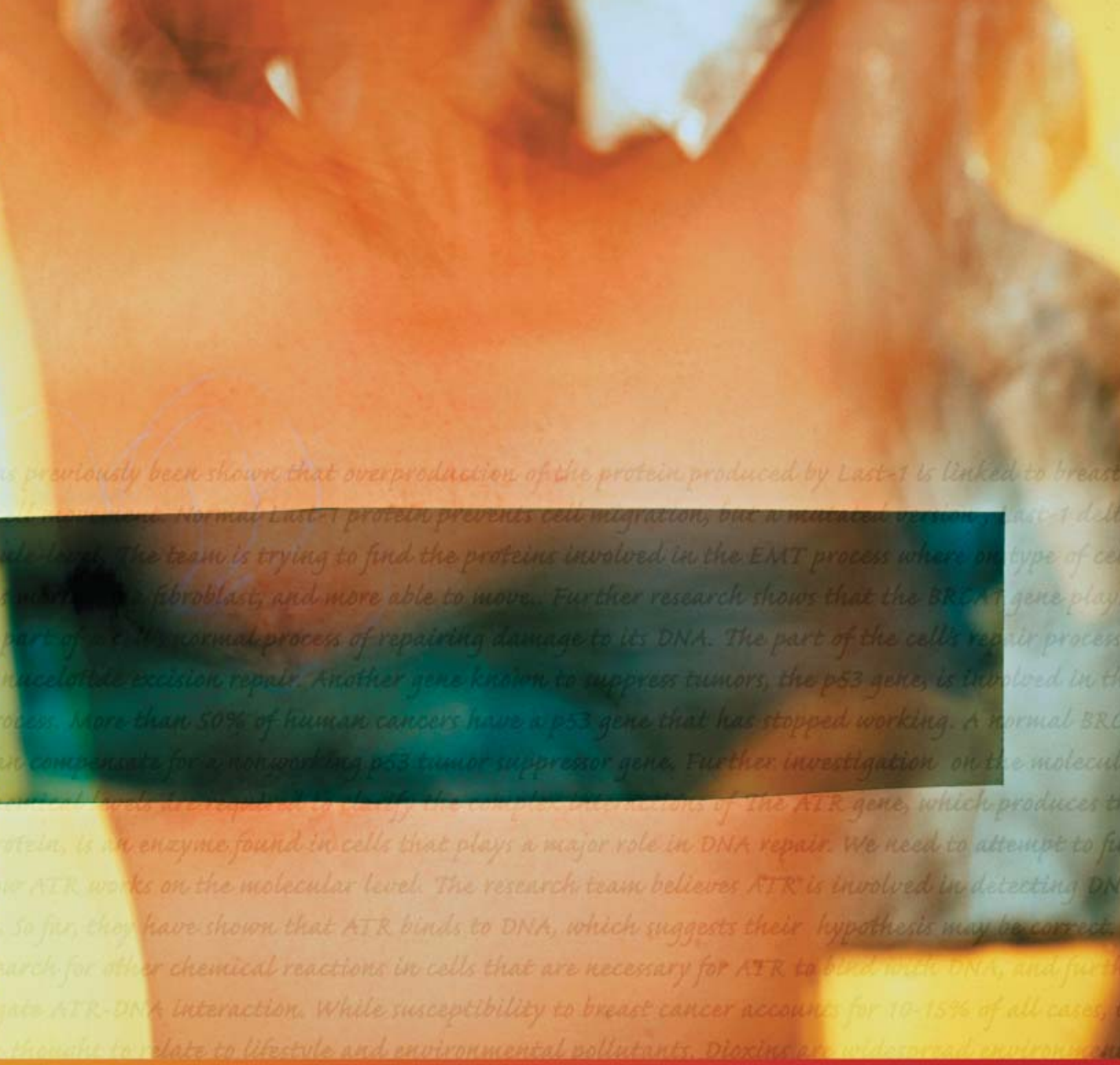

Advances 2004

Advances in Breast Cancer Research

CALIFORNIA
Breast Cancer
Research Program

ABOUT THE COVER:

Kit Morris, the photographer of the cover image, is also a local breast cancer survivor. Two years after her surgery and treatment, Ms. Morris, 43, continues to have a very good prognosis.

Recently she participated in ART.RAGE.US, a book and exhibition by survivors of the disease. "The work in ART.RAGE.US was a departure for me," she says. "I cut up the film, reconfigured the pieces, and glued them back together again. Only afterward did I realize that this work parallels my cancer treatment; film like the body is fragile yet durable. I came to an understanding of this disease through the visual therapy of making photographs. It was my way of talking it out."

Ms. Morris' work can also be seen on her Web site at: www.kitmorris.com and in "Transplanting a Miracle", an international traveling exhibition documenting the lives of organ transplant recipients. The show was developed by Roche Laboratories with the National Kidney Foundation to increase public awareness for organ donation.

Research Highlights

After breast cancer surgery, low-income women and Latina women return to work more quickly than other groups of women. They also experience more pain, swelling, depression, and fatigue. See "Return to Work after Breast Cancer Surgery," page 37.

Women who exercise may be less likely to have their breast cancer recur than those who exercise little or not at all. See "Exercise and Risk of Breast Cancer Recurrence," page 51.

A gene may play a role in determining whether hormone replacement therapy raises a woman's risk for breast cancer. See "The Androgen Receptor and Mammographic Density," page 53.

A compound extracted from red wine stopped the growth of tumor cells in laboratory cultures. See "Breast Cancer Prevention with Phytoestrogens from Grape Juice," page 55.

In experiments with rats, a vaccine designed to stimulate the immune system to stop breast cancer from recurring is showing promise. See "A New Genetic Vaccine Therapy for Breast Cancer," page 89.

Researchers have developed a protein fragment that attaches itself to breast tumor vessels, but not normal blood vessels. It could eventually be used to deliver chemotherapy directly to tumors, bypassing normal tissues and causing fewer toxic side effects. See "Blood Vessel Markers in Breast Cancer," page 90.

A breath test could pinpoint the chemotherapy dose that will give an individual breast cancer patient the most therapeutic benefit with the fewest side effects. See "A Patient Decision Support Framework for Breast Cancer," page 94.

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"The need is urgent. Breast cancer is the biggest threat to the lives of our state's young and middle-aged women. More than 200,000 California women are living with the disease. While some women face a higher than average risk, no woman is free from risk."

Message from the Director

Welcome to the California Breast Cancer Research Program's 2004 Annual Report, marking our tenth anniversary year. This report is part of our wide-ranging efforts to make our research available to the public. On these pages, you will find brief summaries of the studies we funded during 2003, along with summaries of studies we funded in previous years that were completed or made progress during 2003. We are one of the few research programs in the world to publish annual reports of studies while they are in progress.

During 2003, we awarded $11,571,451 for 50 single- and multiple-year research projects and 3 supplement awards at 25 California institutions. Since 1995, we've provided a total of $142,330,413 in research funds.

The need is urgent. Breast cancer is the biggest threat to the lives of our state's young and middle-aged women. More than 200,000 California women are living with the disease. While some women face a higher than average risk, no woman is free from risk. And every woman who has had breast cancer knows 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 makes our Community Partners Program, now in its second year, all the more important. Through this program, Californians can make financial contributions to support our revolutionary breast cancer research. "Community Support for Breast Cancer Research," page 14, tells about how Californians are coming together to help end breast cancer.

In this tenth anniversary year, the CBCRP is celebrating a decade of progress. We have become the fourth largest funder of breast cancer in the world. As we look ahead, we confront a great challenge: to make sure the coming decade brings progress against this disease—more, faster, and better.

The purpose of all our investment in research is to eliminate breast cancer from the lives of women who are suffering and dying from it now—and from the lives of all women.

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

Thanks, California Taxpayers!

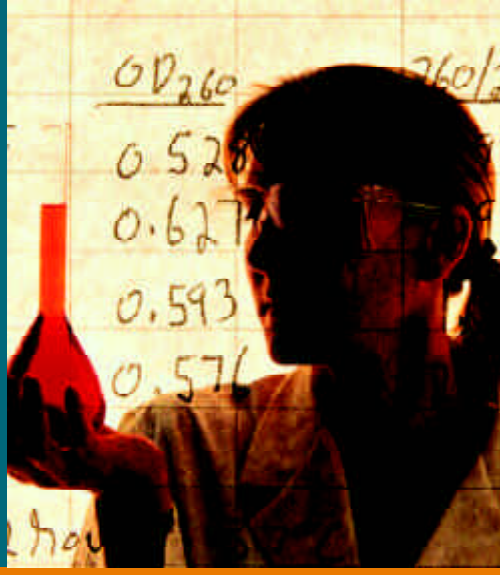
Every year, thousands of Californians participate in Check It Out! Check It Off!, the public education campaign that encourages voluntary donations on Franchise Tax Board Form 540.

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, 58,570 taxpayers donated $646,664 on their state income taxes.

Thanks, California taxpayers!

About the California Breast Cancer Research Program



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 job of 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 portion of a state tax on tobacco, a voluntary contribution box on state income tax forms, and support from individuals, corporations, and other foundations.

In 2003, we awarded $11,571,451 for 50 single- and multiple-year grants and 3 supplement awards at 25 leading research institutions throughout California to investigate ideas that otherwise might not be explored. Since 1995, we have provided a total of $142,330,413 for more than 550 grants to over 60 California research institutions.

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, demanding, trial-and-error science and for people who are working tirelessly 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.

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

CBCRP Structure: Encouraging Public Input

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.

Our Key Strategies

- *Support the best, most innovative research*
- *Build the research talent pool by training new researchers*
- *Encourage creativity by financing collaboration across research fields*
- *Widely distribute research results to scientists, health care professionals, and the public*

CBCRP Listens

The CBCRP invites you to tell us what you consider most important about the job we do and what might best accomplish our mission. We are most interested in your feedback on:

- What do you believe are the most urgent and unanswered questions about breast cancer?
- What do you consider to be the greatest opportunities for making an impact on the burden of breast cancer in California?

We also welcome your feedback on this publication or any other aspect of our work you'd like to comment on. You can reach us by mail (see the back cover of this Annual Report for the address) or through our Web site (www.cbcrp.org). Thank you!

What They're Saying About the CBCRP

Fabulous

"People who lead are those who say, 'There's got to be a better way,' and then they find a way to make it happen. And that's what the California Breast Cancer Research Program is all about. Texas doesn't have anything like this. I think it's fabulous, and it gives me something to work toward in our state."

— Sarah Weddington, J.D.
Litigator, *Roe vs. Wade* case
Former Special Assistant to the President of the United States
Author, *A Question of Choice*
Recent breast cancer survivor
Austin, Texas

Incredible

"This is an incredible program. Every research program should make it as clear to the public how they spend their money as this one does."

—Ana Teresa Garcia
Eleven-year survivor of metastatic breast cancer
Team Leader, National Breast Cancer Coalition
Hawi, Hawaii

Opening the Door

"What I like most about the California Breast Cancer Research Program is that they encourage researchers to apply in areas that have been difficult to research. The CBCRP is opening the door to a research area about which we know very little—advanced breast cancer and why women from some ethnic and socioeconomic groups die disproportionately. I have a lot of admiration for the thoughtful way in which this program is administered."

—Musa Mayer
Survivor and Patient Advocate
Author, *After Breast Cancer: Answers to the Questions You're Afraid to Ask*
New York, New York

Visionary

"In California, you have taken a visionary approach to the funding of breast cancer research, and I applaud you for that."

—Julia Brody, Ph.D.
Executive Director
Silent Spring Institute
Newton, Massachusetts

"This is an incredible program. Every research program should make it as clear to the public how they spend their money as this one does."

No Better Place

"The CBCRP is almost too good to be true. It is wisely and efficiently administered by an amazing team of grant administrators whose depth of knowledge and interpersonal skills elicit the very best from applicants. The CBCRP casts a wide net to fund both established and new investigators in both academic and community settings. As opposed to most other funding agencies, there is an open-mindedness and helpfulness which leaves applicants feeling that their proposals are given the best chance to receive an excellent scientific review and the best chance of funding. This is not just 'nice'. The effect is that creative ideas surface, ideas that would not have a chance with the more traditional agencies, and ideas which hold the hope of finding an innovative way to reduce the impact of this disease. The best and brightest of the new investigators in particular are encouraged to build a career around the quest to eliminate breast cancer. There is no better place for a donation of money for breast cancer research, and there is no other organization that can stretch a dollar as well toward programs supported by academic researchers and advocates alike."

— Ellen Mahoney, M.D., F.A.C.S.

Breast Surgeon, Activist
Arcata, California
and Clinical Assistant Professor of Surgery
Stanford University
Stanford, California

I Love the Blend

"I love the blend of researchers with advocates at the California Breast Cancer Research Program's Symposium. I love that it lasts three days so we can interact, reflect on what people said, and later discuss our ideas and hunches."

— Karen Folger Jacobs, Ph.D.
Filmmaker, *Breast Cancerland*
Breast cancer survivor
Berkeley, California

"The CBCRP is almost too good to be true. It is wisely and efficiently administered by an amazing team of grant administrators whose depth of knowledge and interpersonal skills elicit the very best from applicants."

An Effective Model

"Perhaps no other program has so effectively modeled bringing the university into contact with the people who count, that is, the patients and their families."

