins in fluid from the nipples of women who have had breast cancer with those from women who haven't. The technology (Surface-Enhanced Laser Desorption/Ionization, or SELDI) is a method for rapidly detecting many molecules present in a substance. The advantage of using this technology is that it can detect changes in many proteins at once, whereas conventional technology had restricted researchers to examining a few proteins at a time. So far, the method can determine whether breast fluid is from a normal or cancerous breast. The research team has found one protein that is more abundant in normal breast fluid and another that is more abundant in cancerous breast fluid. This research could lead to an early test for breast cancer based on analyzing a very small amount of fluid obtained from the nipple. If the amounts of various proteins in nipple fluid turn out to be correlated with how tumors respond to various types of chemotherapy, then the potential test could also help physicians select an appropriate treatment.

LPC As a Potential Tumor Marker for Recurrent Breast Cancer.

There are no reliable blood tests to detect recurrence of breast cancer. Two available tests are not accurate enough to be useful. ***Helen K. Chew, Ph.D.***, at the ***University of California, Davis***, will test whether measuring the level of a fat found in the blood, lysophosphatidlycholine, or LPC, can be used to detect breast cancer. The research team is also investigating whether LPC blood levels can detect a recurrence of the disease, or reveal whether treatment is working against breast cancer that has spread to other body parts. They are collecting blood samples from 74 women and plan to enroll a total of 91 women.

Clinical Utility of Breast Cancer DNA Markers in Plasma.

David Hoon, Ph.D., of the ***John Wayne Cancer Institute***, Santa Monica, is trying to determine whether DNA specific to breast cancer can be detected in the blood. The team has blood and tumor tissue samples from over 270 women. They have isolated DNA from the blood and tumors and are now searching for DNA markers, parts of the DNA that are specific to the tumors, and comparing DNA markers in the blood and tumors. So far, they have found that DNA markers are frequently present in the blood of women with breast cancer. The number of markers rises as the disease progresses, and the markers in the blood are similar to those in the tumors. The team has also found DNA markers in the bone marrow of early stage breast cancer patients. They are now developing a more efficient method for testing blood for levels of multiple DNA markers. This study could lead to a blood test that could be used for diagnosis, provide information about whether a tumor has spread, or detect a recurrence well before a woman has any symptoms.

Early Detection of Breast Cancer and Its Recurrence.

Cancer treatment specialists need reliable tests that can be done on tumor cells to predict whether the tumor is likely to recur and whether chemotherapy or radiation will be effective against it. ***Syed Ashraf Imam, Ph.D.***, of ***Huntington Medical Research Institute***, Pasadena, is investigating whether measuring the amount of LEA.135, a protein found on the surface of some breast tumor cells, can predict whether the tumor will recur and which treatment will be most effective. The team has developed a method for measuring LEA.135 and used it to test tissue samples from biopsies of 480 patients, analyzing the protein levels found on both tumor cells and normal breast cells. They are now

Research Initiated in 2002

New Imager to Improve Specificity in Breast Cancer Detection.

Kai Vetter, Ph.D., and ***Christine Hartmann-Siantar, Ph.D.***, at ***Lawrence Livermore National Laboratory***, are collaborating with ***Gerald DeNardo, M.D.***, at ***University of California, Davis***, to build a new type of breast cancer detection system. The system will use gamma rays to detect tumors as small as one millimeter. A woman getting this test would be injected with a drug or antibody that attaches only to cancer cells. This drug or antibody would be tagged with a radioisotope, a chemical that emits gamma rays visible to the detector.

Compositional Breast Density as a Risk Factor.

John A. Shepherd, Ph.D. and ***Steven R. Cummings, M.D.***, at the ***University of California, San Francisco***, are collaborating with ***Karla Kerlikowske, Ph.D.***, at the ***Veterans Affairs Medical Center***, San Francisco, to use novel x-ray approaches to study breast density. On mammograms, some parts of the breast appear more dense than others, and the greater the breast density, the greater the risk for breast cancer. The research team is trying to improve on current methods of measuring breast density, which aren't accurate enough to be useful.

Breast Stromal Genes Act as Early Markers of Malignancy.

Thea Tlsty, Ph.D., at the ***University of California, San Francisco***, is collaborating with ***Stephanie Jeffrey*** at ***Stanford University*** to investigate the potential of detecting cancer by examining the stromal cells, which are connective tissue and supporting cells in the breast. Breast cancer usually arises in epithelial cells, which are supported by stromal cells. The research team is looking for abnormalities in the genes of stromal cells that are adjacent to breast cancer cells and precancerous cells.

Etiology: Finding the Causes

Over the past 50 years, scientists have identified a number of factors that increase cancer risk. They have used an epidemiologic approach, comparing a group of people with the disease to a cancer-free group for differences in environmental exposures, diet, and other lifestyle factors. However, using this approach, they have been able to identify only a portion of the factors affecting breast cancer risk, and haven't been able to explain the biological mechanisms that trigger the disease. Within the last decade, epidemiologic methods have been combined with genetics and molecular biology to gain a new understanding of events at the cellular level. Scientists are investigating the likely role of genes in determining how a cell responds to an environmental exposure, and whether this response begins the cell's journey toward cancer or not. Increasingly, the CBCRP funds research that uses this combined approach, applying knowledge being gained in human genetics to uncover the precise causes of breast cancer.

Environment and Gene/Environment Interactions: Nature vs. Nurture

Oral Contraceptives, Hormonal Risk Factors, and BRCA1.

A large number of women who get breast cancer at an early age may have mutations in the gene BRCA1. Recent evidence suggests, however, that not all women with one of these mutations will develop breast cancer. ***Giske Ursin, M.D., Ph.D.***, at the ***University of Southern California***, Los Angeles, investigated whether oral contraceptive use has any effect on rates of breast cancer among women with mutations in their BRCA1 genes. Dr. Ursin looked at oral contraceptive dose, length of time the women used oral contraceptives, age at first use, and how recently the women used oral contraceptives. She compared the risk of breast cancer associated with oral contraceptive use by women with mutated BRCA1 with data from previous studies for rates of breast cancer associated with oral contraceptive use by women in the general population. Working with tissue samples, she used the new ABI 3700 sequencer to sequence the women's BRCA1 genes. To date, the research team has conducted 1,361 interviews and collected mammograms on 641 women. This research will be completed with funding from another agency, with results available within a year.

Marin County Breast Cancer Study of Adolescent Risk Factors.

Margaret Wrensch, Ph.D., of the ***University of California, San Francisco***, and ***Georgiana Farren, M.D.***, of ***Marin Breast Cancer Watch***, Marin County, are studying women in Marin County, a community with high rates of breast cancer. The research team is looking at a group of women diagnosed with breast cancer between July 1, 1997, and June 30, 1999, and comparing them with women who have not had breast cancer. The team is looking for differences in the age at which the women had their first menstrual period, the age at which the women's breasts developed, major life events before age 21, adolescent and adult socioeconomic status, smoking, alcohol use, standard breast cancer risk factors, and age-adjusted lifetime years of residence in Marin County. The team has completed in-person interviews with 301 women with breast cancer and 305 women without the disease. Although CBCRP funding for this research has ended, the team will continue to analyze the data and publish results when they have them. A recent published finding (*Breast Cancer Res.* 2003;5(4):R88-R102) from this study suggested that alcohol consumption was

a factor in the higher rates of breast cancer for Main County: women who had at least two drinks a day were more than twice as likely to be diagnosed with breast cancer as women who drank less, according to the study. Thus, this finding supports demographics and lifestyle as opposed to geographical (i.e., environmental) risk factors as explanatory factors in Marin County's high rates of breast cancer.

Breast Cancer Susceptibility Genes in Very High Risk Women.

A woman with relatives who have had breast cancer is at a higher risk for the disease than a woman whose relatives haven't had it. A woman whose identical twin has had breast cancer is at an even higher risk. ***Ann S. Hamilton, Ph.D.***, at the ***University of Southern California***, Los Angeles, tested the hypothesis that a variation of the CYP17 gene may occur more often in twins where one or both of the women have had breast cancer than in women who haven't had the disease. This gene codes for an enzyme that helps regulate estrogen levels. Three versions of the gene are possible: A1/A1, A2/A2, and A1/A2. Some studies have shown that women with at least one A2 (A2/A2 or A1/A2) have higher levels of estrogen and higher risk of breast cancer. If identical twins who both had breast cancer had higher rates of the A2/A2 or A1/A2 gene, this would provide evidence of the CYP17 gene being associated with breast cancer. However, in this study, identical twins with only one of the pair having had breast cancer had the highest rate of A2/A2 or A1/A2 (76%) followed by identical twins who both had breast cancer (69%) and identical twins who had not had the disease (53%). The researchers are unable to draw final conclusions about the relationship, if any, between the CYP17 gene and breast cancer.

Unique Genes Expressed in Cancer Cells.

Craig V. Byus, Ph.D., of the ***University of California, Riverside***, identified genes that are turned off or on by the enzyme ornithine decarboxylase (ODC) in cells. It appears that a high level of ODC turns on or off certain genes, and this allows a cell to become more like cancer. Dr. Byus encountered difficulties with the first lab technique he used, so he tried another approach, which succeeded. The research team found 12 genes that become more active in the presence of high levels of ODC. The team also found that these same 12 genes are abnormally active in several types of cancer cells. The genes include jun-d, jun-c, jun-b and c-fos. The research team now believes that high levels of ODC lead to high levels of a series of chemical

reactions within cells known as the MAP kinase cascade. Funding from the CBCRP allowed this research team to accumulate enough data to receive a five-year grant from the National Institutes of Health to continue these studies in breast cancer cells and prostate cells.

Hormones and Nutrition: Understanding the Modern Woman's Lifestyle

Postmenopausal Breast Cancer: Obesity & the Leptin Receptor.

Obese women and women who gain weight during adulthood have an increased risk for breast cancer after menopause. ***Leslie Bernstein, Ph.D.***, at the ***Keck School of Medicine, University of Southern California***, Los Angeles, investigated the relationship between body composition, hormones, and a candidate gene for obesity, the leptin receptor gene. Leptin is a recently-discovered hormone produced by human fat cells. It plays a role in fat storage and metabolism, and may be involved in breast cancer. The leptin receptor gene produces a protein that allows cells to take in leptin. Dr. Bernstein investigated the levels of leptin and variations in the leptin receptor gene in 38 healthy obese women age 40 or over and past menopause. The team found a strong association of total percent body fat and the leptin gene variation Lys109Arg, and a similar, though less precise, association between this gene variation and a high body-mass index. Another leptin receptor gene variation they tested, Gln223Arg, showed no significant associations. Understanding the relationship of genes and obesity could help shed light on the causes of postmenopausal breast cancer.

Obese women and women who gain weight during adulthood have an increased risk for breast cancer after menopause.

Tamoxifen-Induced Endometrial Cell Transformation.

Tamoxifen is a medication for treating and preventing breast cancer, but it also increases a woman's risk for cancer of the endometrium, which is the inner lining of the uterus. Tamoxifen inhibits the activity of a group of enzymes called protein kinase C (PKC). There are more than 11 kinds of PKC; one, a type of PKCδ, can suppress tumor growth. ***Zhimin Lu, Ph.D.***, of the ***Salk Institute for Biological Studies***, La Jolla, investigated whether tamoxifen causes endometrial cancer by inhibiting the action of PKCδ. The team found that cells that had already gone through some early steps toward becoming cancerous went much further along the process when exposed to tamoxifen. Tamoxifen pushed these cells further toward becoming cancerous by activating a series of chemical reactions in the cell called ERK1/2, inhibiting PKCδ, and increasing the activity within the cell of an enzyme called phospholipase D. This research provides important insights into the side effects of tamoxifen and may point toward more effective treatment and prevention for breast cancer.

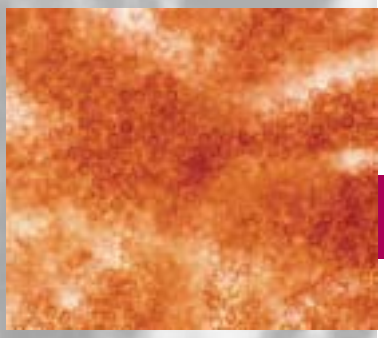
Case Control Study

A case control study, also called a case comparison or retrospective study, compares a group of people with a disease ("cases") and a group of similar people without the disease ("controls"). Researchers gather information about both groups' past, such as exposure to a suspected cancer-causing agent, behaviors (such as smoking, drinking alcohol, occupation), or biological factors (such as history of the disease in the family, age of first menstruation). If the people with the disease have a higher rate of the factor in their past being investigated, then researchers infer that there is an association between the factor and the disease. If the association is very strong, and if it holds in other kinds of studies, the exposure, behavior or biological factor is a possible cause or contributor to the disease. At this point, the investigation often shifts to the lab or clinic to uncover the biological mechanisms behind the association.

As examples, case control studies have identified smoking as a cause of various cancers, determined the health risks associated with certain occupations, and pointed to sun exposure as a risk factor for skin cancer.

Genes Determining Estrogen Susceptibility in Breast Cancer.

Many breast tumors depend on the hormone estrogen for growth and survival and can be treated with anti-estrogen drugs like tamoxifen. However, some tumors eventually progress to an estrogen-independent form and become drug resistant. All women with advanced breast cancer eventually progress to the state where their tumors resist drug treatment. ***Wensheng Wei, Ph.D.***, at the ***Stanford University School of Medicine***, attempted to identify, isolate, and map the structure of estrogen susceptibility genes that are required for breast cells to respond to estrogen stimulation. Dr. Wei used a new technique, random homozygous knock-out (RHKO), removing genes from cells and observing the cells for changes in behavior. Dr. Wei solved some technical problems with the RHKO technique and began screening genes in human breast cancer cells. With this research, Dr. Wei made progress toward the goal of identifying changes in estrogen susceptibility genes that lead to tumors becoming estrogen independent.



Environment and Gene/Environment Interactions: Nature vs. Nurture

Influence of Localized DDT Exposure on Breast Cancer.

The pesticide DDT can mimic or interfere with the action of hormones in humans and animals and is stored in body fat, so DDT has tremendous potential to influence the development of breast cancer. In the body and in the environment, DDT is broken down into compounds that either act like the female hormone estrogen, or inhibit male sex hormones. ***Vicki L. Davis***, ***Ph.D.***, at the ***Cedars-Sinai Medical Center***, Los Angeles, is examining how the individual compounds into which DDT breaks down in the body influence the development of mammary tumors in mice. Mammary tumors are the mouse equivalent of breast tumors. So far, the team has found that two compounds into which DDT breaks down accelerate the development of tumors, although it is unclear if these compounds make tumors more likely to form. One of these compounds inhibits male sex hormones and accelerates tumor development the most, the other acts like estrogen and accelerates tumor development to a lesser extent.

Pesticides and Breast Cancer in Hispanic Women in California.

Paul Mills, ***Ph.D.***, at the ***Public Health Institute***, Berkeley, is attempting to determine if the risk of breast cancer in Hispanic California women is increased due to their exposure to two classes of commonly-used pesticides, the organochlorines and the triazines. The research team has compared breast cancer rates among Hispanic women and amounts of the pesticides applied in each of 58 California counties. There was no elevated risk in the first time period they studied, 1988–1993. But for 1994–1999, a higher risk of breast cancer was found among Hispanic women in the counties with the highest use of several pesticides, including DDT and toxaphene. The research team will also compare the pesticide exposure of women farm workers who have breast cancer with those who do not.

Hormones and Nutrition: Understanding the Modern Woman's Lifestyle

Dietary Fat, Fat Metabolizing Genes, and Breast Cancer Risk.

A diet high in certain types of fat may promote breast cancer. ***Sue Ann Ingles, Ph.D.***, of the ***University of Southern California***, Los Angeles, is investigating whether genetic differences in fat metabolism make some women more prone to breast cancer if their diets are high in these fats. So far, her team has identified many previously-undiscovered genetic differences in dietary fat metabolism. They have tested the genes from 814 women with breast cancer and 910 women without the disease from three ethnic groups: white, Hispanic, and African American. If a high-fat diet is found to increase breast cancer risk for women with certain genes, then diet changes could be recommended to these women. If certain fat metabolizing genes raise a woman's risk for breast cancer, then drugs to inhibit the enzymes these genes produce could be used for prevention or treatment.

Other Searches for the Causes

Migration and Breast Cancer Risk in Hispanics.

Foreign-born Hispanic women living in the San Francisco Bay Area have a lower risk of breast cancer than second- and third-generation migrants. Women who migrated after age 40 have a lower risk than women who migrated at a young age. ***Esther John, Ph.D.***, of the **Northern California Cancer Center** in Union City, is investigating breast cancer risk and migration-related lifestyle changes in Hispanic women. The lifestyle changes include menstrual and reproductive events, physical activity, diet, body size, weight change, hormone use, smoking, and alcohol consumption. In addition, her team will see if exposure to chemicals formed when meats and fish are cooked at high temperatures or infection with Epstein Barr virus increase breast cancer risk. To date, they have completed interviews with 189 Hispanic women with breast cancer and 37 who do not have the disease. The team plans to interview a total of 1,050 women and merge their data with a previous study of over 2,500 Hispanic women. The team has also collected 225 DNA samples that will be stored for future molecular studies.

Breast Cancer in California Teachers—Regional Variations.

Scientists have known for a long time that breast cancer rates vary widely by geographic area, but they don't know

She found that breast cancer rates are 20% higher for teachers in the San Francisco Bay Area and 17% higher for teachers in the Los Angeles–Orange County–San Diego area than for teachers in the rest of the state.

why. ***Peggy Reynolds***, ***Ph.D.***, at the ***Public Health Institute***, Berkeley, is attempting to discover if women face a higher risk of breast cancer because they live in certain geographic areas, or if more women at high risk of getting the disease for other reasons happen to live in those geographic areas. She is using personal information available on 133,000 active and retired school employees participating in the California Teachers Study. She found that breast cancer rates are 20% higher for teachers in the San Francisco Bay Area and 17% higher for teachers in the Los Angeles–Orange County–San Diego area than for teachers in the rest of the state. These numbers are consistent with the rates for women as a whole in California. The researchers are considering characteristics of the geographic area, such as living near traffic or pesticide use, as well as personal characteristics of the teachers, such as family history and diet. So far, no characteristics of the geographic areas or the women themselves fully explain the higher risk for teachers in some parts of the state.

Research Initiated in 2002

The Androgen Receptor and Mammographic Density.

Women with breasts that appear denser on a mammogram have an increased risk of breast cancer. ***Elizabeth Lillie**, **M.S.***, of the ***Keck School of Medicine, University of Southern California***, Los Angeles, is investigating the androgen receptor gene, which produces a protein that allows breast tissue to be affected by the hormone androgen. She is trying to determine whether varying versions of this gene are related to breast density. There are conflicting studies in cells, animals, and humans about whether the variations in the androgen receptor gene are associated with breast cancer risk.

Androgen Receptor Gene and PSA Gene in Breast Cancer Risk.

Androgens are hormones; although they are usually thought of as male hormones, they play important roles in the female body, and may protect against breast cancer. ***Wei Wang**, **M.D.***, at the ***University of Southern California**,* Los Angeles, is analyzing DNA samples from African American women, half of whom have breast cancer and half of whom do not. The team is looking for genetically-determined differences in the PSA pathway, which is a series of chemical interactions within breast cells that is affected by androgen.

USC/NCCC Breast Cancer Research Training Program.

The CBCRP encourages and supports training in breast cancer for new research scientists. ***Ronald K. Ross**, **M.D.***, maintains the multifaceted Breast Cancer Research Training Program at the ***University of Southern California***, Los Angeles. Five trainees are supported each year in areas such as pathology, molecular biology, cell biology, and cancer control. The trainees work under a multi-disciplinary faculty from USC and the Norris Comprehensive Cancer Center.

Health Policy and Health Services: Better Serving Women's Needs

If research findings are going to lead to action and change, gathering information that will be important for policy makers at the national, state, and local level is vital. Research in this area is aimed at developing strategies to serve women more effectively by investigating the organizational and sociopolitical context of breast cancer prevention, detection, and treatment.

The CBCRP funds research aimed at making the health care system more responsive to the needs of women with breast cancer and better at preventing the disease. We're looking for ways to reduce waste and increase access to breast cancer care. We also encourage research on actions that will reduce inequalities in access to prevention and treatment among California's geographically and ethnically diverse population. The CBCRP encourages more research in the health policy and health services area.

Research Conclusions

...the higher a woman's socioeconomic status, the more likely it is that her breast cancer will be diagnosed at an early stage. This trend is especially true if cases of carcinoma in situ (a precancerous condition of the breast) are counted as part of the category of early stage at diagnosis.

Race/Ethnicity, Socioeconomic Status, and Breast Cancer.