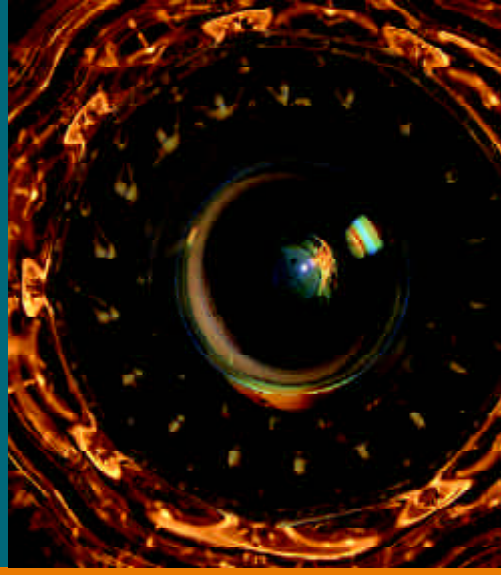
— Cornelius Hopper, M.D.
Vice President for Health Affairs, Emeritus
University of California
Oakland, California

Forward Looking, Collaborative, Uniquely Situated

"The CBCRP is unique in three ways: First, it is forward looking. This is a time when most funding agencies are saying, 'Why? Why should we fund this?' Instead, the CBCRP says 'Why not? Why not fund innovative work?' Second, it is collaborative, the only funding agency that truly rewards and promotes active research that includes community based advocacy groups and leading scientists in basic sciences and epidemiology. Third, it is uniquely situated. California is a state where all of the basic problems in breast cancer research converge: disparities in access to health care, racial and geographic inequalities, exposure to a variety urban and agricultural environmental chemicals, and a huge population base with which to work. The CBCRP is a paradigm of how breast cancer research should be conducted: if anyone can make it work, the CBCRP can.

— Robert C. Millikan, M.P.H., Ph.D.
Associate Professor of Epidemiology
School of Public Health
University of North Carolina
Chapel Hill, North Carolina

The CBCRP and CBCRP-funded Research in the Media



Alcohol Main Risk Factor in High Marin County Breast Cancer Rate

SAN FRANCISCO—The biggest difference between Marin County women with breast cancer and their neighbors without the disease is the amount of alcohol they consume—with the heaviest drinkers raising their risk almost fourfold, researchers report. The length of time spent living in the county had no bearing on their likelihood of developing the disease. That suggests that a mysterious toxin in the air, water, or soil in Marin County is not a likely cause for the area's high breast cancer rate, according to Margaret Wrensch, professor of epidemiology at UCSF and lead author of the study.

— From a May 6, 2003, article in the *San Francisco Chronicle*; coverage of this study also appeared in the May 9 *Los Angeles Times* and the May 8 *Contra Costa Times*

Cancer Linked to Hormone Therapy on the Rise

SAN FRANCISCO—A type of breast cancer associated with the use of combination hormone replacement therapy appears to be on the rise and may account for some or all of the increasing incidence of the disease nationwide, a new study suggests.

Invasive lobular breast cancer, which begins in the chambers that house milk-producing cells, increased 65 percent from 1987 to 1999, the study says, In contrast, the incidence of invasive ductal breast cancer, the most common type, remained largely unchanged.

"The implication of this study is that we should be paying a lot more attention to lobular carcinoma because it may provide really important clues," said Dr. Marion Kavanaugh-Lynch, director of the California Breast Cancer Research Program. "Clearly, something is changing here and when something is changing, it gives you an opportunity to look at causes and mechanisms."

— From a March 19, 2003, article in the *San Francisco Chronicle*

Green Tea Component Shows Cancer-combating Abilities

The potential health benefits of drinking green tea are varied, ranging from preventing bad breath to protecting your heart. Recent studies have also suggested that a topical cream based on the beverage may help fend off skin cancer. Findings presented yesterday at a meeting of the American Association for Cancer Research indicate that components of green tea could be effective at fighting other types of cancer, too.

Nurulain Zaveri of SRI International in Menlo Park, Calif., and her colleagues synthesized compounds similar to a component in green tea, EGCG, that has

been associated with reduced risk of myriad types of cancer in humans. They manufactured two molecules similar to EGCG. One, dubbed SR 13196, is better at slowing the proliferation of breast cancer cell lines than regular EGCG, whereas SR 13193 inhibits the growth factor protein VEGF in cancerous cells, the scientists found. "These analogs are not only valuable tools to clarify how green tea may fight cancer," Zaveri notes, "but are also potential chemopreventive drug candidates themselves, with perhaps better pharmakinetic properties than have been seen with EGCG thus far."

— From the October 29, 2003, edition of *Scientific American*

Wine May Fight Breast Cancer

HEALTHDAY—Red wine might do more than reduce the risk of heart disease. The grape skin and seeds appear to hold a natural cancer-fighting chemical. Scientists at City of Hope Cancer Center in Los Angeles isolated a phytochemical, called procyanidin B dimer, that when given to mice with breast cancer reduced the size of their tumors.

While there are already drugs on the market that can control estrogen-dependent breast cancer development in post-menopausal women, this is the first naturally occurring phytochemical that appears to have the same effect, says study author Shiuan Chen.

Chen, director of surgical research at City of Hope, says natural phytochemicals are more likely to be used in a preventive way than as treatment because existing drugs are far stronger. "By having this in the diet, one can keep the estrogen at a lower level, which can be preventive for breast cancer," he says.

— From an article in the December 8, 2003, issue of *The Olympian* (Olympia, Washington). This article was also released by the online news service HealthDay News.

Study Verifies Id-1 Gene as Target for Breast Cancer Gene Therapy

SAN FRANCISCO—A landmark study published in the November 11, 2003, issue of the *Proceedings of the National Academy of Sciences* shows that curtailing the function of a gene called Id-1 blocks the spread of metastatic cancerous tumors.

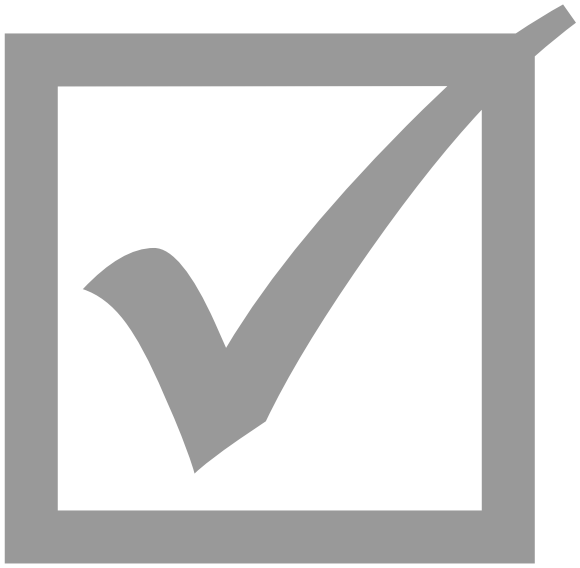
"Our preclinical study with mice confirms that Id-1 gene therapy suppresses the spread of cancer and blocks metastasis," said Pierre-Yves Deprez of the California Pacific Medical Center Research Institute, the lead author of the study.

What does this mean for human cancer patients? According to Deprez, "as soon as the same methodology is applicable to humans, the Id-1 gene could represent a highly promising target for breast cancer patients with invasive or metastatic cancer."

— From a November 28, 2003, article in *Drug Week* via NewsRX.com

Check it Out, Check it Off

Invest in a cure for breast cancer. Check off tax line 57.



California taxpayers can join the battle against breast cancer by making a contribution on their state income tax forms.

Typical cancer research funding agencies won't support research that goes in unusual directions, but the California Breast Cancer Research Program funds research that explores new approaches, like Tibetan herbs, green tea, and snake venom, to find out how to stop breast cancer.

Contributions made on the state income tax form are automatically deductible, and 95 percent of the donation goes directly to research and education.

Today's research could lead to discoveries that help save the lives of more than 4,000 California women who die of breast cancer each year.

CALIFORNIA
Breast
Cancer
Research
PROGRAM

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.

Community Support for Breast Cancer Research

Our primary funding source is a tax on tobacco products, and the revenue goes down every year. That's why California citizens—individually and in groups—are coming together to provide more funds for our groundbreaking research.

California citizens now have a 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; however, 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.

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 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.

A Strong Public Response for 2003

During 2003, we launched new activities to make progress toward the twin goals of the Community Partners Program: increasing public awareness of the CBCRP and increasing voluntary donations through the Income Tax Check-Off Program and new sources.

- The CBCRP became a participant organization in the Community Campaign of the United Way of the Bay Area, opening the way for residents of seven counties to make donations at their place of work.
- To encourage donations, we held rallies and outreach events with CBCRP representatives at work sites.
- The *San Francisco Chronicle* Cause to Run, a 5K race held in July, made the CBCRP a beneficiary.
- The Golden State Warriors professional basketball team featured the CBCRP at a game, providing visibility for the CBCRP and encouraging fans to contribute on their state income tax returns. Both the men's and women's basketball teams at UC Berkeley held similar events at one of each team's games.
- To encourage contributions from the public, the CBCRP provided bus shelter ads and radio, TV, and newspaper public service announcements.
- We added an online contribution opportunity to the CBCRP Web site.
- The California Endowment—a private, statewide health foundation—awarded the CBCRP a grant to help us increase breast cancer research conducted by collaborations between community groups and scientists.

Community Partners Executive Team

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. The Community Partners Executive Team spearheads our outreach and fundraising efforts.

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

Ron Burkle: Managing Partner, Yucaipa Companies, Los Angeles

Sharon Davis: Former First Lady of California, Sacramento

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

Linda Griego: President, Griego Enterprises, Inc., Los Angeles

Judith H. Guggenheim: Philanthropist and Volunteer, San Francisco

Barbara Hopper: Realtor, Prudential California Realty, Berkeley

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

Jan Levine: Attorney, Folger, Feldman, Oster, Ringler & Klevine, Santa Monica

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: Physician and breast cancer survivor, San Mateo

Steve Soboroff: President, Playa Vista, Los Angeles

In October 2003, Executive Team founding member, Faith Fancher, lost her life to breast cancer. Faith Fancher was an Emmy award-winning journalist and news reporter for KTVU (Oakland). As an Executive Team member, Faith spearheaded fundraising and outreach efforts for the Program; she also was the keynote speaker at the 2002 Symposium, where she presented "My Journey through Breast Cancer: A Story of Faith".

Since her original diagnosis in 1997, Faith survived multiple recurrences of the disease and devoted much of her life to raising awareness about breast cancer detection and treatment. She participated in clinical trials and several advocacy efforts, and founded "Friends of Faith", an organization that provides small grants to local organizations that fight breast cancer.

In tribute to Faith's energy and passion, and to commemorate all that she did for breast cancer education and research, the CBCRP has created an annual Faith Fancher Research award, which will be given each July to a researcher, institution, or community-based organization whose work reflects those values that Faith held most closely. This award will fund a breast cancer research project in our portfolio that will extend Faith's work, such as a Community Research Collaboration award or a project in our Racial and Ethnic Differences portfolio, one of our high priority funding issues. The first Faith Fancher Research award will be presented in 2004.

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.

Community Partners Contact Information

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

A major piece of good news is that since 1988, the death rate has been dropping. However, the rate at which California women get the disease is still climbing.

Breast Cancer in California

Each year, breast cancer strikes more than 25,000 California women and kills more than 4,000.

The California Cancer Registry, a state government program, recently conducted research on its database of information covering every case of breast cancer in California through the year 1999.

This research provides the most complete and current picture available of breast cancer's effect on the lives of the women of our state. The picture that emerges is mixed. There is both good news and troubling news.

Death Rate Down

A major piece of good news is that since 1988, the death rate has been dropping. Although the actual number of deaths has gone down only slightly, from 4,121 in 1988 to 4,039 in 1999 (with a high of 4,404 in 1994), because California's population continues to grow, the *rate* of death has gone down more steeply. In 1988, there were about 32 breast cancer deaths per 100,000 California women. In 1999, the number had dropped to 24.5.

The death rate has dropped more among women from some California ethnic groups than among others. The overall drop is mostly due to a lower death rate among white women. The 1988 death rate for white women was 35.6 per 100,000. In 1999, it was 26.8 per 100,000.

In 1988, the group with the highest death rate was African American women, with 39.9 deaths per 100,000. By 1999, the number was down to 31.8 per 100,000, but this was still the highest of any ethnic group in the state. African American women under age 50 have a death rate double that of other women in the same age bracket.

In 1988, the ethnic group with the lowest breast cancer death rate was Asian/Pacific Islander women, at 12.6 deaths per 100,000. In 1999, the figure was still the lowest of any ethnic group, at 13.7 deaths per 100,000, but this is also the only group with a rising death rate.

The 1988 death rate for Hispanic women was 20.8 per 100,000. In 1999, it had dropped to 17 per 100,000.

More California Women Getting Breast Cancer

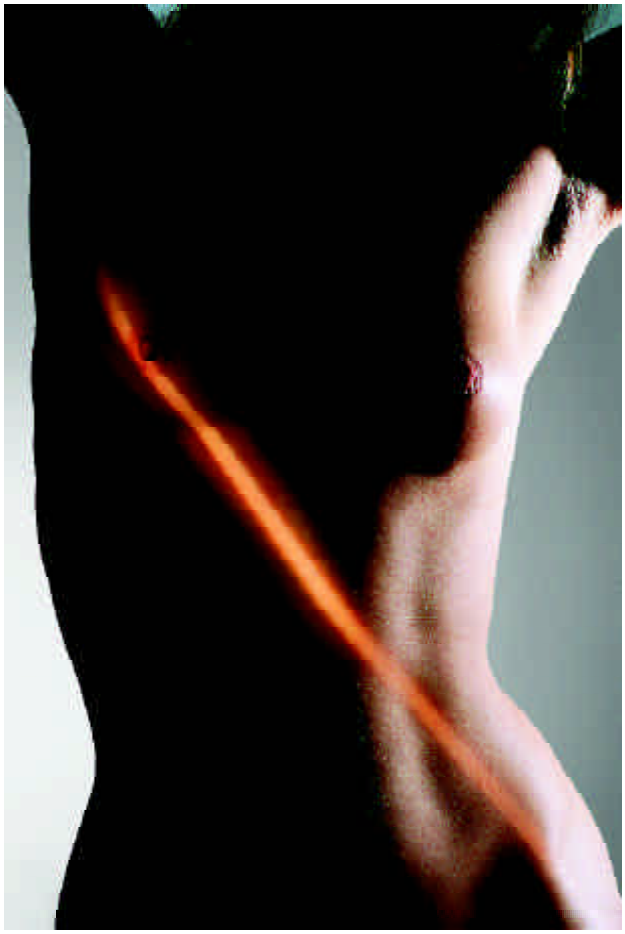
Although the death rate is down, the rate at which California women get breast cancer is still climbing.

Each year, more California women are diagnosed with invasive breast cancer, the type of breast cancer that can spread to other body parts and lead to death. In 1973, about 115 California women per 100,000 were diagnosed with invasive breast cancer. By 1999, the number had gone up to approximately 143.

White women have the highest rate, followed by African American women. Hispanic and Asian/Pacific Islander women have lower rates. Although the risk of getting breast cancer is higher for older women, 55 percent of all California women who get breast cancer are younger than 65 when they are first diagnosed, and 10 percent are under age 50.

More Women Having Mammograms

Researchers believe one reason for the rise in the number of breast cancer cases is that more tumors are being discovered through detection. Many more California women are having mammograms, and they are having them more often. This trend started 15 years ago. In 1987, only 38 percent of California women had had a mammogram during the previous two years. By 2000, the number had risen to 79 percent.



Sharp Rise in *In Situ* Breast Cancer

The increase in mammogram use has also led to more California women being diagnosed with *in situ* breast cancer, a localized tumor that may not spread to other parts of the body and is diagnosed almost exclusively by mammography. In 1973, there were only about six cases of *in situ* breast cancer diagnosed per 100,000 California women. By 1999, there were approximately 32. Over time, some cases of *in situ* cancer will turn into invasive breast cancer. Others will remain harmless. There's currently no way to tell which *in situ* cancers will later cause harm, so physicians treat them all as potentially dangerous.

This means it is likely that screening large numbers of women with mammograms is leading to many women being treated for tumors that would never have caused them any trouble. Yet these women are receiving treatments that cause discomfort and stress, and may also later affect their health.

Fewer Women Losing a Breast

Although more women are being diagnosed with breast cancer, fewer are losing an entire breast. More California women are being treated with breast conserving surgery, instead of with a mastectomy. In 1988, 32 percent of California women with early stage breast cancer had breast conserving surgery. By 1999, the percentage had more than doubled, to 66 percent.

This is an important advance in breast cancer therapy, because breast conserving surgery offers most women the same odds of survival as a mastectomy, while a mastectomy is more disfiguring and can have painful aftereffects.

Too Many Women Still Diagnosed After Their Tumors Have Spread

The widespread use of mammograms was supposed to reduce the number of women who are diagnosed after their tumors have spread beyond their original sites, when treatment is less effective. But the steep rise in mammogram use has led to only slight progress. Each year over 7,500 women in California are being diagnosed with breast cancer that has spread.

Detecting breast cancer before it spreads makes a difference in survival. When breast cancer is detected and treated before it has had a chance to spread, 95 percent of the women who have it are still alive after ten years. When the cancer is detected and treated after it has spread to other parts of the body, only 16 percent of the women survive ten years.

In 1999, the rate at which California women were diagnosed after their breast cancer had spread to nearby tissue or lymph nodes—41 per 100,000—was only a slight improvement over the 1988 rate, 43 per 100,000. In 1988, six California women per 100,000 were diagnosed after their breast cancer had spread to other parts of their bodies. In 1999, the rate had dropped a little, to five per 100,000.

African American women have the highest rate of any California ethnic group for being diagnosed after the tumor has already spread. However between 1988 and 1999 the rate at which African American women were diagnosed at the most dangerous stage, where the tumor has spread to other locations in the body, dropped by almost half.

The rate at which Hispanic women are diagnosed at a dangerous, late stage of breast cancer was lower than that of white or African American women in 1988. It also dropped a little between 1988 and 1999.

White women in California are more likely to be diagnosed with breast cancer than any other ethnic group. They also have high rates for being diagnosed with tumors that have already spread, and these rates dropped only slightly between 1988 and 1999.

Asian/Pacific Islander women are the least likely to get breast cancer among California ethnic groups. However, their rates for the more dangerous breast cancers—those that have spread—which were already low in 1988, did not drop between that year and 1999.

Improvements in detecting breast cancer before it has had chance to spread—including new technology and new methods such as blood tests—are still needed.

Other Facts

The Cancer Registry's research revealed some additional facts about breast cancer in our state:

- **Breast cancer rates vary by county**. Imperial County has the lowest rate; Marin County has the highest.
- **California women who have higher incomes, more years of education, and white-collar jobs get breast cancer more often**. Those with lower incomes, fewer years of education, and blue-collar jobs get breast cancer less often. The gap varies by ethnic group. The one-fifth of African American women with the highest income and most education get breast cancer 22 percent more often than the one-fifth of African American women with the lowest income and least education. But the one-fifth of Hispanic women with the highest income and most education get breast cancer 83 percent more often than the one-fifth of Hispanic women with the lowest income and least education. The differences for Asian/Pacific Islander women and white women at different income levels fall between these extremes.
- Among California women, and women nationwide, **cancer is slightly more common in the left breast than in the right**. Scientists have not been able to figure out why this is so, but it is true for women from all ethnic groups and all age groups, and also true regardless of how far the disease has progressed when it is detected.

- **The most common place on the breast for a California woman to have a tumor is the upper, outer quadrant,** where 36 percent of tumors are found. The pattern of where tumors are found is very similar for women from all ethnic groups and all ages.

More Research Needed

Breast cancer impacts all California women and their families. There are few ways an individual woman can cut down her chances of getting breast cancer, and none are proven to completely prevent it. Treatments can still cause pain, hardship, and loss of future health.

We still need to find ways to prevent breast cancer and treatments that will guarantee that women who have it will survive. Much more research needs to be done.

Note: The information in this section is based on ***Breast Cancer in California: A Closer Look,*** a booklet the CBCRP published in 2004, which is available to the public at no charge. You can order it by calling 888 313-2277, and it can also be downloaded free at our Web site, www.cbcrp.org/publications/whitepapers/. A longer scientific report, *Breast Cancer in California,* on which this booklet is based, is available from the California Cancer Registry; it can be downloaded free at the Registry's Web site at www.ccrcal.org.

We're making the search for environmental causes of breast cancer a high priority because women whose lives have been affected by the disease have urged us to do so.

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 CBCRP's Breast Cancer Research Council and staff set the priorities for research funding. These priorities, which we review yearly, are based on the Council's judgment of what critical research the CBCRP can add to move most rapidly toward the prevention and cure of breast cancer.

Extra Efforts to Encourage Research in Areas that Need More Study

We encourage research in new directions in several ways. One is by identifying areas that need more research and funding these areas first. The CBCRP first funds proposals in the areas of Etiology; Health Policy and Health Services; Racial and Ethnic Differences in Breast Cancer; Sociocultural, Behavioral, and Psychological Issues; Prevention and Risk Reduction; and Biology of the Normal Breast. After all the research proposals meeting the CBCRP's high standards for scientific merit and innovation in these areas are funded, the remaining funds are used to make grants for studies in more widely researched areas. These include Earlier Detection, Innovative Treatments, and Pathogenesis.

We decided to fund some areas first because in past years, even when we made under-researched areas a priority, scientists did not submit enough promising proposals for research in these areas. We first used this system for allocating our research funds during 2002. The effort was successful, and even more successful in 2003. For 2003, we received many more proposals that met our high standards in the areas we've identified as under-researched. The six under-researched areas we funded first during 2003 received 69 percent of the research funds we granted for the year.

A New Emphasis for 2003: Environmental Causes of Breast Cancer

During 2003, the CBCRP emphasized two of our high-priority research areas—Etiology and Prevention, with an emphasis on the environmental causes of breast cancer and their effects on different communities of California women. We're making the search for environmental causes of the disease a high priority because women whose lives have been affected by breast cancer have urged us to do so. The topic has been on the CBCRP's list of research topics to be funded since our founding; however, we have received few proposals in

this area. By making it one of the CBCRP's highest priorities, we hope to inspire more scientists to pursue this line of research.

California is an ideal laboratory for research into the environment-breast cancer connection. The state has varied geography, heavily industrialized areas, and a large agricultural area. It has a mix of urban, suburban, small town, and rural communities. These variations mean that different communities of California women face very different exposures in their environments. The state's ethnic diversity makes it possible to investigate whether exposure to a substance or other factor in the environment affects some ethnic groups differently than others. California also has communities with the highest rates of breast cancer in the nation.

Influencing the Research System Nationwide

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

An example is CBCRP 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 1995, less than 10 percent of research proposals submitted to the federal government's funding agencies were successful. This led the people who decided what got funded—panels of research experts—to look for proposals that seemed most likely to succeed. Research scientists had to have done a significant portion of the research, and have strong preliminary data, before they could even get a grant. This made it hard for anyone to get funding in order to try out a high-risk idea. However, high-risk ideas are often the source of scientific breakthroughs.

We originated our Innovative, Developmental, and Exploratory Awards (IDEAs) to change this situation. IDEA grants are 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, we gave Robert Debs, M.D., from the California Pacific Medical Center in San Francisco, an IDEA grant in 1997 to investigate gene therapy for breast cancer. When the research results 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.

To get creative new research going, 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 even developed a new scoring system to help reviewers read proposals with a perspective toward rewarding high-risk research.

Enlarging the Pool of Breast Cancer Researchers

Another one of our major goals is to increase the number of talented scientists engaged in breast cancer research. We make several types of grants to meet this goal. These include 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 even earlier in their careers. This led us, during 2002, to institute

three new types of grants. Dissertation grants fund masters' and doctoral students' dissertation research into breast cancer; Mentored Scholar awards fund new researchers who are not yet ready to become independent investigators for work under an experienced researcher-mentor. Diversity Supplements allow scientists we fund to support and mentor promising graduate or undergraduate students who face economic or social barriers to pursuing a career in breast cancer research.

Two Criteria: Priority Issues and Award Types

Every research grant we fund must qualify under 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. The Award Types, which include the IDEAs discussed above, are narrowly targeted. The narrow targeting is designed to jumpstart underfunded areas of research, encourage creative new thinking, and bring new investigators into the fight against breast cancer.

On the following pages, we provide statistics on the 50 projects we funded in 2003 by Priority Issue, then by Award Type.

Statistics on Funds We Awarded in 2003 by Priority Issue

CBCRP Priority Issues:

The Community Impact of Breast Cancer: The Social Context

- Health Policy and Health Services: Better Serving Women's Needs
- Sociocultural, Behavioral, and Psychological Issues Relevant to Breast Cancer: The Human Side
- Racial/Ethnic Differences in Breast Cancer: Eliminating Disparity

Prevention and Risk Reduction: The Environment of the Disease

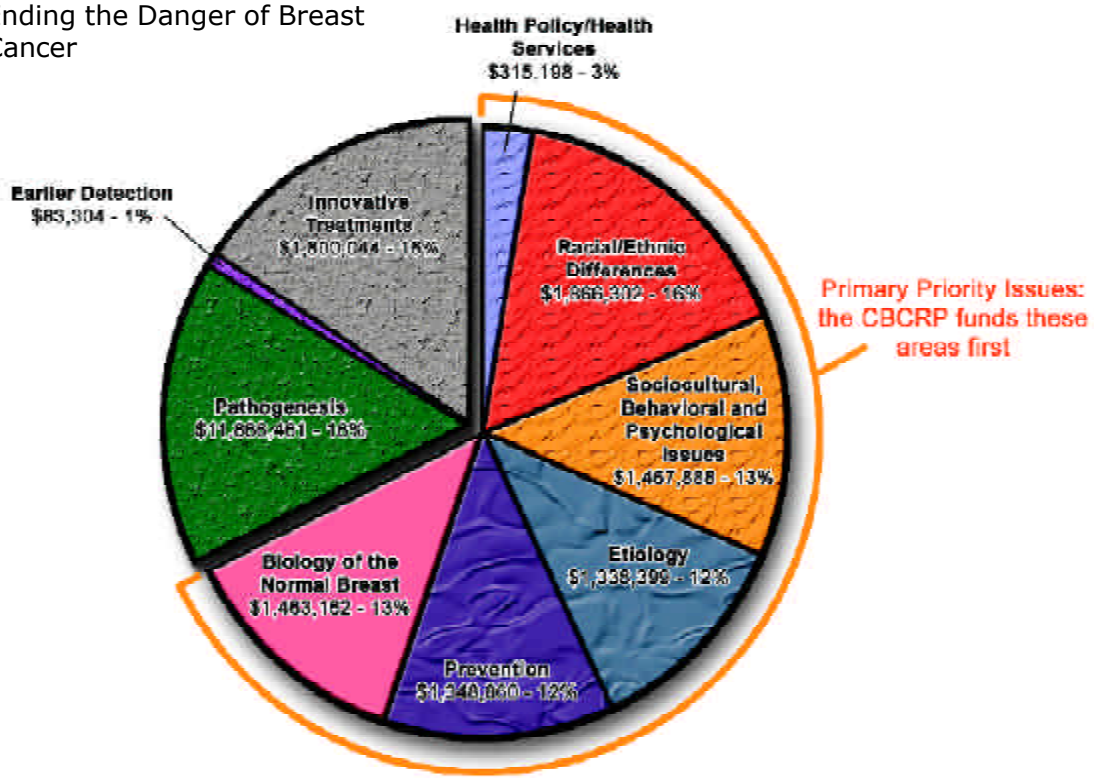
- Etiology: Finding the Causes
- Prevention and Risk Reduction: Ending the Danger of Breast Cancer

Biology of the Breast Cell: The Basic Science Study of the Disease

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

Diagnosis and Treatment: Delivering Clinical Solutions

- Earlier Detection: Improving the Chances for a Cure
- Innovative Treatments: Search for a Cure



Every research project that the CBCRP funds must fit under one of our Award Types and also one of our Priority Issues.