William Wright, ***Ph.D.***, at the ***Public Health Institute***, Berkeley, investigated the relationship between race/ethnicity and socioeconomic status and how likely it is that a woman's breast cancer will be detected early, when treatment is most effective. Dr. Wright used innovative statistical methods to analyze data from California's statewide cancer registry and the Women's Health Survey, an annual telephone survey that collects information on health practices on a random sample of California women. Dr. Wright found that the higher a woman's socioeconomic status, the more likely it is that her breast cancer will be diagnosed at an early stage. This is most true for Hispanic women, followed by African American, then white, then Asian women. This trend is especially true if cases of carcinoma in situ (a precancerous condition of the breast) are counted as part of the category of early stage at diagnosis. The research team also found that high socioeconomic status is related to several known breast cancer risk factors. Women of higher socioeconomic status give birth to a lower number of babies, which raises breast cancer risk. To a lesser extent, women of high socioeconomic status are older at the birth of their first babies, which also raises the risk of breast cancer. Women of high socioeconomic status, on average, have a low body mass index, which lowers the risk of breast cancer. Dr. Wright has also shown that because the 2000 US Census allowed people to select more than one race on their census forms, researchers will not be able to obtain accurate estimates of the population of various races in the state. This means the California Cancer Registry may not be able to calculate breast cancer rates by race in 2000 and beyond, or monitor trends in breast cancer by ethnicity.

Does a Peer Navigator Improve Quality of Life at Diagnosis?

Women with breast cancer say they have the greatest need for counseling when they are newly diagnosed. Many women don't seek formal counseling services because they feel overwhelmed, are unfamiliar with available resources, or are concerned about stigma in seeking counseling. ***David Spiegel***, ***M.D.***, of ***Stanford University***, collaborated with ***Caroline Bliss-Isberg***, ***Ph.D.***, of the community organization ***WomenCARE***, in Santa Cruz, to evaluate the effectiveness of matching women who have just learned they have

breast cancer with trained volunteer breast cancer survivors (peer navigators). Each navigator and woman with cancer make at least one contact a week for three months. The relationships can be renewed by mutual agreement every three months. In this preliminary study, the research team matched 42 newly-diagnosed women with peer navigators. The team found that women matched with a navigator maintain their quality of life and actually improve in some areas. The more empathic and effective the navigator, the better the quality of life for the recently-diagnosed woman. However, more successful navigators showed some trauma and depression symptoms, although most navigators reported high quality of life and low stress levels. The CBCRP is funding a 3-year expansion of this research. A well-designed peer counseling program could cut the human and economic costs of breast cancer in California by increasing newly-diagnosed women's knowledge about strategies for making medical decisions and knowledge about other helpful resources. Based on this pilot study, the researchers urge organizations providing peer counseling for women with breast cancer to provide training, supervision, and support for their volunteers.

Research in Progress

Geographic Variation in Breast Cancer Stage at Diagnosis. Women whose breast cancer is diagnosed at the earliest stage, before it has spread to surrounding tissue or to distant sites in the body, have a better chance of surviving. Among California counties, the percentage of breast cancer patients who are diagnosed at this early stage ranges from 40% to 71%. ***Pamela Davidson***, ***Ph.D.***, at the ***University of California***, ***Los Angeles***, is investigating how community-level factors, such as the health care delivery system, influence the stage at which a woman's breast cancer is diagnosed. During the first year, the team has collected data from a variety of databases that track cancer cases, from the federal census, and from sources of information on the health care system. One goal of this research is data-driven recommendations for community-level interventions to raise the percentage of women whose breast cancer is diagnosed at an early stage.

Return to Work After Breast Cancer Surgery.

Diane R. Estrin, of the ***Women's Cancer Resource Center***, a Berkeley community organization, and ***Rani B. Eversley, Ph.D.***, of the ***University of California***, ***San Francisco***, are looking at what helps—and what hinders—women returning to work after breast cancer surgery. They will interview 588 women from various ethnic groups, 6 and 12 months after surgery. So far, they have developed and tested their questionnaire and are translating it into Spanish and Cantonese. Next year, they will enroll women in the study. The researchers hope to have an impact on employer policies regarding return to work and also on disability benefit eligibility for breast cancer survivors.

Determinants of Receiving Breast Cancer Treatment in the Underserved.

Low-income and less-educated women are more likely to be diagnosed with advanced breast cancer, less likely to receive standard treatment, and less likely to survive 5 years, compared to breast cancer patients from the general population. ***Rose Maly***, ***Ph.D.***, of the ***University of California***, ***Los Angeles***, will survey 230 low-income breast cancer patients, survey their health care providers, and analyze their medical records. The goal is to identify factors in the patients' lives (for example, lack of transportation) or in the health care system (for example, problems with doctor-patient interactions) that could be changed to reduce the

suffering and death in this vulnerable population. So far, the research team has begun identifying and enrolling patients, developed questionnaires for patients and health care providers, and held focus groups to identify relevant questions for the questionnaires. The team hopes to use the results to directly improve care for this population of women.

Research Initiated in 2002

Impact of Breast Cancer and Its Therapy on Osteoporosis.

After women go through menopause, their bones can become weaker and smaller, which puts them at risk for osteoporosis. ***Carolyn Crandall***, ***M.D.***, at the ***University of California***, ***Los Angeles***, is investigating whether having had breast cancer affects the risk of osteoporosis. She will also investigate whether levels of hormones in the blood can predict the rate at which breast cancer survivors lose bone mass.

African American Women and Breast Cancer: What Works?

African American women are less likely than other American women to be diagnosed with breast cancer, but those who have the disease are more likely to die from it. Lack of access to care is one factor, but not the whole story. ***Carol Somkin***, ***Ph.D.***, at the ***Kaiser Foundation Research Institute,*** Oakland, and ***Priscilla Banks***, ***M.S.***, at the ***African American Advisory Committee on Cancer***, Hayward, are investigating what aspects of health care settings and interactions with health care providers promote or inhibit culturally-sensitive care for African American women.

Innovative Treatments: Search for a Cure

To stimulate the development of more effective treatments, the CBCRP funds a variety of research topics. These include alternative medicines, novel clinical approaches, testing of promising drug and drug target leads in animal models of breast cancer, and rational drug design, which is a methodical approach based on understanding the molecule-level interactions between a potential drug and the disease process. For many of our investigators, research under this Priority Issue is an extension of their research previously funded under our Priority Issue of Pathogenesis.

We have divided the innovative treatment priority issue into four broad areas of research:

- Immune Therapy: Mobilizing the Body's Defenses
- New Drug Design: Creative Science
- Hormone and Chemotherapy Targets: Improving Today's Arsenal
- Gene Therapy and Other Treatments: New Frontiers

Research Conclusions

Immune Therapy: Mobilizing the Body's Defenses

Engineering Antibodies Specific for Breast Cancer Proteases.

Breast cancer cells produce enzymes called proteases that break down surrounding tissue and allow the cells to migrate to other locations in the body. ***Jeonghoon Sun***, from the ***University of California***, ***San Francisco***, created six genetically-modified antibodies designed to inhibit the action of a tumor protease called MT-SP1. Using support from other funding agencies, he will test these antibodies in breast and prostate tumor models.

New Drug Design: Creative Science

Novel Inhibitors of Rad51-DNA Repair in Breast Cancer.

Both radiation and chemotherapy kill cancer cells (and also normal cells) by damaging the cell DNA. Breast tumors contain elevated levels of DNA repair enzymes that repair the damage caused by radiation and chemotherapy, creating resistance to these treatments. One DNA repair enzyme found at high levels in breast tumors is called Rad51. ***Anne Vallerga***, ***Ph.D.***, from ***Pangene Corporation***, ***Inc.***, Fremont, found that substances that inhibit Rad51—either by keeping cells from producing Rad51 or by rendering Rad51 ineffective—made breast cancer cells ten times more sensitive to chemotherapy drugs such as cisplatin or doxorubicin. This research could lead to effective breast cancer treatment combining Rad51 inhibitors with much smaller doses of chemotherapy drugs, potentially with fewer toxic side effects.

Arginine Deiminase as an Innovative Anti-Breast Cancer Agent.

Wei-Chiang Shen, ***Ph.D.***, at the ***University of Southern California***, Los Angeles, investigated an enzyme, arginine deiminase, which is found in certain bacteria, as a possible anti-breast cancer treatment. The team cloned the enzyme and investigated how it affected several types of cells at the level of interactions between protein molecules. The results suggest that the compound the team cloned, recombinant arginine deiminase, inhibits the growth of blood vessels. It does so by controlling the production of nitric oxide within the cells that line blood vessels, rather than directly stop-

ping the growth of these cells. This research could potentially provide the basis for a therapy based on choking off a tumor's blood supply.

Computer-Aided Discovery of Novel Breast Cancer Therapeutics.

Danni Harris, ***Ph.D.***, from the ***Molecular Research Institute***, Mountain View, and ***Marcia Dawson***, ***Ph.D.***, from ***The Burnham Institute***, La Jolla, proved that their new method for identifying possible breast cancer drugs works. Their research combines Dr. Harris's previous research in computer modeling of the structure of complex molecules with Dr. Dawson's previous research in the anticancer biology and chemistry of retinoids. Retinoids include both natural and synthetic substances derived from vitamin A. Retinoids cause cells to mature and then die, or simply to die, by undergoing the normal process of cell death. However, retinoids haven't been used to treat breast cancer yet because the doses that must be given also damage normal cells. The research team used a computer program that models the structure of complex molecules in three dimensions. With this program, they determined the structure of a set of retinoid-like compounds, called AHPNs, that work against breast cancer cells that retinoids don't kill. Using the computer program to analyze the AHPNs, the research team found the part of the molecular structure common to them that causes cells to die. This part of a molecule that is active as a drug is known as the pharmacophore. Next, the team searched databases of the molecular structures of known compounds and found 200 with similar properties. Of these, 11 were readily available, and they tried them on breast cancer cells. One worked well against the cells and was under investigation, by another laboratory, as a breast cancer drug. The team then improved the pharmacophore so that it matches fewer compounds that are poor candidates to become drugs. The CBCRP is funding Dr. Dawson to continue these studies to use computer modeling to search for more drug-like molecules that may work against breast cancer.

Hormone and Chemotherapy Targets: Improving Today's Arsenal

Targeted Chemotherapy to Treat Breast Cancer.

Liposomes are laboratory-synthesized microscopic particles with a fatty outer layer and a water-soluble center. Liposomes can circulate in the blood and carry chemotherapy drugs, genes, or other therapeutics to selected locations. ***Francis Szoka, Ph.D.***, at the ***University of California***, ***San Francisco***, attempted to increase the ability of drug-carrying liposomes to locate and bind to breast cancer cells, but not to normal cells. This would isolate the drug from the body until it

is absorbed by breast cancer, minimizing side effects. Dr. Szoka attempted to target liposomes by incorporating into them special sugar molecules that bind to a protein, CD44, found on breast cancer cells. The team's initial approach did not work, and an alternate method only partly succeeded. However, the team developed a human breast tumor system in mice, and all elements are in place to continue this project in the future. The initial phase of this project was published in *Cancer Research* 61:2592-2601 (2001).

Biologic Determinants of Response to Paclitaxel and Radiation.

Locally-advanced breast cancer is defined as a lump larger than 2 inches that has spread to the lymph nodes. This type of breast cancer may also have features of aggressive tumors. The tumor may make the skin swell, form a sore on the breast, or be stuck to the chest wall. The chance that locally-advanced breast cancer has spread to other body parts is high; the chance of surgically removing the entire tumor is low. This type of breast cancer is particularly common among minority women with little access to medical care. ***Silvia Formenti***, ***M.D.***, and ***Peter Danenberg***, ***Ph.D.***, at the ***University of Southern California***, Los Angeles, tested a new way of giving treatment to 82 women with locally advanced breast cancer, 90% of them minority women. Instead of administering chemotherapy or radiation after the women's breast tumors were removed, they administered these treatments first. Then, after the tumors were surgically removed, the research team tested the tumor tissue to see whether the previous treatment had any effect. The chemotherapy drug paclitaxel alone was effective against 12% of the tumors; paclitaxel plus radiation worked against 40%. These treatments were most effective against tumors with low levels of the HER2/neu and estrogen receptor proteins. This research provides information on how to individualize treatments for locally-advanced breast cancer based on the characteristics of tumors.

A New Class of Drugs to Treat Breast Cancer.

Tamoxifen, the leading drug to treat breast cancer, works on breast cancers that need the hormone estrogen to grow. It ties up the protein that cells use to combine with estrogen, the estrogen receptor. ***Thomas Robertson***, ***Ph.D.***, of the ***University of California***, ***San Francisco***, used computer modeling in an attempt to design compounds that would block the growth of breast cancer in a different way from tamoxifen, in order to overcome limitations such as drug resistance and side effects. The team identified a group of chemicals that may inhibit breast cancer growth. All of these chemicals shared part of their chemical structure, so the team tried to synthesize this part, but did not succeed.

Research in Progress

Chemotherapy with Fewer Side Effects

Progress on some CBCRP-funded projects is shedding light on two important questions. First, are there characteristics of tumors at the molecular level that can provide new ways to treat the tumors? Second, how can chemotherapy drugs be delivered to tumors, while sparing normal tissues from the drugs, and women from side effects? These questions are really two sides of the same coin. CBCRP-funded researchers on these pages are using several approaches. These include attempts to design ways to deliver chemotherapy that will only hone in on tumor blood vessels, and packaging drugs in microscopic fat particles that can contain a chemotherapy drug and also have an antibody that can hone in on one type of breast tumor.

New Drug Design: Creative Science

Interaction of PPARγ and Retinoid Ligands in Breast Cancer.

Compounds derived from Vitamin A (retinoids) show promise for prevention and treatment of breast cancers that depend on hormones to survive and grow, but not for hormone-independent breast cancers. ***Sharon James***, ***Ph.D.***, of ***The Burnham Institute***, La Jolla, is testing compounds that may make one class of retinoids more effective against hormone-independent breast cancers. The researchers have found that a type of retinoid, RXR retinoids, combined with two drugs—one called a PPAR specific drug and the other called trichostatin A—make cells produce an enzyme called RAR beta. RAR beta allows cells to take up retinoids and makes treatment with retinoids more effective against hormone-independent breast cancer. The team is currently investigating whether a protein called COUP must also be present in the cells for the combination of drugs and retinoids to work.

Blood Vessel Markers in Breast Cancer.

Erkki Ruoslahti, ***M.D.***, ***Ph.D.***, at ***The Burnham Institute***, La Jolla, is engineering small pieces of protein called peptides that are placed on viruses. These proteins allow the viruses to bind to other specific proteins found on breast tumor blood vessels, but not on normal blood vessels. Eventually, these "homing peptides" could be designed to carry chemotherapy drugs. So far, the research team has identified a breast tumor vessel homing peptide, which they have named BCRP-1. When this peptide is attached to a fluorescent marker molecule, a large amount of fluorescence appears in the tumor, and little or none in normal tissues. The fluorescent molecule has a chemical structure similar to drug molecules, so a drug coupled with the peptide would also become concentrated in the tumor. This could lead to a new way to target chemotherapy to tumors, with fewer toxic effects on normal tissues.

Enhanced HER-2 Directed Liposomal Therapeutics.

Daryl Drummond, ***Ph.D.***, from the ***California Pacific Medical Center***, San Francisco, is formulating liposomes (microscopic fat particles) which contained a chemotherapy drug. On their surface, the liposomes have a HER-2 antibody that convenes on tumor cells. The chemotherapy drug is not released until the tumor cells take it up, which should minimize side effects. The researchers are systematically overcoming formu-

lation problems with this method of delivering chemotherapy. They are attempting to formulate liposomes that allow more of the drug to reach the cancer, which would reduce the total amount of the drug that needs to be administered. They are working on ways to maximize the amount of time the liposomes circulate in the blood, ways to maximize the number of liposomes the tumor retains, and ways to allow the drug to be released inside the cancer cells.

Hormone and Chemotherapy Targets: Improving Today's Arsenal

Role of p14ARF in Metastatic Breast Cancer.

A protein found in normal cells and tumor cells, p53, triggers death of tumor cells after they have been damaged by chemotherapy or radiation. Some breast tumors have defective p53, but many of those with normal p53 appear to be missing another protein normally found in the cell nucleus, p14ARF. The tumor cells without p14ARF appear to have lost the ability to initiate cell death. ***Ruth Gjerset***, ***Ph.D.***, at the ***Sidney Kimmel Cancer Center***, San Diego, has found that P14ARF is generally missing from breast cancer specimens. She has found that restoring p14ARF with gene therapy will make cells more sensitive to therapy that depends on the action of the p53 protein. In addition, p14ARF has a "bystander effect"; adjacent cells are affected even if they don't take up the gene therapy treatment. Results from this research have published in *Cancer Gene Therapy* 9:830-9 (2002).

Novel Technologies to Identify Tissue-Selective Estrogens.

Estrogen-dependent breast tumors contain a specific protein (the estrogen receptor) that binds to the hormone estrogen. This binding causes tumors to grow. ***Fred Schaufele***, ***Ph.D.***, at the ***University of California***, ***San Francisco***, is using novel technology to test many proteins in living cells in order to identify a drug that will block estrogen in the breast, but preserve the beneficial effects of estrogen in other organs. The research team has so far adapted the necessary technology so that a large number of chemical interactions in living cells can be analyzed quickly at low cost.

In Vivo Effects of Chinese Herbal Extracts on Breast Cancer.

Michael J. Campbell, ***Ph.D.***, at the ***University of California***, ***San Francisco***, is testing extracts of Chinese herbs that have traditionally been used to treat cancer. Dr. Campbell's team is identifying the compounds in various herbs that are most active against breast cancer in lab cultures. Next, they are feeding these substances to mice with tumors, or injecting them into mice with tumors, to see if the tumors shrink. So far, one herb, Scutellaria barbata, inhibits tumor growth when injected, but not when given orally. The team is currently testing several compounds derived from this herb and from another herb, Vaccaria segetalis.

Can Molecular Markers Predict Response to Adjuvant Therapy?

Tumor-related markers are genes or proteins found in tumors that may provide information on the nature and severity of the disease. ***Shelley M. Enger***, ***Ph.D.***, of ***Southern California Kaiser Permanente***, and ***Michael F. Press***, ***M.D.***, ***Ph.D.***, at the ***University of Southern California***, Los Angeles, are investigating whether some of these markers—including Her-2/neu, p53 and Bcl-2—can be used to predict whether the patient is likely to respond to various treatments. To date, they have collected data from medical records of 1,517 breast cancer patients. They have found that the presence of tumor markers is not related to whether the tumor was found early or late, but that some tumor markers are more common in tumors that have one type of structure (lobular tumors) or in another (ductal tumors). The team is currently analyzing data to determine if any of the markers can predict response to treatment.

Chinese Herbal Therapy (CHT) for Symptom Management.

Hope S. Rugo, ***M.D.***, of the ***University of California***, ***San Francisco***, is conducting a Phase III clinical trial (the final trial before a medication can be approved for use) initiated by ***Debasish Tripathy***, ***M.D.*** The purpose of the trial is to investigate whether Chinese herbs will relieve the side effects caused by chemotherapy. So far, 28 women receiving chemotherapy treatment with doxorubicin and cyclophosphamide have taken part. Half the women are also being given a 21-herb combination designed by experienced acupuncturists, and half a placebo. It is not clear yet whether the Chinese herbal combination reduces side effects overall, but a small number of the women taking the Chinese herbal combination and a small number taking the placebo have experienced serious side effects.

Research Initiated in 2002

Immune Therapy: Mobilizing the Body's Defenses

PPARγ Modulators as Apoptosis Sensitizers for Breast Cancer.

John Reed*, *M.D., Ph.D., of ***The Burnham Institute***, La Jolla, is testing substances called PPARγ modulators for their ability to enable the natural process of cell death in cancer cells. Some PPARγ modulators are drugs currently used to treat other diseases, others occur naturally in the human body.

New Drug Design: Creative Science

Novel Retinoids with Enhanced Anti-Breast Tumor Efficacy.

Marcia Dawson*, *Ph.D., at ***The Burnham Institute***, La Jolla, is attempting to improve the effectiveness of a compound derived from vitamin A, called an AHPN, that may be able to stop the growth of breast cancer cells without undesirable side effects.

Regulation of SXR and Drug Resistance in Breast Cancer.

Jennifer Murray at the ***Beckman Research Institute of the City of Hope***, Duarte, is studying a gene involved in the production of SXR, a protein that allows cancer cells to resist drug treatment and often thwarts chemotherapy.

Retinoids in Combination Therapies Against Breast Cancer.

Francisco Javier Piedrafita*, *Ph.D., at the ***Sidney Kimmel Cancer Center***, San Diego, is testing combination therapy for breast cancer in cells grown in cultures and in animals. The combinations of medications include compounds derived from Vitamin A (retinoids) along with medications that choke off a tumor's blood supply or stimulate the body's immune system.

MMP-Directed Synthesis of Invasive Breast Cancer Blockers.

MMPs are proteins that cancer cells secrete in order to invade the surrounding tissue and move to new parts of the body. Researchers have developed drugs to block MMPs.

However, because these drugs also inhibit MMPs involved in normal body processes, they have bad side effects. ***Vito Quaranta***, ***M.D.***, at ***The Scripps Research Institute***, La Jolla, will use a new chemistry method to "instruct" MMPs involved in breast cancer to synthesize substances that block only those particular MMPs.

Potential New Drug therapy for Breast Cancer.

Jack Youngren, ***Ph.D.***, at the ***University of California***, ***San Francisco***, is testing compounds that block the action of IFG-IR, a protein that appears to play a key role in initiating the growth of breast cancer cells. The research team will test whether these compounds stop breast tumors in mice.

TR3-Based Peptides for Apoptosis in Breast Cancer.

Xiao-kun Zhang, ***Ph.D.***, at ***The Burnham Institute***, La Jolla, is investigating how a protein called TR3 destroys cancer cells. The research team, who previously discovered TR3, is also looking for the part of the protein responsible for its anticancer action.

Hormone and Chemotherapy Targets: Improving Tc Arsenal

Chemotherapy-Induced Ovarian Damage: Prevention and Impact.

When young women with breast cancer receive chemotherapy treatment, it generally damages their ovaries and makes them unable to have children. ***Hope S. Rugo***, ***M.D.***, of the ***University of California***, ***San Francisco***; ***Lynn Westphal, M.D.***, of ***Stanford University***; and ***Lucy Berlin***, ***M.S.***, of ***Young Moms with Breast Cancer***, Sunnyvale, are testing a medicine called GnRH-analogues that shuts down the ovaries. They will give this treatment to 32 women ages 35–44 during chemotherapy to see if it protects the women's ovaries and fertility.

Gene Therapy and Other Treatments: New Frontiers

Drug Dose Tailoring Based on Patient-Specific Factors.

The optimal dose of a chemotherapy drug would be strong enough to eliminate the tumor, but not so strong that it is toxic to the rest of the body. ***Christine Case***, ***Ph.Dc.***, at the ***University of California***, ***San Francisco***, is developing a method for creating the optimal dose of the chemotherapy drug docetaxel for individual patients, based on a profile of the patient's blood proteins, liver enzymes, and other factors.

Clotting Breast Cancer.

Michael Samoszuk, ***M.D.***, at the ***University of California***, ***Irvine***, is attempting to activate a normal blood clotting mechanism in a tumor blood supply to starve breast cancer. The research team is trying the concept on cells grown in lab cultures and on mice with tumors.

Pathogenesis: Understanding the Disease

Researchers in breast cancer tumor biology are seeking answers to many key questions. How are breast cancer cells different from normal breast cells? How do breast cancers escape the limits of growth placed on normal cells? What are the critical underlying genetic characteristics for the major types of breast cancer? Why do breast cancer cells fail to respond to therapies and the body's own immune system? How do breast cancers gain a blood supply and spread in the body? These questions are being addressed at the cellular, molecular, and genetic levels using CBCRP funding. The research grants summarized in this section generally employ the modern tools of molecular biology to understand the unique genes and protein interactions that allow breast cancers to grow, progress, and spread in the body.

We divide the pathogenesis priority area into five subtopics:

- Outbreak—How Cancer Spreads: Angiogenesis, Invasion, and Metastasis
- Too Much Cell Growth: Defective Messages and Internal Signaling
- Mistakes on the Master Blueprint: Molecular Genetics and Gene Regulation
- Searching the Unknown: Novel Breast Cancer Genes
- Unraveling the Path to Breast Cancer: Tumor Progression

Research Conclusions

Angiogenesis

When tumors grow larger than 1–2 millimeters, they can no longer survive with the blood supply from the vessels that feed surrounding tissue. To grow, the tumors need to hijack the body's blood supply and generate their own internal blood vessels, a process known as angiogenesis. Angiogenesis is also a key event in tumors developing the ability to spread to other parts of the body (metastasis). Researchers are investigating the cell-level biochemical processes involved in tumors forming new blood vessels, many of which are not yet understood. The eventual goal is to develop treatments that shrink tumors and prevent their spread by blocking angiogenesis. Even though the promise of angiogenesis inhibitors to become a universal anticancer therapy has faded, the CBCRP continues to funding promising research into angiogensis.

Outbreak—How Cancer Spreads: Angiogenesis, Invasion, and Metastasis

Profiling Serine Protease Activities in Breast Cancer.

The functional molecular activities that allow breast cancer cells to invade other tissues are complex and not well understood. One generally accepted hypothesis is that proteins called proteases play a central role in promoting the aggressive behavior of cancer cells. Proteases are enzymes; they break down other proteins. The identities of the individual proteases involved in breast cancer remain elusive. ***Benjamin Cravatt***, ***Ph.D.***, from ***The Scripps Research Institute***, La Jolla, developed a technique to detect and characterize the protease "profile" of cells and bodily fluids. This approach is valuable because it is based on the protease's chemical activity, not just the amount present. Thus far, this research has been promising, because the team has detected previously undiscovered proteases that are active in breast cancer cells, but less or not at all active in normal cells. Some of these proteases are from aggressive, ER-negative cell lines, a type of breast cancer that is difficult to treat. In addition, the protease profiles can be used to tell one cancer subtype from another—for example, skin cancer from breast cancer. This research was published in five articles, with recent ones in *Nature Biotechnology* 20:805-9 (2002) and *Proceedings National Academy of Sciences, USA* 99:10335-40 (2002). Dr. Cravatt is continuing this work with additional CBCRP funding. This research could lead to a therapy based on inhibiting the action of selected proteases.

FAS as an Anti-angiogenic Target in the Treatment of Tumor Metastasis.

Tumor endothelial cells, the cells that line tumor blood vessels, are an attractive target for cancer therapy. Drugs delivered through the blood would have access to them, and they are not genetically altered cells, like cancer. ***Elizabeth Hindmarsh, Ph.D.***, from ***The Burnham Institute***, La Jolla, began her research under the title of "Analysis of Angiogenic Pathways in Metastatic Breast Cancer." She was investigating chemical interactions between proteins during the process of tumor blood vessel formation. During the course of these experiments, Dr. Hindmarsh saw another opportunity for research. She shifted her attention to the process of fatty acid metabolism. Endothelial and tumor cells have a fatty acid synthase (FAS) enzyme that plays a

Cell Growth

Cancer is the continued growth of abnormal cells in settings where normal cells either would not divide or would die. Much current breast cancer research investigates the complex chemical interactions between genes and proteins within cells that lead to cell division, cell growth, and the normal process of pre-programmed cell death (apoptosis). This research will give insight into tumor formation and the ability of breast cancer cells to survive chemotherapy treatment and the body's own immune response.

role in these cells' growth and survival. A drug that inhibits this enzyme, called Orlistat, is used to treat obesity. Dr. Hindmarsh found that Orlistat inhibited the division of endothelial cells grown in lab cultures. Much lower concentrations of Orlistat were effective on endothelial cells, but not on another type of cell that is part of the supporting framework for tumor cells, the fibroblasts. The CBCRP funded additional support to ***Lynn Knowles, Ph.D.***, in the same laboratory to pursue Orlistat's effect on tumor cells.

Too Much Cell Growth: Defective Messages and Internal Signaling

Studies on the Role of the ER-ß in Breast Cancer

Estrogen receptors are proteins in cells that bind with the hormone estrogen, which circulates in the blood. Once this bonding takes place, it triggers other chemical reactions in the cell. Breast cancer cells that have the most widely-studied estrogen receptor, ER-α, depend on estrogen for their growth. This type of breast cancer is the most commonly occurring subset of the disease; it grows more slowly than many other types and can be treated with anti-estrogen drugs like tamoxifen. ***Eli Gilad***, ***Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, investigated a recently-discovered estrogen receptor, ER-ß. He introduced ER-ß into breast cancer cells grown in lab cultures. Some of these cells also had ER-α and others did not. ER-ß appeared to play an important role in inhibiting the growth of cells lacking the ER-α. In cells that had ER-α, adding ER-ß allowed them to grow even without estrogen. Results from these studies were presented as posters at the 2000 and 2002 American Association for Cancer Research meetings.

The Role of the BMK1-MEKK3 Pathway in Breast Cancer.

The search has been on for more than a decade to explain how cell surface growth receptors, such as Her-2 and the EGFR, start a chain of chemical reactions inside breast cancer cells. These chemical reactions activate genes that cause the cells to divide and tumors to grow. MAP kinases are a collection of molecules that are part of these chemical reactions. ***Ta-Hsiang Chao, Ph.D.***, from ***The Scripps Research Institute***, La Jolla, working in ***Jiing-Dwan Lee's*** lab, investigated how BMK1 (Big MAP Kinase-1) puts cells into the phase where they divide into two. Using a special method (two-hybrid screening in yeast), the team discovered that BMK1 first interacts with another molecule called a growth factor. Next, BMK1 interacts with SGK, a type of molecule called a protein kinase. This process is necessary for the cell to begin to divide and discovering it completes a key missing piece of the puzzle.

Specificity of Ras Signaling in Breast Cancer.

Signaling proteins in cells are functionally a chain of reactions between molecules within cells that eventually trigger growth response and genetic changes. Collectively, Ras is a large family of signaling proteins that relay messages from proteins on the surface of cells that cause cells to divide. In about 30% of human cancers Ras becomes mutated in a way that continuously stimulates cell growth. Human cells contain four Ras proteins with similar structures. ***Janis Jackson, M.D***., from ***The Scripps Research Institute***, La Jolla, studied these four Ras proteins—Ki-Ras4A, Ki-Ras4B, N-Ras and Ha-Ras—and found that each one may participate in different chains of chemical reactions inside the cells, that each may have a different biological role. This research also helps explain why human cancers frequently have mutations that activate KiRas, but not N-Ras or Ha-Ras. This research was published in the *J. Biol. Chem*. 274:17164-70 (1999).

SBP-1: A Novel Survivin Binding Protein in Breast Cancer.

Survivin is a molecule that is present in the cells of human fetuses. Survivin is not produced in normal adult tissue and is consistently overproduced in breast cancer cells. It inhibits the normal process of cell death. Chemotherapy drugs work by triggering the normal process of cell death, and chemotherapy-resistant breast cancers keep these drugs from working by stopping the normal cell death process. ***Kazuya Okada***, ***M.D.***, ***Ph.D.***, of ***The Burnham Institute***, La Jolla, discovered a protein that binds to Survivin, SBP-1. He described the molecule-level process that promotes the destruction of the Survivin molecule, involving SBP-1 and other proteins found in cells. This work is an important step toward possibly controlling Survivin to allow cancer cells to better respond to drug treatments.

The Control of Breast Cancer Cell Death.

Daria Mochly-Rosen, Ph.D., from ***Stanford University***, applied expertise and prior research in heart disease to investigate how breast cancer cells overcome the body's restraints that should keep them from growing inappropriately. There are two levels of restraints; first, control mechanisms that keep cells from dividing, and second, controls that cause cells to die. The protein kinase C (PKC) family of enzymes is part of the chain of chemical reactions within cells that controls both division and death, in normal and cancerous cells. Dr. Mochly-Rosen's team found that blocking the action of one type of PKC, called delta-PKC, would accelerate tumor growth in animals, and, under

certain conditions, prevent the death of breast cancer cells in lab cultures. The research team plans future research to see whether it is possible to make delta-PKC more active in breast cancer cells, and whether this will stop cell growth or cause cell death. If so, this research could provide the basis for a future therapy.

A Novel Signal Transduction Pathway in Breast Cancer.

The CBCRP has funded several studies of the NF-κ-B pathway, a series of chemical reactions within cells that is involved both in cell death and cell division. This pathway is also involved in many aspects of cell function, including stress, injury and especially the immune response. Although the precise role of NF-κ-B in breast cancer is uncertain, this pathway does allow cancer cells to evade cell death and contributes to cancer cells' resistance to immune attack and drug therapy. ***Yixue Cao***, ***Ph.D.***, from the ***University of California***, ***San Diego***, working in the lab of ***Michael Karin***, ***Ph.D.***, used mouse genetics to investigate a specific protein necessary for the NF-κ-B chain of chemical reactions to take place. Dr. Cao found that this protein, called IKK-α, was essential for the mammary gland (the mouse equivalent of the breast) to produce milk. However, this protein was not necessary for mammary development. A therapy based on blocking the action of IKK-α might make breast cancer cells more likely to go through the natural process of cell death, and this approach might be relatively free from side effects. This research was published in *Cell* 107:763-75 (2001). Dr. Karin has received further funding from the CBCRP to pursue this line of research.

Role of the EphB4 Receptor Tyrosine Kinase in Breast Cancer.

Elena Pasquale, ***Ph.D.***, at ***The Burnham Institute***, La Jolla, investigated a molecule called EphB4. EphB4 is present at high levels in breast tumors that grow quickly and spread to other body parts. It is also present in other breast cancer cells and probably plays a role in breast cancer, especially in more aggressive tumors. EphB4 is a receptor protein. Part of its chemical structure is exposed on the surface of the cell, the rest of it inside the cell. The exposed portion combines chemically with a protein called ephrin-B2, and this causes the inner portion to start a chain of chemical reactions within the cell. Ephrin-B2 is necessary for embryos to develop blood vessels and is also present in tumor blood vessels. The research team found that the outer portion of EphB4 on the surface of tumor cells promotes the growth of the tumor's blood vessels, and therefore growth of the tumor. However, when EphB4 combines with ephrin-B2, the resulting chemical reaction within the cells may stop the growth and spread of the tumor. There

Proteins

Many researchers on these pages are investigating proteins. Proteins are complex, highly varied molecules that interact chemically within the cells of the body and are involved in all cellular processes. Changes in one protein can cascade throughout the cell, changing other proteins until the cell itself has changed. Genes, which cause cells to have the characteristics they have by making proteins, can be turned on and off by some proteins. By studying proteins and their actions in breast cancer cells, researchers are hoping to find new ways to stop or prevent the disease.

fore, a therapy aimed at EphB4 should either stop the cell from producing it, or promote the chain of chemical reactions caused by EphB4 combining chemically with ephrin-B2.

Novel Mechanisms of ErB-2-Mediated Breast Cancer Metastasis.

In approximately 30% of breast cancers, the ErbB-2 (also known as HER-2/neu) gene has mutated. These cases of breast cancer are likely to spread to other body parts and be deadly. Researchers believe the ErbB-2 gene facilitates this spread. ***Richard Klemke***, ***Ph.D.***, at ***The Scripps Research Institute***, La Jolla, investigated interactions between the proteins produced by the ErbB-2 gene with other proteins in breast cells. The team found that once the ErbB-2 protein is interacting within a cell, the combining of two other proteins, CAS and Crk, plus a chain of chemical reactions (a signaling pathway) among proteins called ERK are critical for the cells to move and spread to other body parts. The ERK pathway is part of a family of pathways that trigger normal processes, such as inflammation, and also are involved in the transformation of normal cells into cancer. Another protein, the Abl tyrosine kinase, keeps CAS and Crk from combining and thus keeps cells from being able to move. Breast cancer cells that have the ability to move have lower levels of Abl than those that can't move. Dr. Klemke plans to continue this line of research.

Mistakes on the Master Blueprint: Molecular Genetics and Gene Regulation

A Role for RAD51B in Breast Cancer.

Every cell in the human body contains DNA, a "blueprint" for the cell. When cells divide, errors can occur in replication, and DNA can get damaged during normal cell function. DNA repair proteins found naturally within cells are continually removing small sections of DNA and repairing them. RAD51 is a DNA repair protein that works with the hereditary breast cancer genes BRCA1 and 2. Normal BRCA genes prevent tumors. When mutations in the BRCA genes are present, then RAD51 cannot repair DNA and mutations are passed on to the next generation of cells. ***Joanna Albala***, ***Ph.D.***, from the ***Lawrence Livermore National Laboratory***, investigated five proteins with structures very similar to RAD51, focusing on one called RAD51B. She found that RAD51B does not interact with the BRCA1 and 2 breast cancer genes. Her research also shed light on how RAD51, RAD51B, and the four other proteins associate and their locations in breast cancer cells. Dr. Albala published four articles on this work, including a recent paper, *J. Biol.*

Breast Cancer Genes

Scientists estimate that 200 or fewer genes are involved in causing breast cancer to start and to progress. Each new suspected piece of the genetic puzzle needs to be validated as relevant to breast cancer and accurately placed within the overall biology of the disease.

Chem. 277:8406-11 (2002). In the course of this project, Dr. Albala received a National Cancer Institute Shannon Award to further support her research on the role of RAD51B in breast cancer.

A New Gene Regulation Factor, LMO-4, in Breast Cancer.

Transcription factors are proteins that turn genes on or off. In search of the causes of breast cancer, many researchers became interested in transcription factors involved in normal breast development. ***Bogi Anderson***, ***Ph.D.***, at the ***University of California***, ***Irvine***, identified a new transcription factor, LMO-4. In rabbits and guinea pigs, LMO-4 is most abundant in these animals' equivalent of breast epithelial cells (the cells where most breast cancer arises) during mid-pregnancy. Other investigators have shown that LMO-4 is found in a large portion of human breast cancer that has spread to other body parts. The team found several proteins that may also have to be present for LMO-4 to turn genes on or off. One of these proteins is present in higher than normal amounts in breast cancer cells. It is too early to tell whether LMO-4 is an important protein in breast cancer, but it does appear to be involved in normal breast development, and, perhaps, the early stage of the disease.

Searching the Unknown: Novel Breast Cancer Genes

Analysis of a New Human Caspase in Breast Cancer.

Caspases are proteins that split other proteins, causing the normal process of cell death (apoptosis). The growth of cancer is caused by an imbalance between the rates at which cancer cells are produced through cell division and the rate at which they die through apoptosis. Defects in the cell processes that lead to apoptosis allow cancer cells to survive for prolonged periods of times, accumulate genetic errors, and live in a suspended state that permits them to spread to other body parts. Researchers are in the final stages of cataloging all the human caspases, and work is progressing on understanding how caspase activity is held in check until apoptosis starts. ***Sug Hyung Lee***, ***M.D.***, ***Ph.D.***, at ***The Burnham Institute***, La Jolla, cloned and studied a new human caspase that was initially discovered in mice. Dr. Lee succeeded in isolating the gene that produces this caspase. Dr. Lee also found another gene that produces a protein similar to a caspase, called COP, which may also play a role in breast cancer. This work was published in the *J. Bio. Chem.* 276:34495-500 (2001). Dr. Lee conducted this research in the laboratory of ***John Reed***, ***M.D.***, ***Ph.D.*** Dr. Reed is a world leader in apoptosis research, funded through the CBCRP as a Principal Investigator and through fellowships to many researchers in his lab.

Tumor Suppression by Dystroglan in Breast Epithelial Cells.

Normal breast epithelial cells (the cells where most cancers arise) are organized in a single layer, with one side of each cell attached to another type of cell, collectively called the basement membrane. Proteins attach the cells together. The cell-basement membrane interaction helps prevent uncontrolled cell growth. There is considerable evidence that restoring critical attachment functions in the very early stages of breast cancer will reverse the disease. ***John L. Muschler***, ***Ph.D.***, of the ***Lawrence Berkeley National Laboratory***, studied a basement membrane protein, called laminin, which interacts with a protein present on the surface of breast cells called dystroglycan. In addition to interacting with laminin, dystroglycan tells the cell to stop growing. Dystroglycan appears to be absent or nonfunctional in breast cancer. Dr. Muschler described two forms of dystroglycan, α and ß, on tumor cells. As epithelial cells transform into tumor cells they start producing enzymes that break dystroglycan-α off the surface of epithelial cells. As dystroglycan-α is lost, the cells become unable to attach to basement membrane. If more were known about this dystroglycan process, it could possibly be used to turn cancer cells back into normal ones. Dr. Mushcler is completing this project with CBCRP funding.

A Novel Antigen Associated with Breast Cancer Metastasis.

Jacqueline Testa, ***Ph.D.***, at the ***Sidney Kimmel Cancer Center***, San Diego, identified a previously undiscovered protein that plays an important role in the spread of breast cancer cells to other body parts. The team found the protein by creating a molecule called a monoclonal antibody in the lab. This monoclonal antibody, named mAb 41-2, attaches chemically to proteins in cancer cells that are involved in the spread of tumors. In lab experiments, mAb 41-2 blocks the spread of breast cancer cells. The protein to which mAb 41-2 attaches is present at higher levels in breast cancer cells that have the ability to spread than in normal breast cells. This new antibody could be useful in both diagnosis and treatment of breast cancer.

Unraveling the Path to Breast Cancer: Tumor Progression

Are EGF-Receptors Activated by IL-8 in Breast Cancer?

Normal breast epithelial cells, the cells where most cancers arise, are firmly attached to another structure of cells called the basement membrane. As normal cells turn into cancer,

they can become mobile, and they stimulate another type of cell from nearby blood vessels, the endothelial cells, to migrate into the tumor mass to form the tumor's blood vessels. ***Ingrid Schraufstatter***, ***M.D.***, from the ***La Jolla Institute for Molecular Medicine***, looked at how tumor and endothelial cells are able to move from the standpoint of proteins that stimulate the normal movement of white blood cells in the body. Interleukin-8 (IL-8) is one of these proteins. IL-8 also controls the movement of cancer cells. Dr. Schraufstatter studied the chemical reactions between IL-8 and two other proteins, one found on the surface of epithelial cells called the epidermal growth factor receptor (EGFR) and the second a protein that allows cells to take in IL-8, CXCR2. This portion of the research was not resolved, but the team found that cathepsin B, a type of protein called a protease, is the key connection between IL-8 and the EGFR. Dr. Schraufstatter presented this research at the FASEB and Keystone meetings in 2002. She will continue investigating the best possible combination of IL-8, EGFR, and cathepsin B inhibitors. This could provide the basis of a therapy that would work by keeping tumor and endothelial cells from moving.

Targets of B Cell Infiltrate in Medullary Breast Cancer.