Statistics on Funds We Awarded in 2003 by Award Type

CBCRP Award Types:

Collaboration Awards

To encourage thinking outside traditional research modes, the CBCRP offers four types of awards to bring together new combinations of researchers. 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) Award:** Encourages researchers from other disciplines to team up with breast cancer researchers and apply tools, insights, and ideas from another field of study to breast cancer.
- **Community Research Collaboration (CRC) Award**: Brings community organizations—such as breast cancer advocacy organizations, community clinics, or organizations serving minority women—together with experienced scientists to investigate breast cancer problems that are important to that community, using culturally-appropriate research methods.
- **Translational Research Collaboration (TRC) Award:** Generates creative research partnerships from several fields of science to turn discoveries in the laboratory into ways to detect, treat, or prevent cancer.
- **Joining Forces Conference Award:** Brings breast cancer researchers into dialog with creative thinkers working in other scientific fields to exchange concepts, methods, and discoveries that could lead to breakthroughs.

Topic-Targeted Awards—RFAs

These awards encourage more creative research in under-researched areas. The areas for 2003 were our six Primary Priority Issues: Health Policy and Health Services; Racial and Ethnic Differences in Breast Cancer; Sociocultural, Behavioral, and Psychological Issues; Etiology; Prevention and Risk Reduction; and Biology of the Normal Breast.

Training Awards

By investing in training for researchers early in their careers, the CBCRP increases the pool of scientific talent working to end breast cancer.

- **New Investigator Award:** Encourages scientists who have recently completed their training to set up their own research programs.
- **Postdoctoral Fellowship Award:** Advanced training for Ph.D.s under a breast cancer research mentor.
- **Mentored Scholar Award:** Encourages new researchers who are not yet ready to become independent investigators to work under a breast cancer research mentor.

- **Dissertation Award:**
  Funds dissertation research by masters or doctoral candidates.
- **Training Program Award:**
  Funds programs that train undergraduate or graduate students in disciplines important to breast cancer research.
- **Career Enrichment Award:**
  Funds research in a field important to breast cancer that is new to an experienced researcher or a clinician.

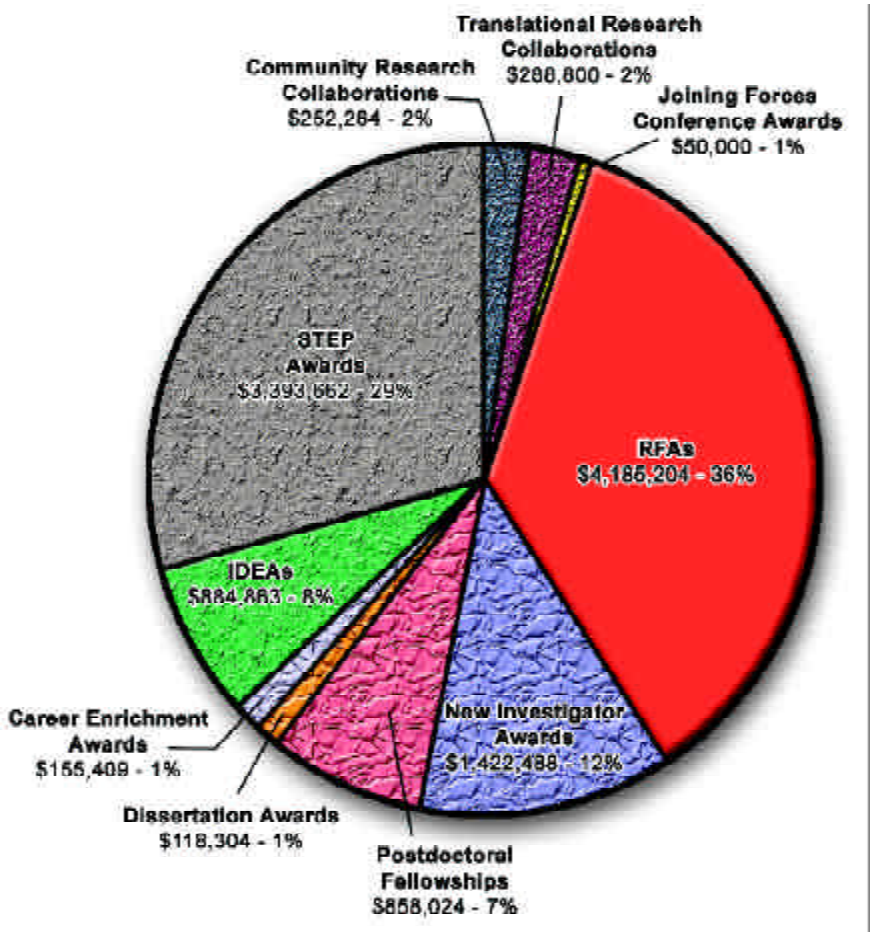
Innovative Research Awards

- **Innovative Developmental and Exploratory Awards (IDEAs):**
  Funds research with a high potential for scientific payoff, understanding that trying out new concepts also means a high risk of failure.
- **STEP Awards:**
  Allows research teams that have done innovative preliminary research into exceptionally promising topics to develop their research further, as a step toward getting funding from a major research agency for a full-scale study.

Diversity Supplement Award

Brings students who face economic or social barriers to entering a career in breast cancer research into the field, to work under a scientist whose research project is already funded by the CBCRP.

In addition, the CBCRP provided $10,000 for a Diversity Supplement Award, with funding from donations made by California taxpayers on their state income tax returns.



Scientists present the research we fund at scientific conferences and publish it in journals. However, we are committed to making research results available to a much wider public.

Sharing Our Research With Scientists and the Public

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, and we do 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 progress and results in a variety of ways:

Research Symposia

Every other year, we host a research symposium, a statewide conference presenting the results of the research the CBCRP funds. Six hundred people attended our fourth symposium, "From Research to Action: a Decade of Progress", held September 12–14, 2003, in San Diego.

The Symposium 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.

We make a special effort to bring women who have, had, or are at risk for breast cancer to our symposia. For this symposium, 75 women received scholarships that covered their travel and accommodations.

A Saturday Keynote Lunch brought all participants together. Sarah Weddington, J.D., the attorney who took the landmark *Roe v. Wade* case to the US Supreme Court, gave the keynote address, discussing her own experience with breast cancer.

Researchers funded by the CBCRP discussed the implications of their results in workshops and panels, including "Diet and Breast Cancer" and "New Treat-

ment Strategies." Scientists and breast cancer advocates were also on hand to discuss research projects showcased on over 100 colorful posters.

The three-day event included a breakfast session where scientists, clinicians, and lay people discussed topics of interest in small groups.

An art exhibition, ongoing throughout the symposium, used paintings, quilts, photography, sculpture, and other media to reflect the far-reaching impact of breast cancer. Some of the work was done by seasoned, award-winning artists and other pieces were done by people new to art's transforming power. The exhibiting artists included women diagnosed with breast cancer, their family members, and their friends.

Representatives of community organizations from around the state provided information on their breast-cancer-related programs. The event included an additional day of training for members of community organizations and research scientists interested in teaming up to conduct research with funding from the CBCRP's Community Research Collaboration (CRC) grants.

The symposium included a community town-hall "CBCRP Listens" meeting. Everyone attending was invited to give feedback on the research we fund, the symposium, and our other activities. The CBCRP takes this feedback from the public seriously. We've changed our research priorities as a result of previous feedback sessions like this one, and we also use this feedback to help set the agenda for the symposium itself. At the last symposium, participants asked, "Why don't you do more research on cancer and the environment?" One result was this symposium's plenary panel on "Environment and Breast Cancer Prevention."

The next symposium, scheduled for September 9–11, 2005, will be held in Sacramento.

Web Site

The CBCRP Web site (www.cbcrp.org) has summaries of all completed research projects and annual progress reports for ongoing projects, in language accessible to the general reader. During 2003, all research on the CBCRP Web site became fully searchable. The summaries also link to the National Institute of Health's (NIH's) PubMed, a public-access database of biomedical journals, when researchers publish the results of their studies. Our Web site contains a list of each year's awards and information on applying for grants. In addition, all CBCRP publications are available and downloadable. The site links visitors to a wide variety of information on breast cancer research going on today across the nation. During 2003, we upgraded the site to include an online opportunity to make donations to the CBCRP.

Annual Reports

Our annual *Advances in Breast Cancer Research*, available free of charge to the public, contains summaries of all ongoing and completed research for the year. Multiple copies are available free of charge to organizations. Annual reports are also available on the CBCRP Web site.

Summary of Awards

To make it easy for scientists and the public to follow 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 is also posted on the CBCRP Web site.

Newsletter

Our newsletters, also available free to the public and posted on our Web site, report on new awards, research results, other program news, and important questions that arise among breast cancer researchers and women with the disease.

Serving the Media

We do regular outreach to the media about the Program and about CBCRP-funded research projects that are of interest to the general public. When reporters from TV, newspapers, magazines, or other media need information on breast cancer research, we link 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.

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 are also investigators on a rising number of our research projects.

Collaborating with Breast Cancer Activists and California Communities

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. Non-scientist 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 providing 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—women who have or have had the disease, or who represent organizations that serve women with the disease—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 ten-year history, an advocate has always served as the Council's Chair or Vice-Chair. In addition, out-of-state panels of research scientists and advocates review all CBCRP research proposals for scientific merit. Out-of-state breast cancer advocates are full voting members of these review panels and a California advocate observes each one.

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 (CRC) awards are open to nonprofit organizations or ad-hoc community groups in any California community affected by breast cancer. The majority of community collaborators 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 breast cancer patients

- 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

The CBCRP's Community Research Collaboration Awards have had a major impact on the community organizations that have received funding.

- **Marin Breast Cancer Watch**, funded in 1998 to study possible causes for the high rate of breast cancer in Marin County, was featured as a model at the 2002 International Summit on Breast Cancer and the Environment. The organization also received funds from the National Institute of Environmental Health Sciences (NIEHS) to do more work on breast cancer in the county in partnership with the University of California, San Francisco.
- **Breast Health Access for Women** received CBCRP funding in 1998 to determine the prevalence of barriers to breast cancer screening among women with physical disabilities, to develop successful outreach strategies, and to disseminate the program to other areas in the country. The organization has since educated many organizations about the breast screening needs of women with disabilities.
- **The Wellness Community** received CBCRP funding to test whether online support groups for women with breast cancer could significantly increase the women's quality of life. They found that these groups are helpful for women who are too ill to attend a support group or live too far from a place where they can access face-to-face support. The Wellness Community currently provides nine online support groups, and their Web site averages 1,000 to 4,000 new visitors per month.

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 CRC 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 more members of 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 percent of our research funds going for Community Research Collaborations during 2001, compared to 1 percent 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.

During 2003, we conducted training at sites throughout California to encourage and educate community groups to get involved in breast cancer research. During 2004, with a grant from the California Endowment, we will continue providing this training across the state. We'll also formally evaluate the Community Research Collaboration awards for a second time, to measure the outcomes of this funding.

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.