Medullary carcinoma of the breast is a distinct subtype of human breast cancer that is less likely to be fatal than other types of the disease. Scientists have proposed that this is because the body's white blood cells, part of the immune system, move into the tumor. ***Henrik Ditzel, M.D.***, ***Ph.D.***, at the ***Scripps Research Institute***, La Jolla, studied one type of white blood cell found in medullary carcinoma tissue, the B white blood cells. The research team cloned the cells and found that they homed in on a protein that is not specific to cancer. This previously-discovered protein is called actin; it plays a role in muscle contraction. The team also found that dying medullary carcinoma cells have the actin protein on their surface, which allows the immune system to recognize the cells. The team further found pieces of the actin protein in medullary carcinoma tissue. The pieces of the protein were similar to those seen after they have been split by a cell death enzyme found in another type of white blood cell, the T cell. The results indicate that the immune system's white blood cells keep medullary carcinoma in check by causing the cancer cells to die, possibly with enzymes found in T white blood cells.

Genes Involved in Immortalization of Human Mammary Cells.

Normal cells stop dividing into two after a limited number of cell divisions. Tumor cells acquire immortality, which is the ability to keep dividing into two indefinitely. ***Martha Stampfer***, ***Ph.D.***, at ***Lawrence Berkeley National Laboratory***, studied

a cancer gene, Raf. When Raf gets turned on in immortal cells, it promotes tumor growth. When it gets turned on in normal cells, it causes them to rapidly lose the ability to divide in two. The research team found that human breast epithelial cells, the type where most cancer arises, must go through a process called conversion to become immortal. The conversion process is triggered by an enzyme that comes from outside the cell, telomerase. After conversion, turning on the Raf gene promotes tumor growth. If the cells have not undergone conversion, turning on Raf keeps them from dividing. The team also found that other types of mouse and human cells stop dividing when Raf is turned on, but the internal chemical reactions involved are different for different types of cells. Understanding how cancer cells acquire immortality may lead to new therapies.

TGF-ß Receptor Signaling and Breast Cancer.

TGF-ß is a protein inside breast cells. It inhibits the growth of normal cells, but not the growth of breast cancer cells that have the ability to spread to other body parts. ***Kunxin Luo***, ***Ph.D.***, of the ***Lawrence Berkeley National Laboratory***, is investigating TGF-ß's role in the normal process of breast cells becoming specialized and in the process that changes normal cells to cancer. Dr. Luo discovered two proteins located in the breast cell nucleus, Ski and SnoN, that block TGF-ß. Overproduction of the two proteins kept TGF-ß from inhibiting cell growth. Both block the action of another type of protein, Smad. Smad proteins activate a gene necessary for TGF-ß to inhibit cell growth, so blocking their action also blocks TGF-ß. The research team tested normal and cancerous cells for levels of SnoN. They found little or no SnoN in normal cells, very high levels in early tumor cells that didn't have the ability to spread, and moderate levels in tumor cells with the ability to spread. Thus, a high level of SnoN is a sign that cells are becoming cancerous, and SnoN may play a role early in this process. The team plans future experiments to find out if cells that produce high amounts of Ski or SnoN change from normal to cancerous, and if reducing the amount of these proteins turns the cells back to normal.

Metalloproteinases (MMPs)

A group of enzymes, called matrix metalloproteinases (MMPs), play a role in normal tissue development. They are also involved in inflammation, degradation of bone and joints, autoimmune disease, and the invasive migration of cancer cells to other body parts. MMPs are important for angiogenesis, the process where tumors develop their own blood supply, which tumors must do to grow beyond a certain size. MMPs promote angiogenesis because they allow normal body endothelial cells to invade the tumor tissue and form both blood and lymphatic vessels. Over 20 types of MMPs are known. Some are secreted from cells and others remain at the cell surface. In all cases, MMPs work by digesting proteins in the cell's immediate environment, the extracellular matrix. Normally, the extracellular matrix maintains cell and tissue structure and restricts cell movements. Because MMPs are outside the cell, they might more easily be inhibited by drugs than the breast cancer proteins and genes within cells. Drugs to inhibit MMPs, such as

Continued next page sidebar

Outbreak—How Cancer Spreads: Angiogenesis, Invasi and Metastasis

Role of MMPs in Breast Tumor Initiation and Aggressiveness.

Metalloproteinases (MMPs) are enzymes that normal cells secrete to perform a variety of normal processes. Breast cancer cells produce more MMPs than normal; this allows tumors to grow and spread. ***Jimmie Fata***, ***Ph.D.***, of the ***Lawrence Berkeley National Laboratory***, is investigating how MMPs can cause normal breast epithelial cells (the type of cells where most cancer arises) to develop an unusual characteristic called epithelial to mesenchymal transition (EMT). EMT allows cells to spread to other body parts and is associated with aggressive breast cancers. The team created cells with EMT characteristics, then inhibited the action of MMPs in these cells. This caused the cells to lose the ability to move individually, the way cancer cells spread, but the cells retain their ability to move in sheets, the way cells move when they close a wound. The team is now investigating how MMPs break apart a protein called E-cadherin, and whether this chemical reaction is a crucial step in breast cancer spreading to other body parts. E-cadherin attaches epithelial cells to other cells in breast tissue.

Analysis of Genes Predictive of Breast Cancer Metastasis.

Jeffrey Gregg, M.D., from the ***University of California, Davis***, is following up on an observation about experimental mouse tumors with an enzyme called phosphoinositol kinase 3 (PI-3 kinase). When PI-3 kinase is turned on, the tumors will spread more often to the lung than to other parts of the body. PI-3 kinase works by activating a series of other enzymes and proteins, and the chain of chemical reactions produced is called the P13-K pathway. The research team has examined the action of PI-3 kinase in two lines of mouse mammary tumor cells (mammary tumors in mice are the equivalent of breast tumors in humans). In a type of mammary tumor cells that always spreads to the lung, the activation of the P13-K pathway is necessary. In another cell line that seldom spreads to the lung, proteins that block the P13-K pathway are active. The team has also found a gene and a protein that are directly involved in the cells developing the ability to migrate to the lung.

Marimastat (British Biotechnology) and BMS-275291 (Bristol-Myers Squibb), are being tested in humans to see if they block cancer progression and angiogenesis. This therapeutic approach does not directly kill cancer cells, but can shrink tumors and is attractive in combination therapy with other drugs. In another clinical application, MMPs are potential biomarkers of breast cancer for early detection. They, or their digested fragments, are released into the blood and can be detected in plasma and urine. In addition, the action of MMPs in digesting proteins in the extracellular matrix leaves behind a "signature" of digested matrix proteins, which might be detected in biopsy. Researchers are investigating whether this digested ECM might cause less aggressive tumor cells to become more active. Thus, research into MMPs holds potential for detection, diagnosis, and treatment of breast cancer.

TGF-ß3 and small GTPases in Invasive Breast Cancer.

Vesa Kaartinen, ***Ph.D.***, of the ***Children's Hospital Los Angeles***, is investigating the molecule-level interactions that cause breast cancer cells to become able to move to other parts of the body and form new tumors there. The team is trying to find the proteins involved in the EMT process where one type of breast cell, the epithelial cell, becomes more like another, the fibroblast, and becomes more able to move. Epithelial cells are where most breast cancers arise; mouse mammary epithelial cells are the equivalent of human breast epithelial cells. So far, Dr. Kaartinen has found that one type of protein, transforming growth factor (TGF-ß3), changes the locations and amounts of two adhesion molecules (integrins) in mouse mammary epithelial cells. The team has also found that a molecule involved in a chain of chemical reactions within these cells, Rac3, plays a role in the growth of mammary epithelial cells and in the formation of cells that are in transition from normal to cancerous.

Lasp-1 Signaling in Breast Carcinoma Cell Invasion/Migration.

Yi Hsing Lin, ***Ph.D.***, at the ***Scripps Research Institute,*** La Jolla, is investigating the Lasp1 gene. Dr. Lin's research team had previously shown that overproduction of the protein produced by Lasp-1 is linked to breast cancer cells moving to other body parts. In this study, they have found that the normal Lasp-1 protein prevents cells from moving, but that a mutated version, Lasp-1 deltaC, does not. The mutated version has lost the part of the protein structure, called the SH3 domain, that allows normal Lasp-1 to interact with other cell proteins to prevent cells from moving. The information may lead to new drugs that block the spread of cancer.

Smoking Effect on Pulmonary Metastasis from Breast Cancer.

Smokers are more likely to die of breast cancer than nonsmokers, but they don't get breast cancer any more often. ***Susan Murin***, ***M.D.***, of the ***University of California, Davis***, injected mice with breast cancer cells, then exposed some to a level of cigarette smoke comparable to that experienced by actively smoking adults. The mice exposed to smoke had more tumors in their lungs, compared to mice not exposed to smoke. When the researchers halted the animals' exposure to smoke at the time the breast cancer cells were injected (a model for a woman who stops smoking when her breast cancer is diagnosed), the mice had fewer tumors in the lung than the mice exposed to smoke.

Research on Metastasis, the Spread of Breast Cancer

Breast cancer spreads through the blood and lymph system to form tumors in other parts of the body. This process is very inefficient. Scientists believe perhaps only one in a million cancer cells released into the blood from a primary tumor will successfully implant in another organ, such as the lung. In addition, in the new organ, the cancer cells often remain quiescent or grow very slowly for years. However, it is the growth of tumor cells in distant organs from the breast that eventually compromises the function of the organ, leads to a critical tumor load (1–2 kg), and overwhelms any therapeutic intervention.

Research in metastasis is focusing in the cell surface adhesion receptors and proteases of cancer cells that allow them to migrate, enter the blood/lymph, and exit into other organs. Any breakthroughs that might reduce metastasis and growth in secondary organs is likely to represent a huge advance in reducing deaths from breast cancer.

Next, the researchers will investigate how smoke exposure increases the spread of breast cancer to the lungs.

Too Much Cell Growth: Defective Messages and Internal Signaling

Cell Growth Control of Breast Epithelial Cells.
Ulla Knaus, ***Ph.D.***, at ***The Scripps Research Institute***, La Jolla, is investigating two proteins that appear to be involved in the growth of normal breast cells. The two proteins are called Rac3 and Rac1. They are turned on by hormones and by proteins (called growth factors) that come from outside the cell. Rac3 is also consistently turned on in tumors, while Rac1 is not; Rac3 may be tricking cells into growing at inappropriate times. Rac3 does not have mutations, so Dr. Knaus is investigating where inside breast cells this protein is attached. Her team introduced fluorescent copies of both proteins into normal human breast cells. Rac1 distributed itself throughout the cell, but Rac3 attached to membranes inside the cell. They found that Rac3 combines chemically with a particular cell structure called Golgi, and found the part of the Rac3 protein that attaches it. They are now looking for proteins that associate with Rac3 and Golgi that may play a role in growth control.

Molecular Characterization of ErbB2 Positive Breast Cancers.

The ErbB2 protein is present at high levels in 20–30% of all breast cancers, and these tumors are more deadly. The role of this protein is complex; fewer than 20% of these tumors respond well to Herceptin, a drug targeted at ErbB2. ***Richard Neve***, ***Ph.D.***, of the ***Buck Institute for Age Research***, Novato, is attempting to find a way to better classify ErbB2-positive breast cancers into distinct molecular subtypes, so that effective therapies could be developed for each subtype. So far, the research team has found that a transcription factor (a type of protein) called ESX is also found in cancer cells that are high in ErbB2, and that ESX may play a role in this type of cancer. Results of this phase of the project were published in *Oncogene* 21:3934-8 (2002).

Mistakes on the Master Blueprint: Molecular Genetics and Gene Regulation

The Role of BRCA1 in Nucleotide Excision DNA Repair.

Mutations in two genes, BRCA1 and BRCA2, are responsible for 5–10% of all breast cancers. ***Anne-Renee Hartman***, ***M.D.***, at ***Stanford University***, has found that the normal BRCA1 gene plays a role in part of a cell's normal process of repairing damage to its DNA. The part of the cells repair process is called nucleotide excision repair. Another gene known to suppress

Gene Mutations and Breast Cancer

Normal cells effectively repair the DNA that makes up their genes. Mutations in DNA can occur when the cell is dividing in two and the DNA is replicating itself. Damage from the environment, such as UV radiation or tobacco smoke, can also cause mutations. Normal cells can correct these mutations, and if this system of correction fails, then cells stop dividing and undergo programmed cell death.

In breast cancer, this normal DNA monitoring and repair goes awry. Compared to normal breast cells, breast cancer cells have many mutations in their genes. Some breast cancer cell genes are missing normal parts, others have duplications in their DNA, and in others, the DNA is rearranged in order. Researchers believe many of these changes in cells genes are caused by defects in the normal cell DNA repair processes. Scientists have recently confirmed that the normal BRCA1 gene plays a role in DNA repair; a woman who has a mutated BRCA1 gene is at higher risk for breast cancer. The normal version of the other main inherited breast cancer gene, BRCA2, is also involved in DNA repair.

tumors, the p53 gene, is involved in this same process. More than 50% of human cancers have a p53 gene that has stopped working. Dr. Hartman found that a normal BRCA1 gene can compensate for a nonworking p53 tumor suppressor gene.

The Functions of BRCA2 in Repairing DNA Damage.

Women with an abnormal version of the BRCA2 gene are more likely to get breast cancer. The protein produced by the normal BRCA2 gene interacts chemically with a protein complex in cells, Rad51. Rad51 is involved in a part of the process of DNA repair called homologous recombination repair. ***Yi-Ching Lio***, ***Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, is using molecular biology methods to investigate the normal BRCA2 protein. This research could shed light on why a mutated BRCA2 gene leads to a high number of mutations in tumor genes, and also help scientists understand why cancer cells can still repair their DNA, even after being treated with chemotherapy that damages DNA.

Regulation of the ATR Checkpoint Response in Breast Cancer.

Dawn Yean, ***Ph.D.***, at ***Stanford University***, is investigating the ATR gene, which produces the ATR protein, an enzyme found in cells that plays a major role in DNA repair. Dr. Yean is attempting to find out how ATR works on the molecular level. The research team believes ATR is involved in detecting DNA damage. So far, they have shown that ATR binds to DNA, which suggests their hypothesis may be correct. Next, they will search for other chemical reactions in cells that are necessary for ATR to bind with DNA, and further investigate ATR-DNA interaction.

Unraveling the Path to Breast Cancer: Tumor Progression

A Study of the Molecular Heterogeneity of LCIS.

Women who have the breast disease lobular carcinoma in situ (LCIS) have an increased breast cancer risk. However, LCIS may actually be several diseases, and only a subset of them may lead to a high risk for breast cancer. ***Sanford Barsky***, ***M.D.***, at the ***University of California***, ***Los Angeles***, compared the genetic profiles of 200 tissue samples of LCIS. The research team has found that genetically, LCIS can be divided into three types. The first type share characteristics in their genes that suggest that they have progressed to invasive cancer. The second type have genetic profiles that suggest that the disease could develop into cancer. The third type shows no obvious differences in genes with normal breast tissue, suggesting that this type may be harmless.

Immortalization of Human Mammary Epithelial Cells by ZNF217.

The ZNF217 gene is present at higher than normal levels in many breast tumor cells, and it allows cells to continue dividing past their normal limits. ***Paul Yaswen***, ***Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, has found that higher than normal levels of ZNF217 may support the survival and growth of cells early in the process when they are becoming cancerous, by allowing the cells to continue growing when they would otherwise stop. In later stages, high levels of this gene may make cancer cells resist chemotherapy and radiation therapy. The research team is studying the chemical reactions within cells in which ZNF217 is involved. If this gene is involved in the earliest stages of breast cells turning into cancer, then further studies could lead to a way to prevent the disease. Results from this research were published in the *International Journal of Biochemistry and Cell Biology*, 34:1382 (2002).

Genes That Modulate Dioxin-Induced Breast Cancer.

While inherited susceptibility to breast cancer accounts for 10–15% of all cases, the rest are thought to relate to lifestyle and environmental pollutants. Dioxins are widespread environmental toxins known to cause cancer. They are accumulating in foods, including breast milk. Several studies suggest dioxin may be responsible for some breast cancer cases. ***Quan Lu***, ***Ph.D.***, of ***Stanford University***, is searching for genes that either promote or suppress breast cancer initiated by dioxin. The research team is using two techniques. The first is RHKO, which has been used to discover genes that inhibit tumor growth. RHKO involves inactivating normal breast cell genes, one gene at a time, then looking for cells that, when a certain

Tumor Suppressor Genes

A group of genes implicated in cancer are the "tumor suppressor genes." These are normal genes whose absence or mutation can lead to cancer.

Perhaps the best described tumor suppressor is called p53. The name refers to the molecular size of the protein the p53 gene produces—53,000 daltons—which is just an average size. The p53 protein signals cells to commit programmed cell death (apoptosis). In at least 20% of breast cancer cases, p53 has been mutated and its protein rendered ineffective. The main function of p53 is "the guardian" of the chromosomal DNA. When genetic damage becomes detected within cells, the p53 protein pathways are activated and serve to halt cell division and cause cell death.

Another well known tumor suppressor is retinoblastoma (Rb), which was first described in children having tumors developing from the immature retina. Further research has shown that Rb is found in all cells of the body, where under normal conditions it acts as a "brake" on cell division. Rb works by

Continued next page sidebar

preventing certain regulatory proteins from triggering DNA replication. If Rb is missing, a cell can replicate itself in an uncontrolled manner, resulting in tumor formation.

The BRCA1 gene is also a tumor suppressor. When a woman says "I have the BRCA1 gene," she's speaking in convenient shorthand. Everyone has the BRCA1 gene, but inheriting the mutated form raises a woman's risk for breast cancer. Considerable research is underway to find other possible candidate tumor suppressors that might be involved with blocking tumor metastasis or other aspects of the disease.

For complex reasons, new tumor suppressors are more difficult to identify and study than their counterparts, the tumor-inducing oncogenes. Finally, tumor suppressors are being scrutinized for their possible role for increasing the risk of developing breast and other cancers. Normally, there are two functional copies of each gene. But if one copy (allele) is missing or defective, then an individual could be at much higher risk. This is because a single subsequent mutation (due, for example, to environmental causes) could readily inactivate the remaining functional copy of a given tumor suppressor and lead to cancer.

gene is inactivated, are immune to dioxin-induced cancer. The second is microarrays, a technology that allows a researcher to study thousands of genes at the same time. The team has assembled the necessary technology and is now testing breast cells.

Tumor Suppression by Dystroglycan in Breast Epithelial Cells.

Cells sense their environment through proteins called receptors, which are located on their cell surface. Receptors combine chemically with molecules outside the cell and then start chemical reactions in the cell that regulate cell behavior. ***John L. Muschler***, ***Ph.D.***, of the ***California Pacific Medical Center***, San Francisco, is studying a receptor called dystroglycan. Dystroglycan combines chemically with a protein from outside the cell, laminin, which leads to the cell adopting a particular shape and stops the cell's growth. The molecule is nonfunctional in most breast cancers. Restoring dystroglan function in breast cancer cells makes them more like normal breast cells. Dr. Muschler has found that an important portion of the dystroglycan molecule is detached from the cell surface in the majority of breast cancer cells in lab cultures, and this keeps dystroglycan from working. The loss of dystroglycan function is the result of structural changes that occur in the molecule, not genetic mutation. Dystroglycan also does not function well in the presence of competing chemical reactions in the cell that cause the cell to grow.

Overcoming Drug Resistance in Breast Cancer.

Most chemotherapy drugs work by activating mechanisms in cancer cells that cause the cells to "commit suicide." It has been hypothesized that resistant cancer cells somehow refuse to commit suicide in response to chemotherapeutic drugs. ***Kristiina Vuori***, ***M.D., Ph.D.***, at ***The Burnham Institute***, La Jolla, is investigating how this happens. She has previously found that certain molecules that are on the cell surface, known as integrins, block the suicide process in cancer cells. Normally, integrins anchor cells in their place within a tissue. Integrins on cancer cells appear to have lost their normal function and instead, they may aid the cells' movement and spread. In this study, Dr. Vuori's team has shown that integrins are crucial for the development of drug resistance in cancer cells grown in lab cultures. Dr. Vuori's team is also testing anti-integrin monoclonal antibodies for their ability to make chemotherapy drugs more effective against breast tumors in mice. In addition, they are examining this process at the level of a chain of chemical reactions within tumor cells known as PI 3-kinase/Akt pathway. Results of this study were published in *Oncogene* 20:4995-5004 (2001).

Research Initiated in 2002

Outbreak—How Cancer Spreads: Angiogenesis, Invasion, and Metastasis

Hox Transcriptional Regulation of Angiogenesis.

Audri Charboneau, Ph.D., at the ***University of California, San Francisco***, is investigating two genes called HOX D3 and D10. These genes may control the molecule-level processes in blood vessel cells that allow breast tumors to create the blood supply that allows the tumors to grow and spread.

The Role of Matrix Metalloproteinase 13 in Breast Cancer.

Mikala Egeblad, ***Ph.D.***, at the ***University of California***, ***San Francisco***, is studying an enzyme called Matrix Metalloproteinase 13. This enzyme is secreted by a type of breast cell that supports the epithelial cells where cancer arises. The supporting cells do not themselves become cancerous, but the enzyme they secrete may allow cancer cells to grow and spread.

Method to Profile Active Metalloproteases in Breast Cancer.

Arul Joseph, ***Ph.D.***, at ***The Scripps Research Institute***, La Jolla, is using a new chemical method to analyze the amount and activity of a family of enzymes in living breast cancer cells growing in lab cultures. The enzymes are called metalloproteases; there is evidence that they play a role in tumor growth and spread.

Identifying Accessible Targets in Human Breast Tumors.

Jan E. Schnitzer, ***M.D.***, at the ***Sidney Kimmel Cancer Center***, San Diego, is attempting to discover new proteins in the blood vessels of breast tumors that are not found in normal blood vessels. This research could open up new opportunities to develop a medication that could neutralize these proteins, kill off a tumor's blood vessels, and starve the tumor.

Too Much Cell Growth: Defective Messages and Internal Signaling

Cell-Killing Effect of Orphan Receptor TR3 in Breast Cancer.

Naathalie Bruey-Sedano, ***Ph.D.***, at ***The Burnham Institute***, La Jolla, is investigating a protein found in both human and fruit fly cells called TR3. TR3 may have potential as a breast cancer treatment; the research team will investigate what chemical reactions within cells are necessary for TR3 to trigger the normal process of cell death.

Novel Ligands as Probes of Estrogen Receptor Signaling.

Estrogen receptors are proteins on the surface of breast cancer cells that combine chemically with the hormone estrogen. This can start several chains of chemical reactions within the cell, some of which turn on and off various genes. ***Nicola Clegg***, at the ***University of California***, ***San Francisco***, is creating and investigating molecules that combine chemically with estrogen receptors, but cause or prevent only selected parts of the chains of chemical reactions in the cells.

Cyclin E Affects Growth Arrest in Breast Cancer Cells.

Navdeep Dhillon, at the ***University of California, Davis***, is investigating the protein Cyclin E, which is found in abnormally large quantities in some breast cancer cells, to see if Cyclin E allows cancer cells to become resistant to the drug tamoxifen.

A Novel Anti-estrogen Resistance Mechanism in Breast Cancer.

Kathryn R. Ely, ***Ph.D.***, at ***The Burnham Institute***, La Jolla, is investigating the interaction of two proteins, Bcar1/Cas and SHEP2, to see if they play a major role in breast cancer cells becoming resistant to the drug Tamoxifen.

Structure and Function of the Bax Apoptosis Regulator.

Francesca Marassi, ***Ph.D.***, at ***The Burnham Institute***, La Jolla, is investigating the molecular structure of a protein found in many cells, including breast cells, called Bax. The team will also investigate how Bax exerts control over the normal process of cell death.

DNA Damage Response Pathways in Breast Cancer Cells.

Beatriz Maroto, ***Ph.D.***, at ***The Scripps Research Institute***, La Jolla, is investigating the complex chains of chemical interactions that normally keep cells with DNA damage from multiplying, and also the chemical processes in breast cancer cells that override this DNA damage control.

Regulation of Estrogen Response by Corepressors.

Martin Privalsky, ***Ph.D.***, at the ***University of California, Davis***, is investigating chemical interactions between two types of proteins in breast cells, kinases and corepressors. The research team's hypothesis is that these chemical interactions affect the action of the hormone estrogen on both normal and cancerous breast cells.

Analysis of EGFR Transcript Splicing in C. Elegans.

Cheryl Van Buskirk, Ph.D., at the ***California Institute of Technology***, Pasadena, is using nematode worms called C. Elegans to investigate a protein called the EGF receptor. When cells have abnormally large amounts of this protein, they divide excessively and form tumors. Dr. Van Buskirk is investigating whether genes can produce a variant form of this protein that inhibits excessive cell growth.

Mistakes on the Master Blueprint: Molecular Genetics and Gene Regulation

Alterations in the Separase/Securin Balance in Breast Cancer.

Kelly Boatright, at ***The Burnham Institute***, La Jolla, is investigating the possible role of two proteins, called separase and securin, in causing abnormalities found in the chromosomes of breast cancer cells.

Identifying Sources of Genomic Instability in Breast Cancer.

Karlene Cimprich, ***Ph.D.***, at ***Stanford University***, will attempt to catalog and discover detailed information about genes that repair damage to DNA in breast epithelial cells, the cells where most breast cancers arise. The team will also identify which of these genes might be worthy of future study because they are involved in breast cancer.

The Detailed Structure of a Model Breast Cancer Genome.

Colin Collins, ***Ph.D.***, at the ***University of California***, ***San Francisco***, is testing a new technique, called End Sequence Profiling, that has the potential to identify all the genetic differences between breast cancer cells and normal cells. End Sequence Profiling uses some of the same methods that were used to map the human genome.

Global Gene Regulation by SATB1 in Metastatic Breast Cancer.

Terumi Kohwi-Shigematsu, ***Ph.D.***, at ***Lawrence Berkeley National Laboratory***, is investigating SATB1, a protein that turns on or off hundreds of genes in breast cancer cells, and may also be involved in the spread of breast cancer to other parts of the body.

Searching the Unknown: Novel Breast Cancer Genes

Profiling Enzyme Activities in Models of Human Breast Cancer.

Researchers believe that enzymes within breast cancer cells play a role in the cancer spreading to other parts of the body. ***Benjamin Cravatt***, ***Ph.D.***, from ***The Scripps Research Institute***, La Jolla, will use a new method he developed to measure the chemical activity of these enzymes, and not just their abundance, in human breast tumors grafted into mice. Dr. Cravatt is building on research he conducted last year with CBCRP funding, where he used this new method successfully to measure the chemical activity of these enzymes in breast cancer cells growing in lab cultures.

Regulation of the Rad1 Checkpoint Complex in Breast Cancer.

Cells are constantly exposed to agents that can damage their DNA, and cells that don't respond properly to this threat can get cancer-causing mutations in their DNA. Checkpoint proteins in cells sense DNA damage and activate processes to repair them. ***Patrick Lupardus***, at ***Stanford University School of Medicine***, is investigating how two checkpoint proteins, ATR and Rad1, interact to start the DNA repair process.

Cloning of Putative Tumor Suppressor Gene on the X Chromosome.

Sergei Malkhosayan, ***Ph.D.***, at ***The Burnham Institute***, La Jolla, is searching for a gene that may prevent tumors in its normal form, and allow tumors to grow when it gets mutated. The team is searching an area of DNA known as the q25 region of the X chromosome. More than 50% of breast tumors are

missing some DNA from this region, suggesting that they have lost a gene that suppresses tumors.

Locating Novel Breast Cancer Genes Using DNA Microarrays.

Breast cancer cells often have one or more extra copies of a gene found in normal breast cells, or they are missing a normal gene. Cataloguing the extra and missing genes could improve treatment. For example, Herceptin is a medication used to treat breast cancers with excess Her-2/neu genes on the cell surface, and it became most effective after a test for multiple copies of the gene was developed. ***Jonathon Pollack***, ***M.D., Ph.D.***, at ***Stanford University School of Medicine***, is using a new technique called DNA microarrays to find extra and missing genes in more than a hundred tumor samples and in 25 types of breast cancer cells grown in lab cultures.

Unraveling the Path to Breast Cancer: Tumor Progression

Role of PTEN in Progression of Ductal Carcinoma In Situ.

Ductal carcinoma *in situ* (DCIS) is a pre-cancerous condition of the breast. About 25–30% of DCIS cases become cancer that can spread to other body parts. Currently, there's no way to predict whether DCIS will become cancer, so some women needlessly undergo chemotherapy and radiation treatment. ***Shikha Bose, M.D.***, at ***Cedars-Sinai Medical Center***, Los Angeles, is investigating the hypothesis that measuring the level of a protein called PTEN in DCIS cells can predict whether they will become cancerous.

Prognostic Value of Ras Activation in Breast Cancer.

Gerry Boss, ***M.D.***, and ***Anne Wallace, M.D.***, at the ***University of California***, ***San Diego***, are testing 300–400 breast tumor tissue samples for a protein called activated Ras, then following up to see which tumors recurred or spread to other parts of the body. High levels of activated Ras may predict which tumors are more dangerous.

Infinite Expansion of Breast Tumor Samples in Culture.

Research on breast cancer cells growing in lab cultures is limited to about eight types of cells. These cells came decades ago from tumors that had spread to other parts of the body. This makes it hard to investigate genes and proteins present at earlier stages of the disease. Drugs tested

against the currently available cells may not work the same way against tumors caught in early stages of breast cancer. Previous attempts to grow more kinds of breast cancer cells in lab cultures have failed. ***Shanaz Dairkee***, ***Ph.D.***, at the ***California Pacific Medical Center Research Institute***, San Francisco, is attempting to develop a new method that would allow scientists to grow cells in lab cultures from the majority of breast cancer cases. This could lead to the discovery of new molecules involved at all stages of the disease, and possibly drugs to target these molecules. It could also lead to individualized therapy, where drugs could be tested against a woman's tumor cells before treatment.

Does the BLM Gene Co-Regulate BRCA1 in DNA Damage Response?

The normal form of the BRCA1 gene prevents uncontrolled cell growth, and women with a mutation in this gene are more likely to get breast cancer. ***Albert Davalos***, ***Ph.D.***, at ***Lawrence Berkeley National Laboratory***, is investigating another gene called BLM to see if the protein BLM produces interacts with the normal BRCA1 gene to prevent uncontrolled cell growth. The team will also investigate whether turning off the BLM gene may contribute to breast cancer.

Molecular Pathogenesis of Metastatic Breast Cancer.

Robert Debs, ***M.D.***, at ***California Pacific Medical Center Research Institute***, San Francisco, is searching for combinations of genes that all work together to allow breast cancer cells to spread to other body parts.

Studies of Telomere Capping Dysfunction in Breast Cancer.

David Gilley, ***Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, is studying the structures called telomeres, which are found on the ends of chromosomes, and the dysfunction of telomeres in breast cancer cells. His research team is also investigating proteins associated with telomeres to see if these proteins play a role in breast cancer cells developing the ability to multiply indefinitely.

Fatty Acid Synthase and Breast Cancer Breast Cells.

Lynn Knowles, ***Ph.D.***, at ***The Burnham Institute***, La Jolla, is investigating how Orlistat, a drug approved for treating obesity, also inhibits fat production in, and kills, tumor cells. The research team will also figure out how orlistat works and identify genes it controls.

Identification and Prognostic Value of ERß in Breast Cancer.

Estrogen receptors are molecules in breast cancer cells and other cells that chemically combine with the hormone estrogen. This starts many other chemical changes in the cells. Tamoxifen, a treatment for tumors that depend on estrogen for survival, chemically combines with estrogen receptors to block the action of estrogen. A new estrogen receptor, ERß, has recently been discovered. ***Dale Leitman***, ***M.D.***, ***Ph.D.***, at the ***University of California***, ***San Francisco***, is attempting to develop an accurate test to measure the level of ERß in tumors.

Three-Dimensional Modeling of Breast Cancer Progression.

Carlos Ortiz de Solorzano, ***Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, is investigating where in the breast and when in breast development breast cancer is most likely to start. The research team will use mice that have been genetically engineered to develop tumors that mimic a deadly type of breast cancer, erbB2-positive. They will study where in the mouse mammary gland (the mouse equivalent of the breast) the tumors arise, and plot the cell-by-cell presence of key proteins. The end result will be a 3-dimensional "atlas" to visualize the disease.

BRCA-1-Dependent Ubiquitin Ligase Activity in Breast Cancer.

Yan Xia, ***Ph.D.***, at ***The Salk Institute for Biological Studies***, La Jolla, is studying the BRCA1 gene. Mutations in this gene predispose women to breast cancer. The normal version of the gene suppresses tumors, but no one knows how. Dr. Xia will try to find out how BRCA1 functions through mechanisms that cause protein degradation.

Prevention and Risk Reduction: Ending the Danger of Breast Cancer

Prevention is the ultimate solution to the breast cancer crisis; however, our lack of understanding of what actually causes breast cancer hampers the development of effective prevention strategies. Nevertheless, CBCRP-funded researchers are using several plausible theories about causes of breast cancer to devise new ways to prevent the disease:

♦ Safer Preventive Drugs: Investigating Naturally Occurring Compounds. The chemotherapy drugs currently available for prevention do not have ideal risk/benefit ratios. CBCRP studies investigate compounds from foods that show potential for preventing breast cancer.

♦ Diet and Other Active Lifestyle Modification: What Women Can Do Now. Because our diet is something we can change, many of the studies we fund explore the components of the diet that increase or decrease the risk of breast cancer.

♦ Hormones or Environmental Contamination Interacting with Known Risk Factors. The connection between environmental contaminants and breast cancer is difficult to prove, because the interactions between cancer-causing substances in the environment and breast tissue are complex. Our studies are designed to investigate those complex interactions, identify those most susceptible to cancer-causing environmental substances, and devise prevention methods.

Research Conclusions

Safer Preventive Drugs: Investigating Naturally Occurring Compounds

Breast Cancer Prevention by Inhibition of Estrogen Action.

Many types of breast cancer need the female hormone estrogen to develop and grow. However, estrogen has enormous benefits to most other tissues in the body. So researchers are looking for ways to reduce estrogen action in the breast, without reducing estrogen in the rest of the body. ***Vicki L. Davis, Ph.D.***, at ***Cedars-Sinai Medical Center***, Los Angeles, studied mice that were genetically engineered to develop tumors in the mammary gland (analogous to the breast in humans). The test group of mice also had a gene, called ERΔ3, that appears to block estrogen action in the breast. The mice with the ERΔ3 gene had fewer tumors than control group mice, probably because the tumors appeared at later ages. Late age at onset of tumors is a benefit to the test group; a comparable delay in women would allow them to remain tumor-free for more years of life. This research could potentially lead to a therapy that turns on the ERΔ3 gene to inhibit estrogen action in the breast, while maintaining normal estrogen levels in the rest of the body. The team also treated both groups of mice with isoflavones, substances found in soy products, at levels 3 times higher than the equivalent amount generally recommended to postmenopausal women. This provided no protection from mammary tumors for either group of mice.

Research in Progress

Safer Preventive Drugs: Investigating Naturally Occurring Compounds

Evaluation of Essiac Tea to Prevent Mammary Tumors.

Essiac tea, an herbal mixture introduced in the 1920s to treat cancer, is commonly used today by breast cancer survivors to try to prevent recurrence. The individual herbs used in one Essiac tea mixture have biological activities associated with decreasing cancer risk. Many herbs used in Essiac tea have long histories of use in Asian diets and medicine. Yet there are no published scientific studies evaluating Essiac tea's effectiveness in preventing breast cancer. ***Michelle Bennett***, ***Ph.D.***, of the ***Lawrence Livermore National Laboratory,*** fed one group of rats with water and another with a 3% solution of an Essiac herbal tonic. All rats were then exposed to the same cancer-causing substance. Eighty-two percent of the rats fed the Essiac tonic had mammary tumors, which are the equivalent of breast tumors in humans, compared to 71% of those fed water. The rats fed Essiac also had twice as many tumors as the rats fed water. The Essiac tonic appeared to promote, rather than prevent, the formation of tumors. The researchers plan to test Essiac tea on rats whose Her-2/Neu genes have been altered to cause the mice to spontaneously form mammary tumors.

Mechanisms of Reduced Metastasis by Conjugated Linoleic Acid.

Conjugated linoleic acid is a naturally-occurring compound found in some sources of dietary fat, including beef and dairy products. In small amounts, it has been shown to reduce the spread of mammary cancer in mice. ***Kent L. Erickson***, ***Ph.D.***, of the ***University of California, Davis***, is investigating how conjugated linoleic acid can reduce the growth and spread of tumors. Dr. Erickson has found that mice fed various amounts of conjugated linoleic acid produced lower levels of proteins called matrix metalloproteinases that are known to enhance the formation of tumors. It took longer for tumors to form in mice fed conjugated linoleic acid than in mice with a diet free of the substance. Fewer tumors spread to the lung in mice fed conjugated linoleic acid, even at a level of 0.1% of the diet. Conjugated linoleic acid also appears to keep breast cancer cells from lodging in the lung and growing, even after they

Upregulation of BRCA1 as a Cancer Preventive Strategy.

Colin K. Hill, ***Ph.D.***, at the ***University of Southern California***, Los Angeles, is investigating how tumor suppressor genes interact with hormones in the breast, and how these interactions might translate into breast cancer risk. Normal BRCA1/BRCA2 genes produce proteins, also called BRCA1 and BRCA2, that help to prevent cancer. The team has found that, in rats, levels of the BRCA1 protein rise as the animals enter puberty. They also found that rats bred to be susceptible to mammary cancer (the equivalent of breast cancer in humans) have lower levels of BRCA1 than rats bred to resist mammary cancer. In addition, the team found strong evidence that hormones control the levels of BRCA1. The ultimate aim of this research is to understand the critical points in breast development where risk is greatest so that strategies can be designed to offset that risk. It may be possible, for example, to increase the amount of BRCA1 protein in cells during susceptible years of development, or later in life.

Breast Cancer Prevention by Analogs of EGCG from Green Tea.

Nurulain Zaveri, ***Ph.D.***, at ***SRI International***, Menlo Park, is building on previous successful CBCRP-funded research to improve the breast cancer preventive action of a compound found in green tea, epigallocatechin-3-gallate (EGCG). Because of the way EGCG is absorbed and digested in the body, a woman has to drink 8–10 cups of green tea per day to get a preventive effect. Since each cup contains 70 mg. of caffeine, drinking large amounts of green tea leads to caffeine-related side effects. Dr. Zaveri has synthesized a chemically-modified version of EGCG. In the lab, this EGCG analog inhibits the growth of breast cancer cells, both those that need estrogen for survival and those that do not. Dr. Zaveri also has evidence that this EGCG analog might be better absorbed in the human digestive tract than the EGCG found in green tea.

Estrogen Metabolizing Genes, Soy, and Breast Cancer in Asians.

Anna H. Wu, ***Ph.D.***, at the ***University of Southern California***, Los Angeles, is studying genes that may interact with soy foods in the diet of Asian women to affect the development of breast cancer. Building on two studies previously funded by the CBCRP, Dr. Wu is collecting and analyzing blood specimens from 1,300 Asian women with breast cancer and an equal number from women who don't have the disease. She is investigating whether the risk of breast cancer is higher in women with particular types of CYP17 and COMT genes, two genes that metabolize the female hormone estrogen, and whether these genes interact with soy in the diet to cause breast cancer. The team has collected and

analyzed blood samples from 90% of the women. So far, the researchers have found that eating soy foods during teenage and adult years lowers the breast cancer risk of Asian women, and that physical exercise can reduce one's breast cancer risk.

Active Lifestyle Modification: What Women Can Do Now

Mammographic Density, HRT and Hormonal Activity Genes.

Women whose breast tissue appears denser than average on a mammogram have a higher risk of breast cancer. ***Thomas Mack***, ***Ph.D.***, of ***University of Southern California,*** Los Angeles, is investigating whether density of breasts is inherited and how certain hormones affect breast density. Dr. Mack's team is comparing the breast density of identical twins who are taking or have taken various kinds of hormone replacement therapy. After adjusting for any other pertinent characteristics, they will determine if the hormones are causing any difference in breast density. The team is also investigating how estrogen metabolism genes influence breast density by comparing breast density among sets of identical twins (who have identical estrogen metabolism genes) and fraternal twins (who are more likely to have different estrogen metabolism genes). So far, the team has collected mammograms and interviewed approximately 700 pairs of twins, received DNA samples from 239 women, and documented hormone replacement therapy from medical records from 155 physicians.

Genetic and Environmental Modifiers of Breast Cancer Risk.

Argyrios Ziogas, ***Ph.D.***, of the ***University of California***, ***Irvine***, is investigating how three types of genes interact to raise or lower breast cancer risk. The first types of genes are BRCA1 and BRCA2, on which abnormalities are already known to increase a woman's risk of breast cancer. The second type of gene interacts with cancer-causing chemicals in the environment and may elevate breast cancer risk. The third type of gene is involved in the metabolism of the hormone estrogen. Dr. Ziogas is using data from the unique resource of a breast and ovarian cancer registry of 1,176 families, a questionnaire providing environmental exposure and lifestyle information, and analysis of the families' genes. Preliminary results show that starting menstruation at an early age changes the breast cancer risk posed by two genes called CYP1A1 and COMT. Another gene, called GSTT, is associated with breast cancer risk. In this population-based sample, 3.3% of women with breast cancer have cancer-promoting mutations in their BRCA1 genes, and 1.2% of women have this type of mutation in their BRCA2 genes. Results from this study could improve risk prediction for individual women.

Research Initiated in 2002

Safer Preventive Drugs: Investigating Naturally Occurring Compounds

Breast Cancer Prevention with Estrogen.

Having a baby before age 20 protects a woman from breast cancer. ***Satyabrata Nandi***, ***Ph.D.***, at the ***University of California***, ***Berkeley***, is testing in mice and rats a 7–21 day hormone treatment with levels of estrogen comparable to those during pregnancy. Those mice and rats, along with mice and rats that haven't had the hormone treatment, will then be given a cancer-causing substance, to see if the hormone treatment provides protection from mammary cancer (the mouse/rat equivalent of breast cancer).

Fiber, Estrogen, and Breast Cancer in Mexican American Women.

Mexican American women in the US have the lowest rate of breast cancer of any major ethnic group. ***Malcolm C. Pike***, ***Ph.D.***, at the ***University of Southern California***, Los Angeles, is investigating whether the high-fiber diet these women eat affects the way their bodies process the hormone estrogen and whether this is responsible for their low rates of breast cancer.

Risk Reduction and Identification

Using Scientific Text to Identify Breast Cancer Risk Factors.