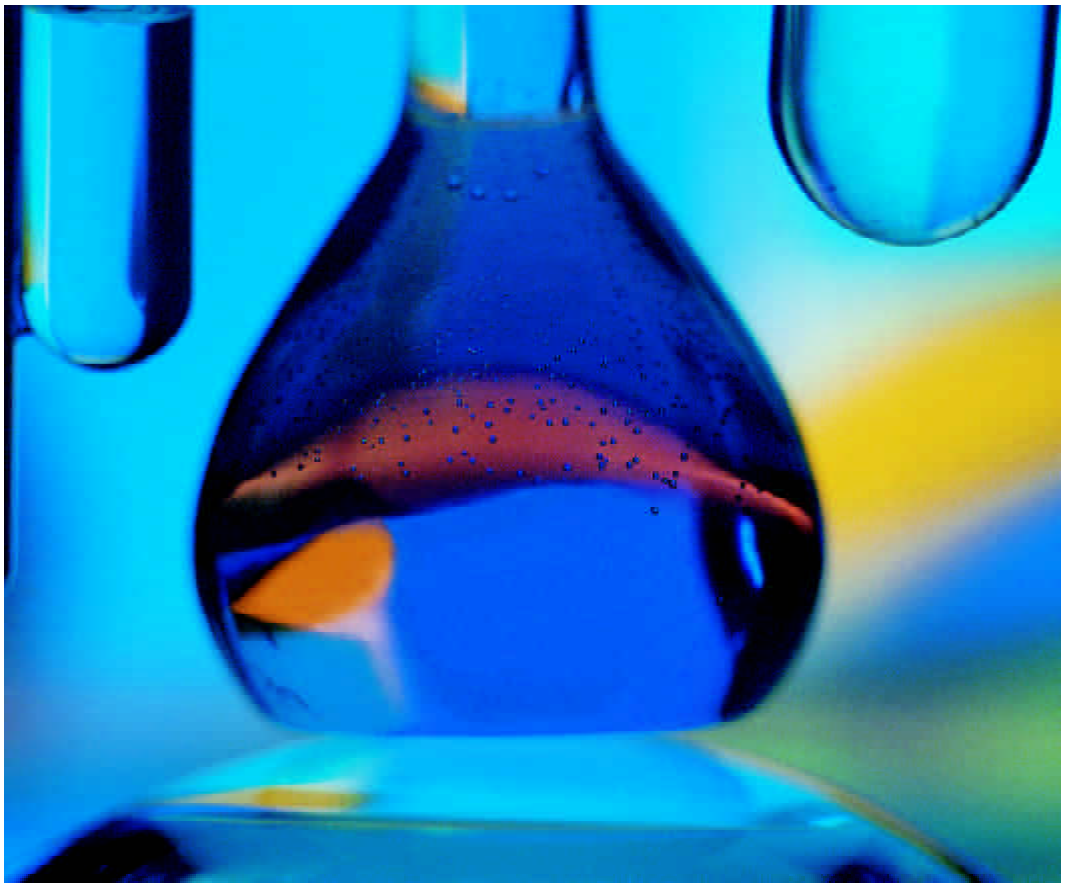
Toward More and Faster Progress Against Breast Cancer

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. Our Community Partners Program provides 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 available funds, 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 percent of women with breast cancer. California's diverse population is ideal for statewide clinical trials.
- **Drug Development.** Developing a new drug can take 10–15 years and cost hundreds of millions of dollars. Pharmaceutical companies select potential drugs most likely to be profitable; discoveries that are too risky or only have the potential to help a small population may never become treatments.
- **Long-term Studies.** A 20- or 30-year study of California women and girls could reveal a lot about risk factors that lead to breast cancer and point to ways to prevent the disease.
- **Tissue Banks.** Samples of tumors from California women, along with the women's medical history, could provide answers to research questions now and in the future.
- **Services.** The CBCRP provides funding for community-based organizations to test services for women with cancer, but once those services have been shown to help women with breast cancer cope or survive, we are unable to provide continued support.
- **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 our potential to efficiently coordinate programs with scientific and medical communities and 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 2003, the CBCRP turned down 174 grant applications that were requesting a total of $45,944,997. 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.



Evaluation helps the program target research dollars where they will do the most to reduce and end the suffering caused by breast cancer.

Improving Our Program through Evaluation

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

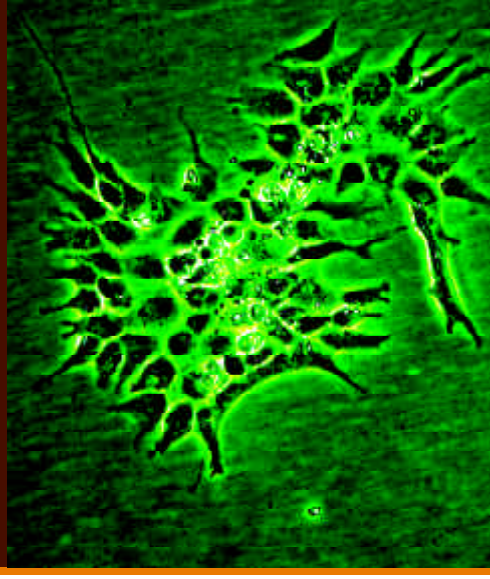
Over the past several years, we have evaluated several of our grant programs: the Community Research Collaboration awards, the Postdoctoral Fellowship awards, the New Investigator awards, and the Innovative, Developmental, Exploratory Awards (IDEAs). The results of these evaluations are being used by our highest leadership body, the Breast Cancer Research Council, to set priorities for the coming years.

Evaluation Leading to Improvement

We use formal evaluations to improve the CBCRP. Examples of changes we've made as a result of evaluations include:

- We used our formal evaluation of our Community Research Collaborations to embark on a successful, ongoing, multi-year outreach and training effort. The goal is to increase the number of community organizations and scientific researchers collaborating on breast cancer research questions of interest to communities of California women.
- Our evaluation during 2002 of the CBCRP's New Investigator awards, combined with our 2001 evaluation of our Postdoctoral Fellowship awards, led us to introduce two new types of grants. During the evaluation, scientists who had received New Investigator awards, which are designed to increase California's pool of talented breast cancer researchers, suggested encouraging people to enter this field even earlier in their careers. In response, the CBCRP instituted Diversity and Dissertation awards. Diversity awards are made 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.

We plan to continue evaluating more of the types of grants we make and to continue 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 2003. 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, arranged in four groups:

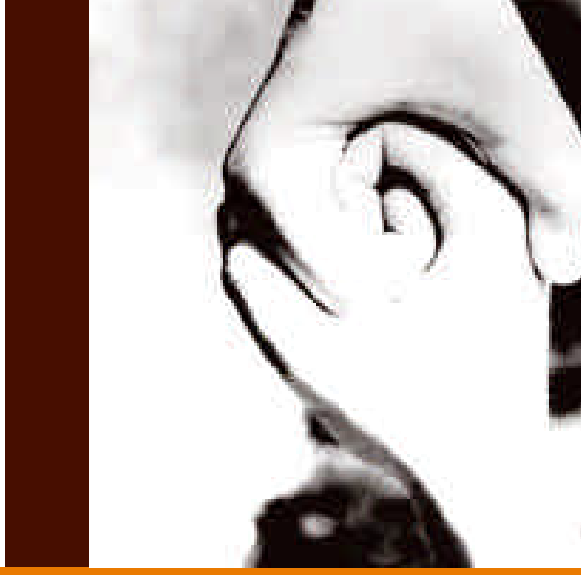
- **The Community Impact of Breast Cancer: The Social Context**
  - > Health Policy and Health Services: Better Serving Women's Needs
  - > Racial and Ethnic Differences in Breast Cancer: Eliminating Disparity
  - > Sociocultural, Behavioral, and Psychological Issues: The Human Side

- **Prevention and Risk Reduction: The Environment of the Disease**
  - > Etiology: Finding the Causes
  - > Prevention and Risk Reduction: Ending the Danger of Breast Cancer

- **Biology of the Breast Cell: The Basic Science of the Disease**
  - > Biology of the Normal Breast: The Starting Point
  - > Pathogenesis: Understanding the Disease

- **Diagnosis and Treatment: Delivering Clinical Solutions**
  - > Earlier Detection: Improving the Chances for a Cure
  - > Innovative Treatments: Search for a Cure

The Community Impact of Breast Cancer: The Social Context



A woman who learns she is at high risk for breast cancer, or who is diagnosed with or is surviving the disease, is changed forever. The CBCRP supports research and formulation of public policies that would contribute to breast cancer prevention, to improving the lives of women who have or have had the disease, and to fewer deaths. We recognize the need to reduce unequal access to prevention, detection, treatment, and survivorship services. We also encourage sociocultural, behavioral, and psychological research to reduce the impact of breast cancer on each woman.

We divide research in this area into three Priority Issues:

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

· Racial and Ethnic Differences in Breast Cancer: Eliminating Disparity

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

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

If research findings are going to lead to action and change, then 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.

Research in Progress

A number of ongoing CBCRP grants in the topic of *Health Policy and Health Services* reported substantial progress in 2003.

We can improve our understanding of how to help breast cancer patients have the best possible physical and emotional outcomes by focusing on the patient herself and on the medical care system that plays such a central role in her prognosis and eventual heath outcome. The following four studies look at the medical care system. The last study in this section looks at place of residence as a surrogate marker for community-level factors that affect access to care (e.g., transportation, distance to medical facilities, socioeconomic status).

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 hinders—women returning to work after breast cancer surgery. So far, they have found that women who had chemotherapy or who had symptoms of depression took longer to return to work. Latina women, low-income women, and women with children at home all returned to work more quickly. Low-income and Latina women may have less access to sick leave and disability pay; returning to work more quickly may put them at risk for complications such as arm swelling and fatigue. Latina women, low-income women, and women who had chemotherapy or a mastectomy reported more depression, pain, swelling, and fatigue after surgery. Women who exercised or who used acupuncture, acupressure, or herbal medicine experienced less pain.

The Impact of Structure on Quality of Breast Cancer Care.

Katherine Kahn, Ph.D., at the ***University of California, Los Angeles,*** is investigating how the financial and organizational arrangements for breast cancer care—in medical offices, medical groups, and health insurance plans—enhance or diminish quality of care. The research team has developed methods for comparing organizational and financial arrangements between health care providers and is applying those methods to compare breast cancer health care providers in the Los Angeles area.

African American Women and Breast Cancer: What Works?

African American women are less likely than white 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 low-income African American women who do not have health insurance.

Determinants of Receiving Breast Cancer Treatment in the Underserved.

Rose Maly, Ph.D., of the ***University of California, Los Angeles,*** is surveying 230 low-income breast cancer patients and their health care providers and analyzing 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. The research team has created and tested questionnaires in English and Spanish for patients. They have also finalized a questionnaire for health care providers, and are now enrolling women to interview. The team hopes to use the results to directly improve breast cancer care for low-income, uninsured women. Results from this study have been published in *Cancer* 97(6) 2003:1517-27.

Does a Peer Navigator Improve Quality of Life at Diagnosis?

Women with breast cancer say they need counseling most when they are newly diagnosed, but many 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,*** is collaborating with ***Caroline Bliss-Isberg, Ph.D.,*** of the Santa Cruz community organization ***WomenCARE,*** to evaluate the effectiveness of pairing women who have just learned they have breast cancer (sojourners) with trained volunteer breast cancer survivors (peer navigators). Each pair makes at least one contact a week for three months. The relationships can be renewed by mutual agreement every three months. In a preliminary study previously funded by the CBCRP, the research team found that women matched with a navigator maintain their quality of life and actually improve in some areas, but the more successful navigators showed some trauma and depression symptoms. This study is a three-year expansion of the previous research. So far, the research team has trained 20 new navigators and enrolled 51 women with breast cancer. The team is working toward recruiting women from a greater variety of ethnic groups than were enrolled in the preliminary study. A well-designed peer counseling program could cut the human and economic costs of breast cancer in California by giving newly-diagnosed women access to helpful resources and strategies for making medical decisions.

Geographic Variation in Breast Cancer Stage at Diagnosis.

Women whose breast cancer is diagnosed 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 percent to 71 percent. ***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. The team is currently analyzing data from the California Cancer Registry, other databases that track cancer cases, the federal census, and 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.

Research Initiated in 2003

The Cost of Breast Cancer in California.

Wendy Max, Ph.D., at the ***University of California, San Francisco,*** will make the first detailed estimate in 17 years of the cost of breast cancer in California, including dollars spent on health care, lost productivity of women living with breast cancer and dying prematurely from the disease, and the lifetime cost of breast cancer for older women on Medicare.

Racial and Ethnic Differences in Breast Cancer: Eliminating Disparity

The rates of breast cancer, results from treatment, and death rates differ for women from different ethnic groups. In addition to cultural disparities, there may be important differences in the biology of the disease, so research into these questions should help reduce inequality among both women with breast cancer and those at risk for the disease. Such research may also uncover important information that could point to new methods of prevention and treatment. California, with its geographic, environmental, economic, and ethnic diversity, provides one of the best laboratories in the nation or the world for this type of research. This priority issue was added in 2002.

Research in Progress

Two ongoing CBCRP grants in the topic of *Racial and Ethnic Disparities* reported substantial progress in 2003.

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. The goal is to see if HLA genes are responsible for some or all of the differences in breast cancer rates between various ethnic groups. So far, the research team has obtained and begun testing blood samples from 214 premenopausal white, African American, and Hispanic breast cancer patients and 269 premenopausal women from the same ethnic groups who do not have the disease.

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, 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 is comparing 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. She has found that Hispanic and Asian women, who have lower rates of breast cancer, had placentas that weighed less when compared to the birth weight of their babies. White and African American women, whose breast cancer rates are higher, had placentas that weighed more when compared to the birth weight of their babies. This suggests that the underlying cause of heavier or lighter placentas may also be a risk factor for breast cancer.

Research Initiated in 2003

Four new studies were funded in 2003 to examine disparities and options for eliminating the unequal burden of breast cancer among Californians.

Reducing Disparities among Korean American Women.