Breast cancer risk factors are characteristics women have—such as a type of gene or not having a baby before age 20—that raise their risk for the disease. ***Catherine L. Blake***, ***M.S.***, at the ***University of California***, ***Irvine***, will construct an interactive computer system to search thousands of scientific articles for information about various characteristics women with breast cancer may have. She will then compare the frequency of these characteristics among women with breast cancer to the frequency in the general population. The goal is to find new risk factors for the disease.

Using Microarrays to Estimate Breast Cancer Risk.

Bradley C. Ekstrand, ***M.D.***, ***Ph.D.***, at ***Stanford University***, is testing the hypothesis that breast cancer is associated with abnormal genes that govern the mechanisms cells use to repair DNA damaged by x-rays. His research team will expose blood samples—from women with breast cancer and those without

the disease—to x-rays, and use a technology called microarrays to measure how the genes respond. The team will then see if differences in the way genes respond can be used to predict which women have cancer.

Racial and Ethnic Differences in Breast Cancer: Eliminating Disparity

Women from different ethnic groups have different rates of breast cancer, different results from treatment, and different death rates. There may be important differences in the biology of the disease. Research into these questions can help reduce inequality among women with breast cancer and among those at risk for the disease in the future. It may also uncover important information about breast cancer that could point to new methods of prevention and treatment, or even a cure. California, with its many diverse ethnic groups, provides one of the best resources in the nation, or the world, for this type of research. This is a new Priority Issue this year.

Research Initiated in 2002

Weight Loss in Public Hospital Breast Cancer Patients. Women who are obese or who gain weight after they are diagnosed with breast cancer are more likely to have a recurrence or die, compared to women who are not overweight. ***Roman Chlebowski*, *M.D., Ph.D.***, at the ***Harbor-UCLA Research and Education Institute***, Los Angeles, is investigating whether a weight loss program for overweight breast cancer patients at a public hospital can change these women's hormone levels in a way that may reduce the risk that their breast cancer will recur.

Can Placenta Factors Explain Race Patterns of Breast Cancer?

During pregnancy, the placenta is the organ that regulates a baby's growth and the production of hormones responsible for changes in a woman's body. ***Barbara A. Cohn*, *Ph.D.***, at the ***Public Health Institute,*** Berkeley, has previously discovered that if a woman's placenta has certain characteristics, she has strong protection against breast cancer 40 years later. Her research showed this to be true only for white women. In this project, she will compare characteristics of placentas of Asian, Hispanic, African American and white women who were pregnant between 1959 and 1967 to see if differences explain the ethnic groups' varied rates of breast cancer.

Immune-Function Genes and Race Differences in Breast Cancer.

Sally Glaser*, *Ph.D., at the ***Northern California Cancer Center***, Union City, is comparing a type of gene involved in immune function called HLA among California women from various ethnic groups. Some of the women have breast cancer and some do not. The goal is to see if HLA genes are responsible for some or all of the differences in breast cancer rates among women from various ethnic groups.

Sociocultural, Behavioral, and Psychological Issues: The Human Side

Until breast cancer can be prevented, understanding how best to provide psychological and emotional support will enable breast cancer patients to have the highest quality of life. CBCRP research reflects the complexity of the non-medical aspects of breast cancer. Topics include: what aspects and types of support groups work best, the impact of cultural beliefs, how and in what ways the support of significant others is important, and how to help women in the transition back to normal life. All of this research is aimed at lessening the isolation, uncertainty and fear experienced by women who are at high risk, newly diagnosed, or coping with treatment and post-treatment. Although there is more knowledge about how to help these women than there was a decade ago, much remains to be discovered and put into practice. The CBCRP continues to encourage and support this research.

Research Conclusions

Beliefs and Risks of Breast Cancer Among African Immigrants.

Understanding cultural beliefs can help shed light on why some groups of women don't get early breast cancer detection services and tend to consult a doctor when their disease has progressed to later stages. Women diagnosed with breast cancer in Africa are, on average, a decade younger than their counterparts in this country, and the disease is most often advanced at the time of diagnosis. Over one million African immigrant women live in the United States, the majority in California. ***Yewoubdar Beyene***, ***Ph.D.***, of the ***University of California***, ***San Francisco***, conducted a qualitative anthropological study, interviewing in depth 20 African immigrant women and holding focus groups with 100. The goals were to identify culturally-specific factors that influence how African immigrant women in California understand breast cancer symptoms and perceive their risks, and find out how these beliefs create barriers to early detection. Dr. Beyene found that immigrant African women do not generally feel comfortable with breast self-examination, even in private, because touching the breast is considered sexual. They often associate breast cancer with death. African immigrant women generally have little knowledge about treatments available when a diagnosis is made early. The most common consequence of breast cancer they mention and fear is mastectomy. Many Africans believe in reincarnation, and that a person who has body parts removed will return with those body parts missing. If a woman becomes disabled or disfigured, she and her whole family carry a strong stigma; therefore women with breast cancer never disclose their illness to others and have no social support outside of their families. The media and current guidelines are not reaching African immigrant women. Most women interviewed said that small group discussions are the best way to educate their population.

Social Support and Breast Cancer Control Among Latinas.

Nilsa Gallardo, ***Ph.D.***, at the ***University of California***, ***Los Angeles***, interviewed 20 Spanish-speaking low-income women, ages 20–74, who had recently been diagnosed with a breast abnormality that might be cancer. Women in this situation may be so upset that they do not seek follow-up treatment. Research has shown that social support can help women cope and can influence their decision to seek treatment, but this research has mostly been done on white,

English-speaking women. This research was designed to understand better the role of social support for Latinas facing possible breast cancer. The women interviewed generally felt that seeking help for emotional distress outside the family was difficult, although the majority felt they could ask for financial help. Half the participants reported that female family members, such as daughters, provided more emotional support than husbands or sons. A substantial number of the women did not want to overburden their family or friends by asking for emotional support until they knew whether or not they actually had breast cancer. This study was an initial effort; additional research is needed to fully understand the role of social support among Latina women diagnosed with possible breast cancer. There is also a need for an appropriate Spanish-language questionnaire to assess social support and a need to develop and test interventions that can increase social support for this group of women.

Risk Notification for Women at High Risk for Breast Cancer.

Susan Stewart, Ph.D., at the ***Northern California Cancer Center***; ***Joan R. Bloom, Ph.D.***, at the ***University of California, Berkeley***; and ***Marion Lee***, ***Ph.D.***, at the ***University of California***, ***San Francisco***, investigated telephone counseling for women whose sisters were diagnosed with breast cancer at age 50 or younger. These women have a higher-than-average risk for breast cancer. The research team first used a questionnaire to measure the women's psychosocial and emotional counseling needs. Then the team provided telephone counseling—designed to promote the women getting mammograms and provide a realistic assessment of their risk for breast cancer—tailored to each woman's needs. On average, women overestimated their risk of getting breast cancer by 25%, and the more they overestimated their risk, the greater their breast cancer worries. However, this didn't keep them from getting mammograms. Telephone counseling reduced the women's overestimation of their risk of getting the disease, and was most effective with women age 50 and older. Women who had counseling also increased their use of mammograms during the study. The research team then made this counseling process available over the 1-800-4CANCER help line. Callers also overestimated their risk of getting breast cancer by 25%, counseling was effective in reducing their overestimate, and the women increased their use of mammograms. This shows that the positive effects of this type of telephone counseling can be translated for use in help lines, even though the counseling session is shorter.

Communication, Content, and Impact of Genetics in Breast Cancer.

Deborah MacDonald, ***R.N., M.S.***, ***C.S.***, at the ***City of Hope National Medical Center***, Duarte, investigated how to improve genetic counseling and testing services for women who may have inherited a higher-than-average risk for breast cancer. Using questionnaires from 451 women and focus groups involving 121 women, the research team examined the motivations, concerns and characteristics of women who seek genetic counseling and testing. The team found that genetic cancer risk assessment counseling appropriately impacts these women's perceptions of their risk of breast cancer, their concerns about breast cancer, their discussions about breast cancer with relatives who are at risk, and their decisions about risk-reducing strategies and genetic testing. Study results have allowed the research team to tailor counseling to provide more appropriate services at three City of Hope screening sites, which serve one of the largest groups of women seeking genetic counseling and testing in California. The research team has also used results from this study to educate health care professionals to provide more appropriate and responsive care to women who seek genetic counseling. The team expects that as they continue to present and publish their findings, more women will be appropriately referred for genetic counseling and testing. Women found to be at high risk for the disease could be targeted for preventive strategies, such as tamoxifen therapy. This could help reduce the risk these women face and improve their quality of life.

Tamoxifen Prevention: Is it Acceptable to Women at Risk?

The chemotherapy drug tamoxifen has been shown to reduce the incidence of breast cancer in women at high risk for the disease who have been enrolled in clinical trials. However, numerous concerns remain about tamoxifen's potential adverse effects and the drug's benefits for high-risk women in the general population. ***Joy Melnikow***, ***M.D.***, ***M.P.H.***, of the ***University of California***, ***Davis***, investigated how women at high risk of breast cancer weigh the risks and benefits of tamoxifen. She developed an educational script, which includes a flip chart and color-coded beads to represent probability of risk, and used it to educate women at high risk for breast cancer about the potential benefits and risks of tamoxifen. The team interviewed 255 white, Asian, Latina, African American, and other women who all faced a higher-than-average risk of breast cancer. They found that these women greatly overestimate their risk of getting breast cancer. The women, on average, rated their 5-year risk at 33%, while the estimated risk according

to National Cancer Institute guidelines was only 2.8%. After receiving the education developed for this study, the number of women who were inclined to take tamoxifen (18%) did not change; however, the number disinclined to take tamoxifen increased from 28% to 49%. If women have a realistic estimate of their risk for breast cancer, they can make better decisions about whether to take tamoxifen. This could reduce the number of women taking the drug who would not benefit from it.

Do Community Cancer Support Groups Reduce Physiological Stress?

Research has shown that women with breast cancer benefit from support groups run at Stanford University. ***David Spiegel***, ***M.D.***, at ***Stanford University***; ***Carol Kronenwetter***, ***Ph.D.***, at ***Cancer Support Communities***, San Francisco; and ***Mitch Golant***, ***Ph.D.***, at ***The Wellness Community***, Santa Monica, investigated whether community support groups are providing benefits comparable to those run in a university setting. The team evaluated the strengths and weaknesses of two community support groups run by The Wellness Community and Cancer Support Communities, comparing them with Stanford's Supportive-Expressive group therapy. Stanford groups are run by trained professionals based on a well-researched theoretical model. The Wellness Community Groups are also run by trained professionals; the theoretical orientation emphasizes decreasing unwanted isolation and increasing the women's ability to be effective in their lives. The Cancer Support Communities groups are run from the grassroots by women who have had breast cancer; they emphasize compassionate support for women with the disease, regardless of the women's treatment decisions. Women participating in the community groups changed at about the same level over four months as women in the Stanford group in five ways: fewer depression symptoms, fewer trauma symptoms, better social support, better perception of ability to be effective in life, and post-traumatic growth. The Wellness Community has six California locations and other sites around the US. It is therefore encouraging that women in more widely available community groups benefit at the same rate as women in the well-researched Stanford groups.

Research in Progress

Women with Breast Cancer: Quality of Life and Dietary Adherence.

A diet that includes high amounts of vegetables, fruit, and fiber may protect women from recurrence of breast cancer. ***Wayne A. Bardwell***, ***Ph.D.***, at the ***University of California***, ***San Diego***, is looking for personal characteristics that might determine who will stick with this type of strict diet and investigating whether the diet improves women's mood, daily functioning, and relationships. The team will also look at the women's use of dietary supplements and the role that hot flashes—a common problem after breast cancer treatment—have on how women feel and function. So far, the team has found that younger women see diet as associated with mental health, while older women see diet associated with physical health. Over the coming year, the researchers will analyze their data, which they collected from a 6-year study of over 3,000 women called the Women's Healthy Eating and Living Study.

Breast Cancer Prevention and Control Among Deaf Women.

Breast cancer and breast health programs are often inaccessible and inadequate for women who are deaf or hard of hearing. Little research has been done on deaf women and breast cancer. ***Barbara Berman***, ***Ph.D.***, of the ***University of California***, ***Los Angeles***, and ***Heidi B. Kleiger*** of the ***Greater Los Angeles Council on Deafness***, ***Inc.,*** are conducting the first-ever exploratory research. The team is using signed languages of the deaf to interview 70 deaf women over 40 about their knowledge, behavior, and preferences about detection and other breast health practices. The research team has completed 15 interviews and will use information from this study to craft excellent, tailored breast health and breast cancer programs for deaf and hard-of-hearing women.

Mechanisms of Radiation-Induced Fatigue in Breast Cancer.

Fatigue is one of the most common side effects of radiation treatment, significantly disrupting the lives of women who receive this therapy. Little research has been done on radiation-induced fatigue, and women have few resources to help them manage this symptom. ***Juliene Bower***, ***Ph.D.***, at the ***University of California***, ***Los Angeles***, is investigating factors that contribute to fatigue during radiation treat-

ment, including immune system changes, as well as psychological and behavioral responses women have to breast cancer. Dr. Bower is collecting blood samples and questionnaires from women diagnosed with early-stage breast cancer—before, during, and after radiation treatment. The research team has recruited 28 women so far and completed gathering data on 20 of the women. Over the coming year, the researchers plan to recruit more women to the study and analyze their data. This research could pave the way for the development of methods to reduce fatigue during radiation treatment and also may help identify women at risk for fatigue.

Efficacy of a Community Program in Increasing Access to STAR.

Although African American women have a lower rate of breast cancer than other ethnic groups, their death rate from the disease is higher. African American women are under-enrolled in clinical trials to test whether chemotherapy can prevent breast cancer. ***Patricia Ganz***, ***M.D.***, of the ***University of California***, ***Los Angeles***, and ***Kathleen Brown***, ***M.D.***, of the ***Association of Black Women Physicians***, Los Angeles, are collaborating on methods to increase awareness of chemotherapy prevention trials among African American physicians and women. The goal is a tested method to increase African American participation in these trials. From focus groups, interviews and a survey, they have found that barriers include physicians not having time to discuss chemotherapy prevention with patients, physicians not being familiar with the available research trials, patients distrusting doctors and medical research, and researchers not getting information about previous trial results to the community. To break down these barriers, the research team held a Continuing Medical Education presentation for black women physicians in April 2002, and will hold an educational presentation for African American women in the community.

Breast Cancer Screening in Women Surviving Hodgkin's Disease.

Women who have had radiation treatment for Hodgkin's disease have a risk of breast cancer 5.35 times higher than the general population. Survivors of Hodgkin's disease also get breast cancer at younger ages. ***Steven L. Hancock***, ***M.D.***, of ***Stanford University***, is examining how being notified of this increased risk emotionally impacts survivors of Hodgkin's disease. He is also evaluating whether the women are getting breast cancer screening, and investigating whether telephone counseling helps decrease the emotional impact of learning about being at high risk and increases the women's rates of screening for breast cancer. Finally, he is investigating whether getting frequent mammograms does benefit these women. The

research team is in the process of enrolling 470 women who have received radiation therapy to treat their Hodgkin's disease before age 35, with treatment ending at least five years ago.

Breast Health Project for Hmong Women and Men.

Marjorie Kagawa-Singer, ***Ph.D.***, ***R.N., M.N.***, at the ***University of California, Los Angeles School of Public Health***; ***Mary Anne Foo, M.P.H.***, at ***Orange County Asian & Pacific Islander Health Alliance***; and ***Sora Tanjasiri, Dr. P.H.***, at the ***University of California, Irvine***, are investigating whether culturally-tailored health education will motivate Hmong American women to be more aware of breast cancer and obtain mammograms. Breast cancer is among the leading causes of death in Asian American and Pacific Islander women. Only about one-quarter of Hmong women have had mammograms. The research team has surveyed 552 Hmong women in three communities to assess current community practices, breast cancer screening rates and breast health resources. They held culturally-tailored breast health workshops with 327 of the women and also 321 Hmong men. They surveyed the original 522 women after the workshops to determine whether the workshops change their breast health knowledge and attitudes. The researchers are now analyzing their data.

Breast Cancer Prevention: The Views of Women and Physicians.

Celia Kaplan, ***Ph.D.***, of the ***University of California, San Francisco***, is investigating how doctors advise their patients about breast cancer risk, and the knowledge, attitudes, and practices of women and physicians with regard to breast cancer prevention. She is conducting a telephone survey of 1,200 women ages 40–75, from four ethnic groups, who have recently had mammograms. Women at high and low risk of breast cancer from each ethnic group will be included. Dr. Kaplan is also surveying 1,000 randomly selected Bay Area physicians about their views on obstacles to breast cancer prevention. The research team has completed telephone surveys in Spanish and English with 88 women and has received completed questionnaires from over 920 physicians. They have begun entering data into their database. Next steps include telephone surveys with more women, adding a Cantonese version of the survey, and data analysis. Findings from this study could help improve patient-physician decision-making and communication about breast cancer prevention.

Alternative Support for Rural and Isolated Women in an HMO.

Cheryl Koopman, ***Ph.D.***, ***Stanford University***, and ***Mary Anne Kreshka***, ***M.A.***, ***Sierra Nevada Memorial Hospital Cancer Center***, are investigating a support alternative for women with breast cancer who are psychologically, socially, or geographically isolated. The team has adapted a workbook-journal developed in a pilot CBCRP study. They have enrolled 151 women. So far they have found that at the outset, over 63% of the women are clinically depressed and 10% are experiencing post-traumatic stress syndrome. The research team is assessing the women three and six months after diagnosis, to determine whether receiving the workbook-journal reduces the women's distress and increases their coping skills, compared to women who do not receive the workbook-journal. The team will also examine characteristics of women who benefit most from the workbook-journal.

Child's Stress During Mother's Treatment for Breast Cancer.

Ellen Levine, ***Ph.D.***, of the ***California Pacific Medical Center Research Institute***, San Francisco, and ***Dalia Drucker, Ph.D.***, of the ***California School of Professional Psychology***, Alameda, are investigating how teenagers from various ethnic groups react emotionally and cope with their mothers being treated for breast cancer. The team will investigate factors that might influence the teenager's reactions, including the severity of their mother's illness, the intensity of side effects from her treatment, increased household responsibilities the teenager might have to take on, and the teenager's social support. The team is also looking at how the teenager's reaction affects the mother's quality of life. The researchers have developed a method for interviewing teenagers and are recruiting teenagers and their mothers for the study.

Effectiveness of Internet vs. Face-to-Face Support Groups.

Morton A. Lieberman, ***Ph.D.***, of the ***University of California***, ***San Francisco***, and ***Mitch Golant***, ***Ph.D.***, from The ***Wellness Community***, a community organization in Santa Monica, are testing whether Internet support groups improve quality of life as effectively as groups that meet in person. So far, they have developed a Web site, trained facilitators, and recruited women with breast cancer for Electronic Support Groups initiated by the researchers. The researchers have also investigated Internet breast cancer news groups set up by other organizations. They have found that these groups have potential for helping women with breast cancer and are conducting more research on the news groups' effectiveness.

Breast Cancer Survivorship: Partner's Role in Recovery.

The transition from being a breast cancer patient on active treatment to being a survivor on long-term follow-up can be upsetting and disruptive. This is especially true for women who don't get support from their intimate partners. ***Beth E. Meyerowitz***, ***Ph.D.***, of the ***University of Southern California***, Los Angeles, is investigating how partners' reactions during this transition relate to patients' quality of life, relationship adjustment, personal growth, and coping. She has developed, designed, and printed questionnaires. So far, 174 partners of women with breast cancer have completed the first questionnaire 2 months after the women complete treatment; 119 have completed a second questionnaire six month's after the women's treatment ends. Preliminary data shows that women with breast cancer and their partners report good quality of life, marital adjustment, and mood after treatment ends. However, partners are only moderately accurate in judging whether the women with breast cancer experience fear of recurrence or disruptions due to fatigue.

Cognitive Changes After Adjuvant Therapy for Breast Cancer.

Many breast cancer patients who receive chemotherapy say that they suffer memory and concentration problems, even years after therapy. Some previous research shows this may be true. ***Rebecca Rausch***, ***Ph.D.***, at the ***University of California***, ***Los Angeles***, is investigating possible changes in attention and memory in four groups. They are: (1) breast cancer patients receiving standard-dose adjuvant chemotherapy after surgery, (2) breast cancer patients treated with anti-estrogen (tamoxifen) therapy after surgery, (3) breast cancer patients not treated with either of these two therapies, and (4) age-matched healthy women with no history of cancer. Before and after treatment, the women are given a battery of tests that asses their mood, hormone-related behavior changes, quality of life issues, and aspects of memory and cognition processing. The women's hormone levels are also measured. So far, the team has found that women who were going to have chemotherapy were more confused and nervous before treatment than those who were going to receive tamoxifen, and that this was reflected on objective memory test scores. After treatment, the women who thought they were having memory and attention problems have been shown to have them on objective cognitive tests.

A Network-Based Intervention For Chamorros in Southern California.

Sora Park Tanjasiri, ***Ph.D.***, of the ***University of California, Irvine***, is collaborating with ***Lola Sablan-Santos***, of the community organization ***Guam Communications Network***, ***Inc.***, in Long Beach. The research team is testing the effectiveness of using lay health leaders to provide information about breast health and breast cancer to Chamorro women (Chamorros are people indigenous to the Mariana Islands, including Guam). The goal is to increase the number of Chamorro women who have screening mammograms and clinical breast exams. The research team has identified all Chamorro women age 50 years and older in Los Angeles and Orange counties, where the educational intervention will take place, and also in three northern California counties, where the women will be part of a comparison group that does not receive any education. So far, 60 Chamorro women have been recruited for the study. The researchers have designed the survey they will use to test the effectiveness of diffusing information through lay health leaders and held a community kickoff event to promote the study in the Chamorro community.