Low-income Korean American women don't have mammograms very often or at all, after they have had the first one. ***Soo-Young Chin, Ph.D.,*** at the ***Korean Health, Education, Information & Research Center,*** Los Angeles, and ***Annette E. Maxwell, Dr.P.H.,*** at the ***University of California, Los Angeles,*** are testing ways to educate low-income Korean American women to raise the number of these women who have mammograms at regular intervals.

Racial Disparity in Breast Cancer Mortality.

Over the past decade, the death rate from breast cancer has dropped more for white women than for African American women. Hispanic and Asian women have lower death rates, but their death rates are not improving the way the death rate has improved for white women. ***Rebecca Smith-Bindman, M.D.,*** at the ***University of California, San Francisco,*** will analyze data on 95,000 women diagnosed with breast cancer between 1992 and 2001. She will investigate whether differences at the cell level of the tumors, differences in the women's use of mammograms, or differences in treatment explain the differences in death rates between ethnic groups.

Lifestyle Factors and Breast Cancer Prognosis in Asian Americans.

Anna H. Wu, Ph.D., at the ***University of Southern California,*** Los Angeles, is studying 1,200 Asian American women diagnosed with breast cancer between 1995 and 2000. Her team will investigate the effect of diet (including green tea and soy foods), exercise, and body size—both before and after their diagnosis—on whether these women have had a recurrence of the disease and whether they have survived.

Correlates of Lymphedema Severity and Access to Intervention.

Diane R. Estrin, at the ***Women's Cancer Resource Center,*** Oakland; ***Linda Wardlaw,*** at the ***Charlotte Maxwell Complementary Clinic,*** Oakland; and ***Rani B. Eversley, Ph.D.,*** of the ***University of California, San Francisco,*** are testing and developing educational materials to help minority women prevent arm pain and swelling (lymphedema) after breast cancer surgery. The need for this research grew out of the study "**Return to Work After Breast Cancer Surgery**" cited above. Minority women taking part in that study experienced more arm swelling and pain than did white women, and many said they had not been told about the possibility of pain and swelling before their surgery.

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 improve their post-diagnosis quality of life. It may also lengthen their survival time. CBCRP research reflects the complexity of the psycho-social aspects of breast cancer. Topics include: aspects and types of successful support groups; the impact of cultural beliefs; how, and in what ways the support of significant others is important; and how to help women 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.

Research Conclusions

Two CBCRP grants studying the *Sociocultural, Behavioral, and Psychological* issues of breast cancer were completed in 2003.

Do Community Cancer Groups Enhance Well-Being?
Matthew Cordova, Ph.D., at ***Stanford University,*** investigated how women with breast cancer who have had traumatic experiences earlier in their lives think and feel about their illness. The research team is also investigating whether and how several types of support groups can help these women who are at high risk for distress about their disease. The team found: (1) Women who believe more strongly that breast cancer threatens their lives and who have greater resources to deal with this threat may be more likely to experience a sense of personal growth. (2) Women who write about their cancer experience using more cognitive words and fewer emotional words report greater emotional distress. (3) Women who have higher confidence in their ability to manage their feelings about cancer are more likely to use a fighting spirit to decrease their emotional distress. Dr. Cordova is continuing this research, with the goal of improving support group services available to women with breast cancer in California. Results of Dr. Cordova's studies have been published in *Journal of Consulting and Clinical Psychology* 2001 Aug; 69(4):706-11, *Health Psychology* 2001 May; 20(3):176-85, and *Advances in Mind-Body Medicine* 2001 Winter; 17(1):38-41.

Communicating Breast Cancer Risk in Ethnically Diverse Women.

To make informed decisions about taking the chemotherapy drug tamoxifen in order to reduce their risk of getting breast cancer, women need to know the risks and benefits of the medication and to carefully consider their own individual risk for the disease. ***Linda Lillington, R.N., D.N.Sc.,*** at the ***Harbor-UCLA Research and Education Institute,*** conducted research to fill a need for educational materials that health care providers can use to present information about breast cancer prevention to minority women. The materials are written at a 6th-grade reading level and are designed to give women who speak English or Spanish a clear understanding of the risks and benefits of taking tamoxifen. The materials are based on extensive interviews with African American, Hispanic, and white physicians and patients. The educational materials have been evaluated by a panel of physicians and nurses and via focus groups with English- and Spanish-speaking women. Women who took part in the study made very positive comments about these educational materials, saying they wanted to share the information with other women and that they were going to make changes in their own lives to promote breast health.

Research in Progress

A number of ongoing CBCRP grants in the topic of *Sociocultural, Behavioral, and Psychological Issues* reported substantial progress in 2003.

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, and 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 breast cancer patients receiving standard-dose adjuvant chemotherapy after surgery and breast cancer patients treated with anti-estrogen (tamoxifen) therapy after surgery. She is comparing these women's memory functioning with breast cancer patients not treated with either therapy, and with age-matched healthy women with no history of cancer. Before and after treatment, the women are given a battery of tests that assess 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 nine months after chemotherapy, women had decreased performance on objective memory tests of verbal learning, compared to their performance before treatment. On time-coded learning tests, chemotherapy patients had lower scores than healthy 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. ***Julienne Bower, Ph.D.,*** at the ***University of California, Los Angeles,*** is investigating factors that contribute to fatigue during radiation treatment, 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. So far, the research team has found that fatigue levels increase until treatment week 4, then decline after treatment is completed, but there is a lot of variation among individuals. 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.

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 women with breast cancer start out with stronger bones than women who don't get the disease. She is also investigating whether survivors of breast cancer and women who haven't had the disease lose bone mass at different speeds after menopause. Finally, she is investigating whether levels of hormones in the blood can predict the rate at which breast cancer survivors lose bone mass.

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. Initial results show that the partners who decided to take part in this study were married to or living with breast cancer survivors who were more likely to be white, have higher income, refrain from using avoidance to cope, have more support from their partners, have better general health, and have more sexual problems than the survivors whose partners didn't participate. These findings provide evidence of possible biases in recruitment of partners for this type of study.

A Support Group Alternative for Rural and Isolated Women.

Cheryl Koopman, Ph.D., at ***Stanford University,*** and ***Mary Anne Kreshka, M.A.,*** at ***Nevada Memorial Hospital Cancer Center,*** Grass Valley, are evaluating a community-based workbook-journal as an alternative to a support group for isolated and rural women with breast cancer. The workbook, "One in Eight," was developed by breast cancer survivors in a rural community in partnership with academic researchers (*Journal of General Internal Medicine* 2003 Jul; 18(7):499-507). A pilot study funded by the CBCRP showed that the workbook reduced stress and improved coping for a small group of rural women. This larger study includes 151 women. At the beginning of their participation in this study, 64 percent of these women had clinical depression and 15 percent were suffering from post-traumatic stress. These figures are far higher than shown by previous studies, underscoring the need for methods to provide support to isolated and rural women. Results have also been published in *Breast Journal* 7(1):25-33.

Constructed Meaning and Stress in Breast Cancer Experience.

Jill L. Mitchell, M.A., at the ***University of California, Los Angeles,*** is interviewing 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 is also looking at how the meaning changes over time, how each woman constructs meaning, and how the meanings women give to breast cancer are related to the amount of the stress hormone cortisol their bodies are producing.

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 compared Internet support groups led by mental health professionals with Internet support groups led by women with no professional training. Women in groups led by professionals expressed more negative

emotions than women in groups led by non-professionals. The professional leaders encouraged the expression of anxiety, hostility, and depression, because they believe expressing these emotions is therapeutic. The non-professional leaders, on the other hand, offered support and suggested fighting the cause of the negative feelings. Research results have been widely published in several journals, including *Cancer* 97(5):1164-73 and *Group Dynamics* 6(4):267-76.

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 relation-

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Grant follow-up report—Where are they now?

In early 1997, the team of Dr. Cheryl Koopman (Stanford University) and Mary Anne Kreshka (Sierra Nevada Memorial Hospital Cancer Center) were awarded a Community Research Collaboration (CRC) pilot grant ("A Community-based Workbook for Helping Rural Cancer Patients"). This award was aimed at helping rural breast cancer support groups more effectively assist women newly diagnosed with breast cancer to better cope with the consequences of their diagnosis.

This project developed a workbook, "One in Eight", which has as a conceptual basis Stanford's Supportive-Expressive model. The team found that women who received the workbook showed a significantly greater reduction in their fatalism and traumatic stress symptoms, and greater increases in fighting spirit.

With this promising start, the team then focused on rural women's isolation and decided to investigate whether the workbook would be useful for women who suffered social isolation due to cultural, language, economic, or physical reasons. They were awarded a full CRC award ("A Support Group Alternative for Rural and Isolated Women") to test the journal in a larger population and different medical and social setting—an HMO in Sacramento, California.

Most recently, the team (with new member Susan Ferrier, from the Northern Sierra Rural Health Network) has applied for another CRC pilot award to use the workbook in a project to test the feasibility and acceptance of using videoconferencing to provide support groups led by trained facilitators to rural women with breast cancer ("Expanding Rural Access: Distance Delivery of Support Groups").

Thus, this team has moved from looking at support groups for rural women, to ameliorating the impact of social and geographic isolation, to using telecommunication resources to broaden the reach of a proven support intervention technique. Along the way, the workbook has evolved from a local pilot intervention to one of much greater—even national—scope.

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ships. Their data comes from a six-year study of over 3,000 women called the Women's Healthy Eating and Living Study. So far, the team has investigated what caused depressive symptoms in women who had completed treatment for their breast cancer but had not yet begun the diet. Having a more serious diagnosis or a particular type of treatment did not lead to more depressive symptoms. Women who had more depressive symptoms were more likely to be pre-menopausal, younger, less optimistic, and more ambivalent about expressing negative emotions. They also were more likely to experience more pain and menopausal symptoms and have less social support. The fewer years that had passed since their breast cancer diagnosis, the more likely the women were to have depressive symptoms. This research resulted in a publication in *Annals of Behavioral Medicine* 24 (2002):S175.

Efficacy of a Community Program in Increasing Access to STAR (Study of Tamoxifen and Raloxifene).

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. From focus groups, interviews, and a survey, they 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 African American women physicians, developed an educational presentation on chemotherapy to prevent breast cancer, and trained a group of African American women physicians to give the presentation. The education presentation has been given at community churches; 94 percent of the women attending found it useful and 72 percent said they would now consider taking part in a medical research study.

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 conducted face-to-face interviews with 603 women before and after a breast cancer education program presented to Hmong men and women in their language at home, usually with the men and women in different small groups. After the education, 25 percent more women in the communities had a mammogram, compared to only a 5 percent increase in the Hmong communities where no educational programs were held.

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,*** are conducting the first-ever

exploratory research that we know of in this population. The team is using signed languages of the deaf to interview 70 deaf women (10 of whom are breast cancer survivors) over 40 about their knowledge, behavior, and preferences about detection and other breast health practices. The team has completed 49 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.

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*** 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 receiving screening mammograms and clinical breast exams. The research team has recruited and surveyed 422 women. The team has trained six Chamorro women as lay health educators, and developed educational materials, focusing on materials for use with small groups of women in social settings.

Research Initiated in 2003

Six new projects studying the sociocultural, behavioral, and psychological issues of breast cancer began in 2003.

'Art for Recovery': Expanding Access for the Underserved.
Kate Collie, Ph.D., at ***Stanford University,*** is investigating Art for Recovery, a program at the UCSF Comprehensive Care Center. The program provides support services for women with breast cancer based on visual creative expression. Dr. Collie will find out how well the program meets the needs of women with breast cancer, especially minority women, low-income women, and other women who have little access to breast cancer services. She will also investigate how to improve the program.

Assessing the Impact of Shame and Guilt in Recovery.
Janine Giese-Davis, Ph.D., at ***Stanford University,*** is investigating whether women may suffer unnecessarily from shame (about, for example, losing a breast or changes in their sexual feelings) and guilt (about, for example, spending less time with their children) after breast cancer treatment. She will use recently developed methods to measure shame and guilt, including coding of videotapes for head and body movements. She will also investigate whether these feelings impair the women's relationships with family and friends, their interactions with health care professionals, or their recovery from breast cancer.

Interplay of Family Context and BRCA1/2 Testing.
Tests to see if a woman has genes that put her at greater risk for breast cancer have been available for years; however, few minority women have taken these tests. ***Beth Glenn, Ph.D.,*** at the ***University of California, Los Angeles,*** will investigate women from five ethnic groups: white, African American, Hispanic, and two of the largest Asian subgroups in Los Angeles with the highest rates of breast cancer: Filipino and Japanese. She will study the role that families play in decisions about whether to have genetic tests.

Latinas and DCIS: Treatment Decisions and Quality of Life.
DCIS (ductal carcinoma *in situ*) is a small pre-cancerous growth in the breast. Some cases of DCIS will go on to become invasive breast cancer; others will not, but there's no way to tell which is which, so many women with DCIS have

breast surgery. ***Celia Kaplan, Ph.D.,*** at the ***University of California, San Francisco,*** will survey 300 Latinas and 300 white women with DCIS to compare the way they make decisions about treatment, their quality of life, and the follow-up care they receive.

Late Cognitive and Brain Changes after Breast Cancer Therapy.
H. Rebecca Rausch, Ph.D., at the ***University of California, Los Angeles,*** is investigating whether the chemotherapy to treat breast cancer causes long-term loss of memory, attention, and concentration. Building on a study previously funded by the CBCRP that tested the mental function of breast cancer patients before they had chemotherapy or estrogen-blocking therapy, the research team will re-test the women two years later.

Feasibility of a Clinical Trial Matching Tool.
Only 3 percent of breast cancer patients take part in clinical trials. ***John Park, M.D.,*** and ***Morton Lieberman, Ph.D.,*** at the ***University of California, San Francisco,*** are investigating the effectiveness of a Web site (BCT.org) to recruit breast cancer patients and match them, according to their medical history, with appropriate research to test new treatments.

Prevention and Risk Reduction: The Environment of the Disease

What in the environment—interacting with which characteristics or conditions of a particular woman's body—increases her risk of developing breast cancer? Despite efforts to identify genes that cause breast cancer and environmental risk factors, the disease seems to strike women at random. The CBCRP especially encourages new California-based studies to understand the environmental aspects of breast cancer, and how these increase risk and impact different communities of California women.

We divide research in this area into two Priority Issues:

· Etiology: Finding the Causes

· Prevention: Ending the Danger of Breast Cancer

Etiology: Finding the Causes

There has already been intensive study into the contributions of behavior and lifestyle to breast cancer. Investigating the external physical causes of breast cancer means investigating things that women cannot, as individuals, control. The CBCRP's goal is to understand how environmental exposure—to pesticides and other known or suspected cancer-causing substances in the air, food, water, or medications—may lead to biological changes that initiate breast cancer.

Research Conclusions

Five CBCRP grants studying the *Etiology* of breast cancer were completed in 2003.

Influence of Localized DDT Exposure on Breast Cancer. The pesticide DDT can mimic or interfere with the action of hormones in humans and animals. Once inside the body, DDT remains stored in the fat surrounding breast tissue. In the body and in the environment, DDT gets broken down into hormone-like compounds, which may have the potential to influence breast cancer. ***Vicki L. Davis, Ph.D.,*** at the ***Cedars-Sinai Medical Center,*** Los Angeles, tested two compounds that DDT breaks down into (metabolites) to see if they promoted mammary tumors in mice. One compound, pp DDE, inhibits male sex hormones and caused the highest number of tumors at the earliest ages. The other compound, o,p DDE, which acts like estrogen, only slightly promoted tumor growth. The two compounds appear to cancel out each other's effects. This may explain why some previous studies have shown that DDT exposure increases breast cancer risk, and others have not. It also suggests that the ratio of the two compounds in the fat surrounding breast tissue may be important for how exposure to DDT influences the risk for breast cancer.

Breast Cancer Risk Factors: Lesbians and Heterosexual Women. Some scientists have proposed that lesbians may be at two to three times the risk of breast cancer of heterosexual women. However, there have been no definitive population-based studies of this issue, and more information is needed***. Suzanne L. Dibble, D.N.Sc.,*** at the ***University of California, San Francisco,*** and ***Stephanie Roberts, M.D.,*** at ***Lyon-Martin Women's Health Services,*** San Francisco, investigated the distributions of standard risk factors among lesbians and heterosexual women. The research team

surveyed 255 lesbians over age 40, and asked each to have both her sister closest in age and a heterosexual friend fill out the same survey. The estimated lifetime risk for developing breast cancer, based on known risk factors, was 11.1 out of every 100 lesbians and 10.6 out of every 100 heterosexual women. The lesbians in this study had more education than their friends or sisters, fewer live births, abortions, and miscarriages. Lesbians also weighed more in relation to their height than their sisters and friends. In addition, lesbians had more breast biopsies and mammograms than their sisters and were more likely to have been diagnosed with breast cancer than their friends. Based on this sample, lesbians have a higher risk profile for breast cancer than heterosexual women, but the difference is lower than previously surmised. Results of the study were published in the *Journal of Gay and Lesbian Medical Association* 1998 2(3):93-101.

Profiling of Tyrosine Phosphatases in Breast Cancer.

Many of the processes allowing cancer cells to multiply and spread are controlled through a type of reversible chemical reaction among cell proteins. The reaction either adds or subtracts a molecule of phosphorus to the protein, and these processes are also involved in breast cancer acquiring resistance to drug treatments like tamoxifen. Enzymes called tyrosine phosphatases remove a molecule of phosphorus from a protein and other enzymes called tyrosine kinases add one. The balance between the two determines the fate of the cell. ***Clifford Tepper, Ph.D.,*** at the ***University of California, Davis,*** used a novel method to allow his team to examine all the tyrosine phosphatases in a cell and another technique that allowed them to examine 12,500 genes simultaneously. The team found five tyrosine phosphatases affected by levels of estrogen in cells. One of them, DUSP1, increased 3.5-fold when estrogen was withdrawn from cells. DUSP1 inhibits pre-programmed cell death, and DUSP1 was present at higher than normal levels in 4 out of 15 breast cancer tissue samples the team studied. The team generated a breast cancer cell line with high levels of DUSP1, and the cell line was highly resistant to treatment with tamoxifen, a treatment that kills cancer cells. Other parts of this research showed that a treatment to block the action of DUSP1 could be a beneficial addition to other breast cancer therapies.

USC/NCCC Breast Cancer Research Training Program.

The CBCRP encourages and supports training in breast cancer research for new research scientists. ***Ronald K. Ross, M.D.,*** and ***Michael Press, M.D., Ph.D.,*** maintain the multifaceted Breast Cancer Research Training Program at the ***University of Southern California/Norris Comprehensive Cancer Center,*** 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 multidisciplinary faculty. Over the years, 30 scientists have received training. Several have gone on to win grants to pursue breast cancer research on their own, and the majority of the trainees have developed a long-term commitment to breast cancer research.

Exercise and Risk of Breast Cancer Recurrence.

Strenuous lifetime exercise lowers women's chances of getting breast cancer. ***Malcolm C. Pike, Ph.D.,*** and ***Lisa Shames, Ph.D.,*** at the ***Keck School of Medicine, University of Southern California***, Los Angeles, investigated whether exercise can prevent a recurrence of breast cancer. The team contacted women treated for breast cancer at Norris Hospital between 1987 and 1997 and interviewed them about their exercise habits since their diagnosis and treatment. Women whose breast cancer had recurred, or who developed a new breast tumor, were matched with women whose cancer had not recurred, and who had the same stage of tumor at diagnosis, age at diagnosis, and year of diagnosis. Results suggested that women who exercised were only half

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, then the exposure, behavior, or biological factor is a possible cause or contributor to the disease. At that 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.

as likely to have their breast cancer recur as those who exercised little or not at all. However, the number of women studied was so low that the results are not statistically significant. Still, this research suggests that exercise is associated with a much-reduced rate of breast cancer recurrence and is worthy of further research in a larger study population.

Research in Progress

A number of ongoing CBCRP grants in the topic of *Etiology* reported progress in 2003.

Pesticides and Breast Cancer in Hispanic Women in California.

Paul K. 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 investigated exposure to pesticides among female members of the United Farm Workers (UFW) of America, the state's largest agricultural labor union, comparing the pesticide exposure of 90 UFW members with breast cancer, and 450 UFW members without. Women who had breast cancer were 54 percent more likely to have the highest exposure to all the agricultural chemicals covered in this study. Women with breast cancer were more than twice as likely to have the highest exposure to the pesticide chlordane, four times as likely to have the highest exposure to the pesticide Dicofol, and 82 percent more likely to have the highest exposure to the herbicide simazine. However, these results were not statistically significant. The research team is analyzing the data further. The results of the study could further public understanding of the impact of agricultural chemicals and expand justification for integrated pest management and workforce protection from toxic chemicals.

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 504 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 are affected by androgen. So far, the team has analyzed genetic variations among the women for the first of two genes they are studying, the PSA gene, and they are in the process of doing the same for the second, the androgen receptor gene.

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. Some studies have suggested that women with a version of the androgen receptor gene that produces less active androgen receptor protein have a higher breast cancer risk. She has found that post-menopausal women who have ever used estrogen and progestin therapy, and who also have the version of the androgen receptor gene that produces less active protein, have denser breasts. This means that the androgen receptor gene may play a role in determining whether estrogen and progestin therapy (often called hormone replacement therapy) causes breast cancer. Research results have been published in *Breast Cancer Research* 5 (2003):164-173.

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

A diet high in omega-6 fats, which are found in many vegetable oils—including corn, canola, and safflower—may cause breast cancer. Other fats may be harmless or even protective. ***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 omega-6 fats. Her team tested the genes from 814 women with breast cancer and 910 women without the disease from three ethnic groups: white, Hispanic, and African American. So far, the team has found that African American women who do not have the most common version of one fat metabolizing gene, 12-LOX, are 1.5 times more likely to get breast cancer than African American women with the most common version. If those women whose 12-LOX gene puts them at higher risk also eat a higher than average amount of omega-6 fats, then they are 2.3 times as likely to get breast cancer.

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 infection with Epstein Barr virus or exposure to chemicals formed when meats and fish are cooked at high temperatures increase breast cancer risk. To date, they have completed interviews with 408 Hispanic women with breast cancer and 435 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 826 DNA samples that will be stored for future molecular studies. They hope to identify lifestyle factors that can be changed to prevent breast cancer.

Breast Cancer in California Teachers—Regional Variations.

Scientists have long known that breast cancer rates vary widely by geographic area, but they don't know 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 teachers in the San Francisco Bay Area have a rate of breast cancer 22 percent higher, and teachers in the Los Angeles-Orange County-San Diego area have a rate 16 percent higher, than teachers in the rest of the state. These numbers are consistent with the rates for women as a whole in California. Teachers in the Bay Area and three south counties were slightly older, represented a more racially diverse population, and were more likely to live in urban and affluent neighborhoods. While older age and affluence are associated with a higher breast cancer risk, these characteristics of the teachers do not fully explain the excess risk in the Bay Area and the three southern California coastal counties. Results from this study were published in *Epidemiology* 2004 15(1):6-12.

Research Initiated in 2003

Four grants studying external influences on breast cancer began in 2003.

The Hygiene Hypothesis and Breast Cancer Risk.

Recent research shows that children who get exposed to more germs develop a healthier immune system. Children raised in a sanitized, disease-free environment get more allergies and autoimmune diseases. ***Christina Clarke, Ph.D.,*** at the ***Northern California Cancer Center,*** Union City, is investigating whether women with less exposure to germs during childhood later have an increased risk for breast cancer.

Epstein-Barr Virus in Breast Cancer Tissues.

By adulthood, almost everyone is chronically infected with Epstein-Barr virus. Most infections are harmless; a small minority cause stomach cancer, lymphoma, or nasal cancer. This virus may also play a role in some cases of breast cancer. ***Sally Glaser, Ph.D.,*** at the ***Northern California Cancer Center,*** Union City, will use sensitive new laboratory techniques to test 100 tumor samples for the virus and identify characteristics of women whose tumors contain the virus.

Genetics, Obesity, and Breast Cancer Risk.

Catherine Carpenter, Ph.D., at the ***University of California, Irvine,*** will investigate whether various forms of several genes make women more likely to be obese and also more likely to get breast cancer.

Prolactin and Breast Cancer Risk in a Multiethnic Cohort.

The hormone prolactin is important to milk production and to breast development during puberty and pregnancy. Women with higher levels of prolactin in their blood may have a higher risk for breast cancer. ***Brian Henderson, M.D.,*** at the ***Keck School of Medicine, University of Southern California,*** Los Angeles, is investigating whether genes control the levels of prolactin in the blood, and if some versions of these genes are more common among women who have had breast cancer than among women who haven't had the disease.

Prevention and Risk Reduction: Ending the Danger of Breast Cancer

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 should be made? The CBCRP funds research into promising areas, including diet and behaviors that women can change to reduce their risk, and new prevention strategies. 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, and on groups of women who have genes that may raise their risk for breast cancer.

Research Conclusions

Four CBCRP grants examining *Prevention and Risk Reduction* options in breast cancer were completed in 2003.

Bovine Leukemia Virus Infection and Human Breast Cancer Risk.
Gertrude Buehring, Ph.D., at the ***University of California, Berkeley,*** investigated whether being infected with the bovine leukemia virus can increase a woman's risk for breast cancer. She had previously shown that a majority of women have antibodies to bovine leukemia virus. The virus is found in beef and milk; it can be transmitted to humans who eat non-pasteurized dairy products or undercooked beef. It causes mammary tumors in animals (the equivalent of breast tumors in humans). The research team analyzed samples of normal breast tissue and breast tumors. The tumor tissue had a higher rate of infection with bovine leukemia virus than the normal tissue, but the team was not able to test enough tissue samples for the results to be statistically significant. Results of the study were published in *AIDS Research and Human Retroviruses* 18(12): 1105-1113. Dr. Buehring plans to continue this research.

Breast Cancer Prevention with Phytoestrogens from Grape Juice.
Grape juice suppresses breast cancer cell growth by preventing the synthesis of the female hormone estrogen. About 60 percent of breast tumors in pre-menopausal women and 75 percent of those in post-menopausal women depend on estrogen for growth. This suggests that drinking grape juice may reduce the risk of breast cancer. ***Shiuan Chen, Ph.D.,*** at the ***Beckman Research Institute, City of Hope,*** Duarte, isolated and tested compounds from grape juice and red wine for their ability to prevent tumor formation. Grape juice extracts were difficult to isolate because of the sugar in the juice, so the team turned to red wine extracts. They found that a red wine extract

containing compounds known as procyanidin B dimers (which are present in grape seeds) completely stops the action of aromatase, an enzyme that generates estrogen in cells. The extract stopped the growth of tumor cells in laboratory cultures. When the extract was fed to mice genetically engineered to produce extra aromatase, it prevented tumors and the mice also exhibited other signs of estrogen deprivation. Results of the study were published in *Cancer Research* 2003 Dec 1; 63:8516-8522.