Research Initiated in 2002

Constructed Meaning and Stress in Breast Cancer Experience.

Jill L. Mitchell, ***M.A.***, at the ***University of California, Los Angeles***, will interview 40 women with breast cancer that has spread to other parts of their bodies to find out the different ways women give meaning to the experience. Dr. Mitchell will also look at how the meaning changes over time, how each woman constructs meaning, and how the meanings women give to breast cancer are related to a physiological measure of the stress they experience.

CBCRP Staff

Marion H.E. Kavanaugh-Lynch M.D., M.P.H.

Laurence Fitzgerald, Ph.D.

Katherine McKenzie, Ph.D.

Walter Price, Dr.P.H.

Marion H.E. Kavanaugh-Lynch, M.D., M.P.H.
Director

Roslyn Roberts
Assistant to the Director

Laurence Fitzgerald, Ph.D.
Research Administrator

Katherine McKenzie, Ph.D.
Research Administrator

Walter Price, Dr.P.H.
Research Administrator

Janna Cordeiro
Coordinator of Special Projects

Eric Noguchi
Publications

Sharon Simms
Research Analyst

Lyn Dunagan
Communications Project Manager

Brenda Dixon-Coby
Administrative Coordinator

Steven Baratz
Administrative Assistant

Mary Daughtry
Administrative Assistant

Joyce Price
Administrative Assistant

Breast Cancer Research Council

The overall objectives, strategies, and priorities of the CBCRP are set by the Breast Cancer Research Council, which actively participates in overseeing the program and making final recommendations on the research projects to be funded. In each Grant Cycle, the CBCRP awards grants based on the Council's recommendations, which are based on peer reviewers' evaluations, Council members' assessment of responsiveness to program priorities, and available funds.

The council consists of 16 members: five representatives of breast cancer survivor/advocacy groups, five scientists/clinicians, two members from nonprofit health organizations, one practicing breast cancer medical specialist, two members from private industry, and one ex-officio member from the DHS Breast Cancer Early Detection Program.

Council members are appointed by the University, drawn from nominations submitted by Council and the community.

Council Members

Industry

Teresa Burgess (7/1/99—6/30/02)
Research Scientist, Amgen, Inc.

Teresa L. Burgess, Ph.D., earned her BA in Biochemistry with highest honors from the Univrsity of California, Berkeley, after receiving a solid educational foundation from California public schools, including Diablo Valley Community College. Following a move across the San Francisco bay, she received her Ph.D. for original research on peptide hormone secretion from UC San Francisco.

As a Helen Hay Whitney Fellow, Dr. Burgess continued to investigate the basic cellular mechanisms of membrane trafficking at UC Santa Barbara. In 1992 she accepted a position as Research Scientist at the successful biotechnology company Amgen Inc., where she has continued both basic and applied cell biological research. Her investigations have led to numerous peer reviewed research publications relevant to diabetes, cancer, cardiovascular disease, Alzheimer's, and most recently osteoporosis and other metabolic bone diseases. Dr. Burgess brings to the Council not only her scientific expertise, but also an enthusiastic desire to contribute to a healthier future for all women.

Advocate

Lauren John (7/1/01—6/30/02)
Breast Cancer Action

Lauren John, 44, was diagnosed with breast cancer 7 years ago, while in the last semester of a graduate journalism program at boston University. Six months after completing chemotherapy and getting her diploma, she moved west to Silicon Valley when her husband George was recruited to join an Internet startup company.

Lauren is now a freelance science and technology writer based in a home office in Menlo Park, California. She also works part time as a reference librarian at the Menlo Park Public Library. In February 2001, Lauren was named to the board of Breast Cancer Action in San Francisco. She continues her membership in three other outstanding breast cancer organizations: the Massachusetts Breast Cancer Coalition, the Community Breast Health Project in Palo Alto, and the National Breast Cancer Coalition. In July 2001, she was apporinted as a consumer reviewer to the federal Department of Defense Breast Cancer Research Program.

In addition to her journalism degree, Lauren holds an undergraduate degree in English from the State University of New York at Binghamton and a graduate degree in library science (MLS) from St. John's University in Jamaica, New York.

Council Members

Advocate

Akua Jitahadi (7/1/01—6/30/02)
Founder, Black Women for Wellness

Akua Jitahadi is a longtime community activist who has organized around such issues as homelessness, human rights, and women imprisonment.

She is a co-founder of Black Women for Wellness, a community-based organization that focuses on health issues impacting black women.

Ms. Jitahadi coordinates the organization's "Keep in Touch...Do BSEs," an outreach and education program. She is also a member of the Los Angeles County Partnered for Progress African American Breast Cancer Taskforce.

Advocate

Florita Maiki (7/1/01—6/30/02)
Program Manager, Breast Health Access for Women With Disabilities

Florita Maiki, presently the Manager of Breast Health Access for Women with Disabilities (BHAWD) a program of the Rehabilitation Services of Alta Bates Summit Medical Center. Her many grant supported projects include further developing and implementing the BHAWD program to ensure and increase access to breast screening services to women with disabilities within the program and the community through extensive collaborative efforts.

Prior to BHAWD, she had worked over ten years in community and hospital based agencies and organizations in program planning/development and evaluation capacities, serving people with disabilities.

Throughout her tenure, she has had extensive experience and responsibility in developing and monitoring grant proposals and other development efforts.

Council Members

Scientist/Clinician

Susan Blalock (7/1/99—6/30/02)
School of Pharmacy and Health Sciences
University of the Pacific

Susan Blalock, Ph.D., M.P.H., is an Associate Professor in the School of Pharmacy and Health Sciences at the University of the Pacific. Dr. Blalock is a behavioral scientist with expertise in health behavior and health education.

She holds graduate degrees from the Schools of Public Health at the University of Michigan (M.P.H.) and the University of North Carolina at Chapel Hill (Ph.D.). Dr. Blalock has served as a principal investigator on numerous studies investigating behavioral factors associated with illness prevention and disease management. Her current interests include quality of care issues, including economic and ethical issues that influence the delivery of health care services in the United States.

Scientist/Clinician

Tammy Tengs (7/1/99—6/30/02)
School of Social Ecology—University of California, Irvine

Tammy O. Tengs, Sc.D., is the Director of the Health Priorities Research Group and an Assistant Professor in the School of Social Ecology at the University of California, Irvine. Previously she was a member of the research faculty in the Center for Health Policy Research and Education at Duke University. She completed her doctorate in HealthPolicy and Management at the Harvard School of Public Health in 1994. Before coming to Harvard, she earned a master's degree in Industrial Engineering and Operations Research at the University of Massachusetts,Amherst, and studied in the Engineering-Economic Systems Department at Stanford. Dr. Tengs directed the 1990-1994 Lifesaving Priorities Project at the Harvard Center for Risk Analysis, supervising a team of 20 that amassed cost-effectiveness data for hundreds of public health and medical interventions. She is theprincipal author of the papers "Five hundred life-saving interventions and their cost-effectiveness" and "The opportunity costs of haphazard societal investments in life saving." Following considerable media coverage, she has received approximately 1,500 requests for these publications. Dr. Tengs is a "decision scientist." Broadly, her research interests include the economic efficiency of societal investments in health and science. With $2.7 million in grants, she is collecting information on the cost-effectiveness of different interventions aimed at cancer and developing a computer simulation model to predict the long-term economic and public health consequences of any change in federal tobacco policy.

Council Members

Medical Specialist

Robert W. Carlson (7/1/00—6/30/02)
Professor of Medicine/Oncology—Stanford University

Robert W. Carlson received his M.D. degree from Stanford University School of Medicine and did his internship and junior residency in internal medicine at Barnes Hospital in St. Louis, Missouri. He returned to Stanford for his senior residency and postdoctoral fellowship in medical oncology.

He joined the faculty at Stanford after his fellowship and is Professor of Medicine at Stanford University. His primary areas of investigation include breast cancer clinical trials and the use of computer-based systems to assist health care providers in the delivery of patient care.

Dr. Carlson serves as Chair of the Breast Cancer Guidelines Committee and the Breast Cancer Risk Reduction Guidelines Committee for the National Comprehensive Cancer Network (NCCN).

Scientist/Clinician

Hoda Anton-Culver (7/1/99—6/30/02)
College of Medicine—University of California, Irvine

Hoda Anton-Culver, Ph.D., is Professor and Chief of the Epidemiology Division in the Department of Medicine at the University of California, Irvine. She received her baccalaureate degree in pharmaceutical chemistry from the University of Alexandria in Egypt in 1964 followed by a Ph.D. in Epidemiology and Biochemistry at St. Andrews University, Scotland in 1968.

Following her doctoral degree, she began her academic career as a Lecturer at McGill University Medical School, Canada. From 1971 to 1978, she joined Dr. Henry Lynch as an Assistant and then as Associate Professor in the Department of Preventive Medicine and Public Health at Creighton University School of Medicine, Nebraska.

Since 1978, she has been at the University of California, Irvine, as an Associate Professor and then as Professor and Chief of the Epidemiology Division in the Department of Medicine. She also holds a joint appointment with the School of Social Ecology at UC Irvine, and an adjunct appointment with the San Diego State University Graduate School of Public Health.

Council Members

Vice Chair

Sandra Walsh (07/01/00—06/30/03)

A seventeen-year survivor of breast cancer, Sandy was not involved in any breast cancer activities until 1996 when she received a request to be treasurer of Save Ourselves of Sacramento. After serving in this position for 4 years, she co-founded Y-ME of Davis, a breast cancer education, support, and advocacy organization serving Davis, Yolo County, and rural areas west of Sacramento. Y-ME of Davis is a member organization of California Breast Cancer Organizations and Sandy is vice president of CABCO. With CABCO and the National Breast Cancer Coalition (NBCC), she works to promote legislation that will provide funding for research and provide other health care needs for persons with breast cancer. She has served on review panels for the Department of Defense Breast Cancer Research Program and currently serves on the Breast Health Initiative Team for the American Cancer Society, on the Project LEAD committee for the NBCC and on the Scientific Advisory Committee California Teacher's Study, under the Department of Health Services Cancer Registry. Sandy is employed at the University of California, Davis, as a research associate in the Center for the Study of Neuromuscular Diseases studying muscular dystrophies.

Council Chair

Anna M. Wu, Ph.D. (07/01/00—06/30/03)

Anna M. Wu, Ph.D., received her A.B. degree in Biochemical Sciences from Harvard University, and a Ph.D. from Yale University in Molecular Biophysics and Biochemistry. Postdoctoral studies were carried out at Yale University and at the University of California, San Francisco. For many years Dr. Wu was a staff member at the Beckman Research Institute of the City of Hope, in Duarte, CA, where she currently retains an appointment as Adjunct Professor of Molecular Biology. In July 2002 Dr. Wu joined the faculty at the UCLA School of Medicine as an Associate Professor. Dr. Wu's research interests have focused on molecular approaches to the diagnosis and treatment of cancer. Her laboratory has worked on developing engineered antitumor antibodies for delivery of radioisotopes to tumors for detection and treatment. At the Crump Institute for Molecular Imaging, Dr. Wu heads the Biomolecular Targeting laboratory and continues to develop engineered proteins (including antibodies) for targeting and imaging applications in cancer. Dr. Wu has been active with local cancer support groups, and for several years has taught basic science with Project LEAD of the National Breast Cancer Coalition.

ONGOING

Council Members

Scientist

A. Elaine Ashby (06/30/01 - 06/30/04)

A. Elaine Ashby received her Masters degree in Mechanical Engineering from Stanford University. She practiced engineering for 2 years before entering medical school at the University of California, San Francisco. She received her MD degree and residency training from UCSF. She has been in private Family Practice in the East Bay, as well as conducting Biomedical Engineering research at Lawrence Livermore National Laboratory. Her research areas have included Biomechanics and Prosthetics, transmission ultrasonography for breast imaging, and new technologies for prostate cancer detection.

Scientist/Clinician

Dorothy Bainton, M.D. (07/01/02 - 06/30/05)

Dorothy Bainton is Vice Chancellor, Academic Affairs and Professor of Pathology at UCSF. She received the B.S. degree from Millsaps College, Jackson, Mississippi, and the M.D. in 1958 from the Tulane University School of Medicine in New Orleans, Louisiana. In 1963 she came to the University of California, San Francisco, as a fellow in the Department of Pathology, and received the M.S. degree in Pathology in 1966. She has been a member of the faculty in Pathology since 1972. When she was appointed chair of the department in 1987 she became the first woman ever to serve in that capacity in the School of Medicine at UCSF. Dr. Bainton is a nationally recognized leader in academic pathology. Her research is focused on the structural and functional relationships of hematopoietic cells in bone marrow. She is a member of a number of professional societies and has served on the editorial boards of numerous professional publications. She has received many honors and awards during her career, including a ten-year Merit Award from the National Institutes of Health and the Gold-Headed Cane of the American Society of Investigative Pathology. As Vice Chancellor of Academic Affairs she works with the deans of the various schools, and has been responsible for the planning and review of all teaching programs at UCSF. Some of the academic units she currently oversees include the Library and Academic Information Management, Registrar and Student Academic Affairs, Academic Personnel, the Proctor Foundation and Langley Porter Psychiatric Institute.

ONGOING

Council Members

Advocate

Vicki Boriak (07/01/02—06/30/05)

Vicki Boriakof the Women's Health Alliance, San Jose, is a 16 year veteran of the outdoor industry and an avid mountaineer, kayaker, and backpacker. Vicki was 39 years old when she was diagnosed with breast cancer in October 1993. In February of 1995, Vicki climbed Mt. Aconcagua, the highest mountain in the Western Hemisphere, as a member of Expedition Inspiration. The Expedition, comprised of 17 breast cancer survivors, was created to raise 2.3 million dollars for breast cancer research and to raise awareness of the disease. Vicki has since switched careers, and is now working for Community Health Partnership in San Jose as the manager of the Women's Health Partnership program which helps medically underserved women gain access to health care and education. She is a graduate of the Project LEAD training course sponsored by the NBCC, and has participated as an advocate observer during the BCRP Cycle V grant review process.

Advocate

Diana Chingos (07/01/01—06/30/04)

Diana Chingos serves as Chairman of the Cancer Survivorship Advisory Council at the USC/Norris Comprehensive Cancer Center. This group of patients, survivors and caregivers seeks to use their "firsthand experiences and knowledge to generate new attitudes and practices that improve research and treatment, the outcomes of care, and the quality of life for cancer patients and their families." She represents this patient advisory group on the USC/Norris Executive Committee and serves as a patient advocate on the Cancer Center's Clinical Investigations Committee. Diana graduated from Project LEAD, the National Breast Cancer Coalition's course in the science of breast cancer for advocates and more recently, the Project LEAD Clinical Trials Program. She has served as a consumer reviewer for the FY 2001 DOD Breast Cancer Research Program Scientific Peer Review. She supports the NBCC's legislative and policy agenda and serves as a Team Leader and member of the National Action Network. She also works for *MAMM Magazine*, the only national consumer magazine devoted to women affected by breast and reproductive cancer. A former New Yorker, Diana was diagnosed with breast cancer at age 34 and is the third woman in her family to face a breast cancer diagnosis. She is a graduate of Bennington College and holds a graduate degree from the University of Southern California School of Cinema-TV. By profession, Diana works as a freelance TV producer.

ONGOING

Council Members

Medical Specialist

Michael Figueroa, M.D. (07/01/02—06/30/05)

Cancer Care Consultants, Redding

Michael Figueroa is a prominent member of the North State medical community, as the founder of Cancer Care Consultants and as the Director of the Mercy Regional Cancer Center. His colleagues, staff and patients value his gentle good-natured humor, and his deeply spiritual approach to his vocation. Dr. Figueroa's sincerity and respect has set the tone for Cancer Care Consultants. "Patients look to us for answers to their questions regarding cancer. The answers can be very frightening and emotional. Sometimes we just don't have an answer. Nevertheless, we must convey what we know in a kind, compassionate and honest fashion. Although we must never treat our own families, we should treat patients as if they are our families." Dr. Figueroa is currently the Chairman of the Cancer Committee, the Medical Ethics Committee, and the Ida C. Emmerson Endowment Board. In 2001 he received the Person of Distinction Award from Soroptimist International Redding, and was instrumental in creating the new Morgan Family Cancer Resource Center.

Industry

I. Craig Henderson, M.D. (07/01/00—06/30/03)

I. Craig Henderson, M.D., is Adjunct Professor of Medicine at the University of California, San Francisco (UCSF), a member of the staff at the UCSF/Mount Zion Cancer Center, President, Access Oncology, Inc., and a member of the board of ALZA Corporation in Mountain View, California. He was a member of the Harvard faculty for 18 years before moving to UCSF where he was Professor of Medicine, Chief of Hematology/Oncology, and Associate Director of the Cancer Center. In 1995 he became Chief Executive Officer and Chairman of SEQUUS Pharmaceuticals, Inc., Menlo Park, California, and continued there until the merger with ALZA Corporation in 1999. Dr. Henderson founded the multidisciplinary Breast Evaluation Center at the Dana-Farber Cancer Institute. At UCSF he developed the Bay Area Research Program funded by a Specialized Program of Research Excellence (SPORE) grant from the National Cancer Institute. Dr. Henderson has delivered innumerable presentations at medical conferences, and conducted grand rounds at medical schools throughout the United States and Europe. He is a Fellow of the American College of Physicians, a Fellow of the Royal College of Physicians (Edinburgh), and a Member of both the American Association for Cancer Research and the American Society of Clinical Oncology.

ONGOING

Council Members

Advocate

Janet Howard-Espinoza (07/01/02—06/30/05)

Janet Howard-Espinoza is a member of the Women of Color Breast Cancer Survivors Support Project, Los Angeles, which provides support in a nurturing environment through community outreach, encouragement, and support. She conducts an hundreds of motivational seminars and workshops each year, reaching diverse communities of underserved women. She is a Breast Cancer Educator, and participates in several support groups for breast cancer survivors.

Scientist/Clinician

Robert Kaplan, Ph.D. (07/01/02—06/30/05)

Robert Kaplan, Ph.D., is Professor and Chair of the Department of Family and Preventive Medicine, at the University of California, San Diego. He is a past President of several organizations, including the American Psychological Association Division of Health Psychology, Section J of the American Association for the Advancement of Science (Pacific); the International Society for Quality of Life Research; and the Society for Behavioral Medicine. He is currently Chair of the Behavioral Science Council of the American Thoracic Society and President of the Academy of Behavioral Medicine Research. Dr. Kaplan is the Editor-in-Chief of the Annals of Behavioral Medicine, Associate Editor of the American Psychologist, and Consulting Editor of four other academic journals. Selected additional honors include APA Division of Health Psychology Annual Award for Outstanding Scientific Contribution; Distinguished Research Lecturer, 1988; Health Net Distinguished Lecturer in 1991; University of California 125 Anniversary Award for Most Distinguished Alumnus, University of California, Riverside; American Psychological Association Distinguished Lecturer; and the Distinguished Scientific contribution award from the American Association of Medical School Psychologists. His public service contributions include various NIH, AHRQ and VA grant review groups, and service on the local American Lung Association (ALA) Board of Directors and the regional research committee for the American Heart Association. He has served as co-chair of the Behavioral Committee for the NIH Women's Health Initiative, and a member of both the NHLBI Behavioral Medicine Task Force and the Institute of Medicine (IOM) National Academy of Sciences Committee on Health and Behavior. Dr. Kaplan is the author or co-author of more than a dozen books and more than 350 articles or chapters.

Nonprofit Organization

Irene Linayao-Putnam (07/01/00—06/30/03)

Irene Linayao-Putnam is Project Director of the Southeast Asian Health Care Access Project and the Asian and Pacific Islander Communities Against Tobacco Project for the Union of Pan Asian Communities in San Diego. In these roles, she has provided significant leadership in addressing cultural and linguistic barriers to health care access for breast, cervical, liver and lung cancers in AAPI communities. She has also directed UPAC's API Breast Health Project, providing breast cancer community education through role modeling to women over age 40, and the Breast Health Outreach and Education project, raising breast health awareness and community capacities for early detection and risk reduction. She is Site Coordinator of the Life Is Precious Project: Addressing Breast Cancer Among Hmong Women & Men. This is a multi-site study being carried out in collaboration with the UCLA School of Public Health to assess breast health knowledge and practices among Hmong women and men, develop effective educational strategies, and provide interpretation and transportation to mammography sites. She is also Site Coordinator of the Pan Asian Language Services (PALS) for Health, Language Access Program, which is a multi-county, multi-agency collaboration to reduce language barriers to health education.

Nonprofit Organization

M. Ellen Mahoney, M.D. (07/01/00—06/30/03)

M. Ellen Mahoney, M.D. is a practicing breast surgeon in Arcata and Clinical Assistant Professor of Surgery at Stanford. She is the co-founder of the Community Breast Health Project in Palo Alto. Her work there resulted in extensive knowledge of current breast cancer literature and of the questions and problems faced by patients and families. She has used this knowledge to support other nonprofit breast cancer organizations, including the Breast Cancer Fund and the Humboldt Community Breast Health Project. She helps Susan Love M.D. in the maintenance of the Personal Guidance service on www.susanlovemd.com. Her goal is that all patients have the latest concepts and knowledge available in language they can understand. She describes herself as "passionate about the need to improve our knowledge about breast cancer and our care of all whose lives are affected by this disease."

ONGOING

Council Members

Advocate

Debra Oto-Kent (07/01/02—06/30/05)

Debra Oto-Kent is the Founder and Executive Director of the Health Education Council, a private, nonprofit community agency based in Sacramento that conducts health promotion programs for underserved communities. Regional, state, and national programs focus on tobacco use prevention, nutrition, diabetes, breast cancer, and physical activity. Debra received her M.P.H. from UCLA's School of Public Health in 1980. She has since devoted her career to planning, implementing, and evaluating health promotion programs for low income, underserved communities. She has presented numerous papers and presentations and serves on a variety of committees and as a reviewer of grant applications. Debra climbed to the summit of Mount Fuji, Japan, in 2000 as a member of the Climb Against the Odds Breast Cancer Survivors Team. She lives with her husband and three sons and enjoys spending time with her family.

Industry

Jacqueline Papkoff, Ph.D. (07/01/02—06/30/05)

Jacqueline Papkoff, Ph.D. was appointed Vice President of Discovery at diaDexus in January 2002. Jackie joined diaDexus from the Aventis Cambridge Genomics Center (previously Hoechst-Ariad Genomics Center), where she served as Vice President of Cell Biology and Genetics and Head of Genomics Platform Technologies. Prior to her tenure with Aventis, Jackie served as Director of Molecular Oncology for Megabios Corporation and before that served as Senior Scientist in Sugen Inc.'s Department of Cellular Biochemistry. She also held several research scientist positions at Syntex Research. Jackie has been a Consulting Professor of Cancer Biology with Stanford University for over 10 years. She received her B.A. in Biology from the University of California, Santa Cruz, a Ph.D. in Biology at the Salk Institute from the University of California, San Diego, and completed postdoctoral research at Stanford University and the University of California, San Francisco.

Ex-Officio

Georjean Stoodt (10/25/00—Ongoing)

As Chief of the Cancer Detection Section for the California Department of Health Services, Dr. Stoodt implements public health programs that save lives by detecting cancer early so people with cancer can receive timely treatment. The Breast Cancer Early Detection Program, established by the same statute that created the Breast Cancer Research Program, is one of the important public health programs of the Cancer Detection Section. Dr. Stoodt has worked in a variety of human service, public health, and medical settings throughout her public service career. She has been a social worker in Ohio and Indiana, medical director of family planning and maternity services in South Carolina's Trident Health District, and in North Carolina served as Director of the Division of Adult Health, Chief of Chronic Disease, and Director of the Office of Resource Development and Clinical Support. At local, state and national levels, she has been instrumental in shaping public health initiatives and securing funding to prevent and control chronic diseases as well as to advance women's health. She received her B.S. in music and physical sciences from Indiana University, M.D. from the University of Cincinnati, undertook family medicine training at the Medical University of South Carolina in Charleston, and following training in public health and preventive medicine from the University of North Carolina at Chapel Hill became certified by the American Board of Preventive Medicine. She has held offices and leadership positions in several medical organizations, the Association of State and Territorial Chronic Disease Program Directors, their Women's Health Council, the American Cancer Society, the American Heart Association, and the North Carolina Public Health Association. She was elected into the prestigious Women's Forum of North Carolina, and in 1994 was inducted into the YWCA Academy of Women. Her broad interests focus on strengthening organizational capacities, changing public understanding, and advancing public policies that will improve the public's health.

Summary of Awards

INSTITUTION/PI/TITLE	TAX	DUR	INDIRECT	DIRECT	TOTAL
African American Advisory Committee					
Priscilla Banks					
African American Women and Breast Cancer: What Works?	X	1.5		*Collaborative Award*	
Beckman Research Institute of the City of Hope					
Jennifer Murray					
Regulation of SXR and Drug Resistance in Breast Cancer		2	$0	$42,784	$42,784
California Institute of Technology					
Cheryl Van Buskirk					
Analysis of EGFR Transcript Splicing in C. Elegans		2	$6,400	$80,000	$86,400
California Pacific Medical Center Research Institute					
Shanaz Dairkee					
Infinite Expansion of Breast Tumor Samples in Culture		2	$111,400	$200,000	$311,400
Robert Debs					
Molecular Pathogenesis of Metastatic Breast Cancer		2	$111,400	$200,000	$311,400
Subtotal, CPMCRI			$222,800	$400,000	$622,800
Cedars-Sinai Medical Center					
Shikha Bose					
The Role of PTEN in Progression of Ductal Carcinoma in situ		2	$106,000	$200,000	$306,000
Harbor-UCLA Research and Education Institute					
Rowan Chlebowski					
Weight Loss in Public Hospital Breast Cancer Patients		1.5	$40,941	$100,000	$140,941
Kaiser Foundation Research Institute					
Carol Somkin					
African American Women and Breast Cancer: What Works?	X	1.5	$32,550	$99,505	$132,055

INSTITUTION/PI/TITLE	TAX	DUR	INDIRECT	DIRECT	TOTAL
La Jolla Institute for Molecular Medicine					
Longchuan Chen					
Defining a Role for Endothelial Precursor Cells in Breast		1	$103,094	$96,080	$199,174
Lawrence Berkeley National Laboratory					
Jamie Bascom					
Relating Epimorphin and Progesterone-Mediated Morphogenesis		1	$0	$23,825	$23,825
Albert Davalos					
Does the BLM Gene Co-regulate BRCA1 in DNA Damage Response?		2	$672	$80,000	$80,672
David Gilley					
Studies of Telomere Capping Dysfunction in Breast Cancer		3	$202,975	$300,000	$502,975
Terumi Kohwi-Shigematsu					
Global Gene Regulation by SATB1 in Metastatic Breast Cancer		1	$62,564	$98,949	$161,513
Ana Krtolica					
Aging, Mutations, and Breast Carcinogenesis		3	$1,72,304	$276,580	$448,884
Saira Mian					
Statistical Techniques for Breast Biology and Cancer Research			$340,755	$453,613	$794,368
Carlos Ortiz de Solorzano					
Three-Dimensional Modeling of Breast Cancer Progression		2	$136,328	$200,000	$336,328
Aylin Rizki					
Effect of Breast Cell Environment on Repair of DNA Damage		2	$672	$80,000	$80,672
Christine Hartmann Siantar					
New Imager to Improve Specificity in Breast Cancer Detection		1.5	$113,462	$100,000	$213,462

LBNL continued next page

Summary of Awards

INSTITUTION/PI/TITLE	TAX	DUR	INDIRECT	DIRECT	TOTAL
Lawrence Berkeley National Laboratory continued					
Kai Vetter					
New Imager to Improve Specificity in Breast Cancer Detection		1.5		*Collaborative Award*	
Subtotal for LBNL:			$1,029,732	$1,612,967	$2,642,699
Northern California Cancer Center					
Sally Glaser					
Immune-Function Genes and Race Differences in Breast Cancer		2	$53,397	$149,991	$203,388
Public Health Institute					
Barbara Cohn					
Can Placenta Factors Explain Race Patterns of Breast Cancer?		0.8	$13,021	$73,154	$86,175
Salk Institute for Biological Studies					
Yan Xia					
BRCA-1-dependent Ubiquitin Ligase Activity in Breast Cancer		2	$6,400	$80,000	$86,400
Scripps Research Institute					
Benjamin Cravatt					
Profiling Enzyme Activities in Models of Human Breast Cancer		2	$169,990	$199,518	$369,508
Arul Joseph					
Method to Profile Active Metalloprotoeases in Breast Cancer		2	$6,400	$80,000	$86,400
Beatriz Maroto					
DNA Damage Response Pathways in Breast Cancer Cells		2	$6,400	$80,000	$86,400
Vito Quaranta					
MMP-Directed Synthesis of Invasive Breast Cancer Blockers		1	$62,669	$73,555	$136,224
Subtotal for SRI:			$245,459	$433,073	$678,532

Summary of Awards

INSTITUTION/PI/TITLE	TAX	DUR	INDIRECT	DIRECT	TOTAL
Sidney Kimmel Cancer Center					
Francisco Javier Piedrafita					
Retinoids in Combination Therapies against Breast Cancer		2	$196,800	$200,000	$396,800
Jan Schnitzer					
Identifying Accessible Targets in Human Breast Tumors		1.5	$246,000	$250,000	$496,000
Subtotal for SKCC:			$442,800	$450,000	$892,800
Stanford University					
Steven Artandi					
Understanding Telomere Dynamics in the Breast		3	$252,293	$423,398	$675,691
Karlene Cimprich					
Identifying sources of Genomic Instability in Breast Cancer		1.5	$43,657	$75,000	$118,657
Bradley Ekstrand					
Using Microarrays to Estimate Breast Cancer Risk		2	$6,400	80,000	$86,400
James Ford					
Genetic Alterations in MRI Screen-Detected Breast Lesions		1.5	$57,000	$100,000	$157,000
Stefanie Jeffrey					
Breast Stromal Genes Act as Early Markers of Malignancy	X	3	$142,499	$249,999	$392,498
Patrick Lupardus					
Regulation of the Rad1 Checkpoint Complex in Breast Cancer		2	$0	$60,000	$60,000
Slyvia Plevritis					
Genetic Alterations in MRI Screen-Detected Breast Lesions		1.5		*Collaborative Award*	
Jonathan Pollack					
Locating Novel Breast Cancer Genes using DNA Microarrays		3	$170,926	$299,870	$470,796

Stanford continued next page

INSTITUTION/PI/TITLE	TAX	DUR	INDIRECT	DIRECT	TOTAL
Stanford University continued					
Lynn Westphal					
Chemotherapy-Induced Ovarian Damage: Prevention and Impact		1.5	$30,531	$21,824	$52,355
Subtotal for Stanford University:			$703,306	$1,310,091	$2,013,397
The Burnham Institute					
Kelly Boatright					
Alterations in the Separase/Securin Balance in Breast Cancer		2	$0	$60,000	$60,000
Nathalie Bruey-Sedano					
Cell-Killing Effect of Orphan Receptor TR3 in Breast Cancer		2	$6,400	$80,000	$86,400
Hee Kwang Choi					
Rac/STAT5 Signaling		2	$6,400	$80,000	$86,400
Marcia Dawson					
Novel Retinoids with Enhanced Anti-Breast Tumor Efficacy		2	$184,000	$200,000	$384,000
Kathryn Ely					
A Novel Anti-estrogen Resistance Mechanism in Breast Cancer		1.5	$69,000	$75,000	$144,000
Shi Huang					
Steroid Receptor Coactivators in Mammary Gland Development		2	$195,020	$185,220	$380,240
Lynn Knowles					
Fatty Acid Synthase and Breast Cancer		2	$6,400	$80,000	$86,400
Sergei Malkhosyan					
Cloning of the X Chromosome's Putative Tumor Suppressor Gene		2	$147,000	$141,000	$288,000
Francesca Marassi					
Structure and Function of the Bax Apoptosis Regulator		2	$147,000	$141,000	$288,000

TBI continued next page

INSTITUTION/PI/TITLE	TAX	DUR	INDIRECT	DIRECT	TOTAL
The Burnham Institute continued					
John Reed					
PPAR Modulators as Apoptosis		2	$222,991	$242,382	$465,373
Xiao-Kun Zhang					
TR3-based Peptides for Apoptosis in Breast Cancer		2	$184,000	$200,000	$384,000
Subtotal for TBI			$1,168,211	$1,484,602	$2,652,813
University of California, Berkeley					
Satyabrata Nandi					
Breast Cancer Prevention with Estrogen		3	$0	$812,340	$812,340
University of California, Davis					
Gerald DeNardo					
New Imager to Improve Specificity in Breast Cancer Detection		1.5		*Collaborative Award*	
Navdeep Dhillon					
Cyclin E Affects Growth Arrest in Breast Cancer Cells		2	$0	$50,386	$50,386
Martin Privalsky					
Regulation of Estrogen Response by Corepressors		2	$0	$149,942	$149,942
Subtotal for UC Davis:			$0	$200,328	$200,328
University of California, Irvine					
Catherine Blake					
Using Scientific Text to Identify Breast Cancer Risk Factors		1	$0	$29,136	$29,136
Michael Samoszuk					
Clotting Breast Cancer		1	$0	$98,986	$98,986
Subtotal for UC Irvine:			$0	$128,122	$128,122
University of California, Los Angeles					
Carolyn Crandall					
Impact of Breast Cancer and its Therapy on Bone Density		3	$0	$300,000	$300,000

UCLA continued next page

INSTITUTION/PI/TITLE	TAX	DUR	INDIRECT	DIRECT	TOTAL
University of California, Los Angeles continued					
Jill Mitchell					
Constructed Meaning and Stress in Breast Cancer Experience		2	$0	$64,087	$64,087
Cindy Wilson					
The Importance of Growth Inhibitory Signals in Normal Breast		2	$0	$150,000	$150,000
Total for UCLA:			$0	$514,087	$514,087
University of California, San Diego					
Gerry Boss					
Prognostic Value of Ras Activation in Breast Cancer		*3*		*Collaborative Award*	
Anne Wallace					
Prognostic Value of Ras Activation in Breast Cancer		3	$0	$499,796	$499,796
Total for UC San Diego:			$0	$499,796	$499,796
University of California, San Francisco					
Christine Case Lo					
Drug Dose Tailoring Based on Patient-Specific Factors		2	$0	$50,572	$50,572
Aubri Charboneau					
HOX Transcriptional Regulation of Angiogenesis		2	$0	$80,000	$80,000
Nicola Clegg					
Novel Ligands as Probes of Estrogen Receptor Signaling		2	$0	$50,941	$50,941
Colin Collins					
The Detailed Structure of a Model Breast Cancer Genome		2	$0	$194,840	$194,840
Steven Cummings					
Compositional Breast Density as a Risk Factor		1.5		*Collaborative Award*	

UCSF continued next page

Summary of Awards

INSTITUTION/PI/TITLE	TAX	DUR	INDIRECT	DIRECT	TOTAL
University of California, San Francisco continued					
Mikala Egeblad					
The Role of Matrix Metalloproteinase 13 in Breast Cancer		2	$0	$80,000	$80,000
Karla Kerlikowske					
Compositional Breast Density as a Risk Factor		1.5	$0	$100,000	$100,000
Dale Leitman					
Identification and Prognostic Value of ERß in Breast Cancer		2	$0	$150,000	$150,000
Richard Price, Jr.					
Targeting Estrogen Receptors to Mouse Mammary Epithelium		2	$0	$80,000	$80,000
Hope Rugo					
Chemotherapy-Induced Ovarian Damage: Prevention and Impact		1.5	$0	$82,479	$82,479
John Shepherd					
Compositional Breast Density as a Risk Factor		1.5		*Collaborative Award*	
Thea Tlsty					
Breast Stromal Genes Act as Early markers of Malignancy	X	3	$0	249,999	$249,999
Jack Youngren					
Potential New Drug Therapy for Breast Cancer		2	$0	$199,848	$199,848
Subtotal for UCSF:			$0	$1,318,679	$1,318,679
University of Southern California					
Elizabeth Lillie					
The Androgen Receptor and Mammographic Density		2	$0	$59,998	$59,998

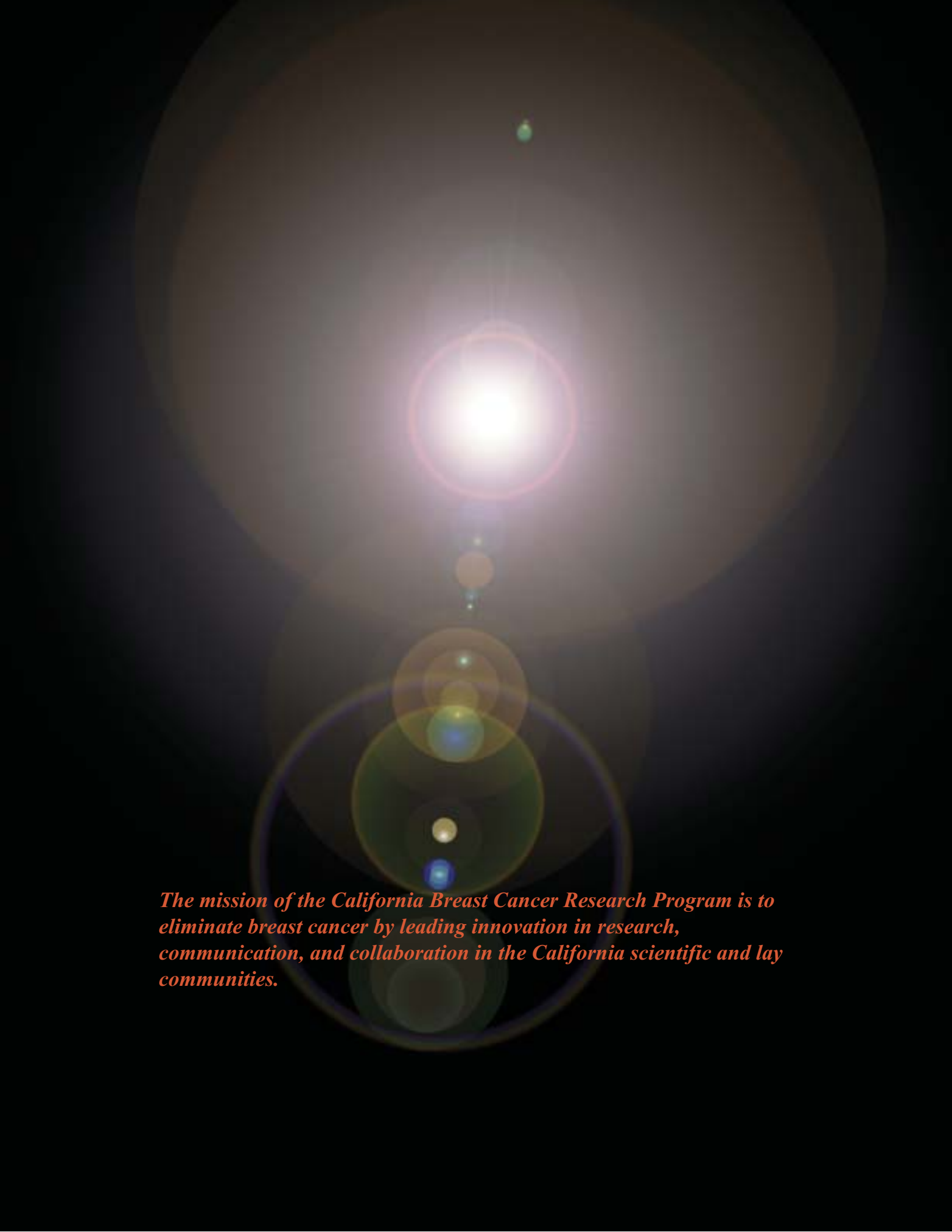
USC continued next page

Summary of Awards

INSTITUTION/PI/TITLE	TAX	DUR	INDIRECT	DIRECT	TOTAL
University of Southern California continued					
Malcolm Pike					
Fiber, Estrogen and Breast Cancer in Mexican American Women	X	1.5	$61,422	$98,275	$159,697
Ronald Ross					
USC/NCCC Breast Cancer Research Training Program		3	$19,978	$249,720	$269,698
Wei Wang					
Androgen Receptor Gene and PSA Gene in Breast Cancer Risk		2	$0	$60,000	$60,000
Subtotal for USC:			$81,400	$467,993	$549,393
Young Moms with Breast Cancer					
Lucy Berlin					
Chemotherapy-Induced Ovarian Damage: Prevention and Impact		1.5		*Collaborative Award*	
Total Awards:			*$4,255,511*	*$10,553,592*	*$14,809,103*
SUPPLEMENTS:					
University of California, Irvine					
Sora Tanjasiri					
A Network-Based Intervention for Chamorros in Southern CA	X	3			$19,900
Stanford University					
David Spiegel					
Does a Peer Navigator Improve Quality of Life at Diagnosis?	X	3		*Collaborative Supplement*	
WomenCARE					
Caroline Bliss-Isberg					
Does a Peer Navigator Improve Quality of Life at Diagnosis?	X	3			$20,000
University of California, Los Angeles					
Rose Maly					
Determinants of Breast Cancer Treatment in the Underserved	X	3			$40,000

UCLA continued next page

INSTITUTION/PI/TITLE	TAX	DUR	INDIRECT	DIRECT	TOTAL
SUPPLEMENTS:					
University of California, Los Angeles continued					
Katherine Kahn					
The Impact of Structure on Quality of Breast Cancer Care	X	3			$40,000
University of Southern California					
Michael Press					
HER-s/neu Gene Variations and Breast Cancer Risk	X	3			$40,000
University of California, Davis					
Colleen Sweeney					
Pathway-Specific Gene Expression in Breast Cancer Cells	X				$40,000
Total Supplements:					*$199,900*



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

California Breast Cancer Research Program
University of California, Office of the President
300 Lakeside Drive, 6th Floor
Oakland, CA 94612-3550
Toll-Free: 1 888-313-BCRP (2277)
Phone: (510) 987-9884
Fax: (510) 587-6325
Email: cbcrp@ucop.edu
Web: www.cbcrp.org

Printed on Recycled Chlorine-Free Paper Using Soy Based Ink