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. Many of the herbs used in Essiac tea have biological activities associated with decreasing cancer risk and long histories of use in Asian diets and medicine; yet there have been no previous published scientific studies evaluating Essiac tea's effectiveness at preventing breast cancer. ***Kristen S. Kulp, Ph.D.,*** of the ***Lawrence Livermore National Laboratory,*** fed one group of rats with water and another with a 3 percent 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 percent of those fed water. The rats fed Essiac also had twice as many tumors. The team then tested Essiac tea on rats whose genes had been altered to cause the mice to spontaneously form mammary tumors that are the equivalent of Her-2/Neu-positive breast tumors in humans. These tumors are among the most likely to spread to other parts of the body and cause death. The mice fed Essiac tea had fewer tumors than the mice that did not receive any. However, the mice fed Essiac tea did not live as long as the others. The results suggest that in some instances, Essiac tea may protect against breast cancer, and in others, promote the disease. The CBCRP is funding further research into Essiac tea.

Breast Cancer Prevention by Analogs of EGCG from Green Tea.

Nurulain Zaveri, Ph.D., at ***SRI International,*** Menlo Park, built 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 that is five times more powerful at inhibiting the growth of breast cancer cells. It works both against breast cancer cells that need estrogen for survival and those that do not. This EGCG analog can also be absorbed by the digestive tract more easily than the EGCG found in green tea. Dr. Zaveri plans to test the new compound further with a goal of developing a pill that could be taken by women who are at high risk for their breast cancer recurring. Results of the study were published in *Synthesis* 2 (2003):267-71 and *Organic Letters* 2001 Mar 22; 3(6):843-6.

Research in Progress

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,*** treated mice and rats with 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 hadn't had the hormone treatment, were then given a cancer-causing substance, to see if the hormone treatment provided protection from mammary cancer (the mouse/rat equivalent of breast cancer). The rodents with the hormone treatment had 80 percent less cancer. This non-toxic treatment is as effective at preventing mammary cancer as a full-term pregnancy, removal of the ovaries, or long term treatment with the preventive drug tamoxifen. The research team also found that the hormone treatment caused genes involved in growth promotion to become less active, and genes involved in growth inhibition to become more active.

Research Initiated in 2003

Four grants studying prevention and risk-reduction options began in 2003.

Preventing Breast Cancer with Ginseng.

Michael DeGregorio, Ph.D., at the ***University of California, Davis,*** is investigating whether ginseng, a natural remedy used for thousands of years in Asia, can prevent breast cancer. He is giving three groups of mice a chemical that causes breast cancer. Some mice will then get ginseng, others a drug that prevents breast cancer, and others no treatment. The research team will then compare the number and type of tumors in all three groups of mice.

Studying the Interaction of an Essiac Tea and a Food Mutagen.

Women who eat well-done meat have a higher risk of breast cancer than those who don't. PhIP is a chemical formed when meat is cooked; it damages DNA in cells and causes breast tumors in rats. Essiac tea is an herbal mixture women with breast cancer often use in addition to treatment prescribed by a physician. ***Kristen Kulp, Ph.D.,*** at ***Lawrence Livermore National Laboratory,*** is investigating whether Essiac tea protects cells against DNA damage and tumors caused by PhIP.

Common Genetic Variation & Breast Cancer: A Genomic Approach.

Women who have mutations in certain genes have a higher than average risk for breast cancer. ***Christopher Haiman, Ph.D.,*** at the ***University of Southern California,*** Los Angeles, is investigating whether some versions of these genes that are considered normal also raise the risk for breast cancer. The research team will study hundreds of subtle differences in the genes of a large group of African American, Latina, Japanese, white, and Hawaiian women in Los Angeles and Hawaii.

The IGF Pathway and Breast Cancer Risk in African Americans.

African American women under age 50 are twice as likely to die from breast cancer as white women from the same age group. ***Susan Neuhausen, Ph.D.,*** at the ***University of California, Irvine,*** is investigating a group of genes called the IGF pathway, which may directly affect cell growth. She will compare the IFG pathway genes in 600 African American women with breast cancer and 232 African American women without the disease to see if there are any differences.

Biology of the Breast Cell: The Basic Science of the Disease

Researchers are beginning to appreciate how changes in the biology of the normal breast are inseparable from the subsequent pathogenesis of breast cancer. Such research topics as hormone responsiveness, aging, programmed cell death, the biology of breast stem cells, and interactions with the supporting stromal tissue are all normal breast processes that can become deregulated and lead to breast cancer. For its part, the CBCRP added the priority issue topic of Biology of the Normal Breast in 1997 to encourage new research activity to investigate the pre- and early-cancerous stages of the disease. Pathogenesis has always been a priority issue for the CBCRP.

We divide research in this area into two Priority Issues:

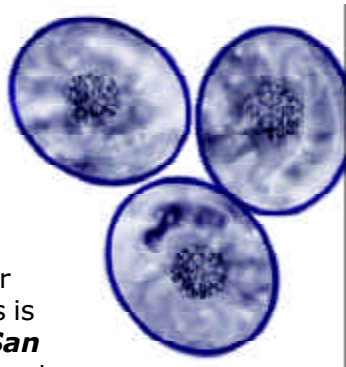
· Biology of the Normal Breast

· Pathogenesis

Biology of the Normal Breast: The Starting Point

The *Biology of the Normal Breast* is a greatly understudied area. The breast is a complex structure composed of several cell types. We know that the milk-forming epithelial cells are most associated with tumors, but there are many questions remaining. How do the different types of cells interact in the breast under normal conditions? What normal changes are necessary for the breast to function properly? Without knowing the answers to these questions, it requires a leap of faith to be able to identify the abnormal changes associated with cancer.

What we do know about the breast is that it is an organ in constant flux. Researchers are finding that how the breast remodels itself under the influence of internal and external factors dictates how it functions. The production of milk depends on the maturity (differentiation) of the breast cells, which in turn is controlled by hormones and growth factors and the immediate environment of the cells, as well as the internal and external physical structure of the cells.



Research Conclusions

Eight CBCRP grants studying the *Biology of the Normal Breast* were completed in 2003.

The Role of N-CoR During Normal Mammary Gland Development.

Tumors that are estrogen receptor positive (ER+) depend on estrogen for their growth. However, precisely how estrogen regulates these processes is still unclear. ***Sung Hee Baek, Ph.D.,*** of the ***University of California, San Diego,*** studied the role of a protein, N-CoR, in the growth and development of the normal mammary gland. N-CoR is a molecule inside the nucleus that is involved in estrogen regulation of cell growth. Using a test called immunohistochemistry, which allows researchers to detect the presence of specific proteins in cells or tissues, Dr. Baek found that some protein signals could lead to a progressive decrease of N-CoR. Dr. Baek also found that when N-CoR is not present, tamoxifen, a drug used to treat breast cancer tumors that are (ER+), stimulates the estrogen receptor. These findings have the potential to impact the diagnosis and treatment of human breast cancer, and have been published in *Cell* 111 (2002):673-685 and *Cell* 110 (2002):55-67.

Coactivators in Mammary Gland Development and Tumorigenesis.

Estrogen and progesterone, two hormones that are produced by the ovaries, control the growth of the epithelial cells in the breast by attaching to the estrogen and progesterone receptors. Once these receptors are turned on, they can turn on genes that play a role in both normal breast development and breast cancer. Two genes that facilitate the function of the p160 gene, p/

CIP and SRC1, increase the activity of the estrogen and progesterone receptors. Also, high levels of the p/CIP gene and its proteins are found in human breast and ovarian cancers. ***Zhiyong Wang, Ph.D.,*** at the ***Salk Institute for Biological Studies*** in La Jolla, looked at whether p/CIP and SRC1 could cause cancer to develop in mice. His team found that when just one gene was not working, no problems developed. But when both genes did not work, the mice developed a defect in their mammary gland after puberty. This suggests that p/CIP and SRC1 are required for normal development of the mouse mammary gland. Dr. Wang's team also developed a mouse that makes too much p/CIP in the mammary gland, and they found that these mice develop tumors as they get older. Dr. Wang published results of his study in *Cancer Cell* 4 (2003):499-515.

Method for Measuring Breast Epithelial Turnover in Humans.
Each time a normal epithelial cell divides, the chance of a genetic mutation increases. The accumulation of genetic mutations is a hallmark of cancer. Thus, a reliable way to measure the division rate of cells in the breast has the potential to increase understanding of how cancer develops and provide a way to test cancer prevention treatments. ***Marc Hellerstein, M.D., Ph.D.,*** at the ***University of California, Berkeley,*** investigated a technique developed in his laboratory to measure cell division rates directly, without using radioactivity or toxic substances. His team found that this technique could successfully measure a woman's cell division rate by using breast tissue from core biopsies. They have also found that genistein, a substance found in soybeans, decreases the epithelial cell division rate in rats. Dr. Hellerstein's team is now conducting a study that aims to establish normal rates of epithelial breast cell division and to determine factors that might be associated with this turnover rate in women, such as age, weight, ethnicity, and diet. His team also intends to look at whether their technique can predict who is most at risk for developing breast cancer. Dr. Hellerstein presented an abstract of his research in *FASEB Journal* 14(4):A786.

Telomeres and Telomerase

Chromosomes will unravel if they are not capped by specialized sequences of DNA, called telomeres. But 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.

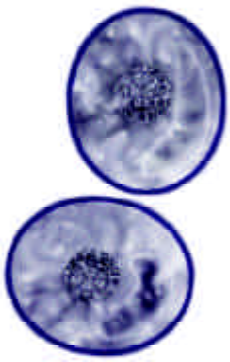
However in early cancer progression, cells acquire the ability to overcome this limitation to cell division, and they become immortal. The presence of telomerase activity in the majority of breast tumor samples indicates the importance of this process in cancer progression. Interestingly, the technical issues with "cloning" adult animals by introducing adult cell nuclei into eggs appear to be partly associated with chromosomal shortening. The resulting clones are prematurely aged animals because the ends of their chromosomes have not been restored to full length, as would occur in normal reproduction.

Telomere Dynamics During Breast Development.

Unlike most other cells, breast cells undergo changes during breast development at puberty and throughout most of adulthood, especially during pregnancy and lactation. ***Sahn-Ho Kim, Ph.D.,*** at the ***Lawrence Berkeley National Laboratory,*** studied how telomeres and telomere-associated proteins influence the development of breast cells. Telomeres are the protective caps that are on each end of a chromosome's four arms (a chromosome looks like an X), and keep the chromosome in working order. TIN2 is a human telomere-associated protein that plays an important role in the cell. Dr. Kim found that the TIN2 proteins regulate telomere length. He also found that removing the TIN2 proteins from cells causes the cell to die, which suggests that TIN2, along with telomeres, are necessary for a cell to survive. In addition, Dr. Kim found that an abnormal form of TIN2, TIN2-13, increases telomere length. This abnormal TIN2-13 also disrupts the development of breast cells in cell culture. Results of this study were published in *Oncogene* 21 (2002):503-11 and the *Journal of Biological Chemistry* 277 (2002):28609-17.

Cell Growth Control of Breast Epithelial Cells.

Intracellular Rho GTPases, including Rac, Cdc42 and Rho, provide an important regulatory mechanism to connect cell-surface generated signals with the nucleus. ***Ulla Knaus, Ph.D.,*** at ***The Scripps Research Institute,*** La Jolla, investigated two proteins that appear to be involved in the growth of normal breast cells. The two proteins are called Rac3 and Rac1. The expression of the proteins is turned on by hormones and by proteins called growth factors that come from outside the cell. Rac3 is consistently expressed in tumors, while Rac1 is not. This might mean that Rac3 is tricking cells into growing at inappropriate times. Rac3 does not have mutations, so Dr. Knaus investigated where inside breast cells this protein is attached. Her team introduced fluorescent copies of both proteins into normal human breast epithelial cells. They found that Rac1 distributed itself throughout the cell, but Rac3 attached to membranes inside the cell. They also found that several growth-stimulating substances that activate Rac1 don't activate Rac3. This information provides clues about the basic biology of the breast that may prove useful in the development of new treatments for breast cancer.



A Vascular Restriction of Mammary Tumor Progression.

A number of growth factors are associated with the tumor and normal cell's blood supply. VEGF (vascular-endothelial growth factor) is a significant part of angiogenesis (blood vessel growth). When a person is injured, VEGF is helpful—it aids healing by stimulating the growth of blood vessels. When cancer is present, VEGF is not helpful—it allows tumors to grow new blood vessels, which enables them to grow and spread. ***Robert Oshima, Ph.D.,*** at ***The Burnham Institute,*** La Jolla, developed a genetically engineered mouse that was prone to have both breast cancer and a higher level of VEGF. Dr. Oshima compared tumor growth in the mice he developed with tumor development in normal mice. He found that the mice with the higher levels of VEGF began to develop tumors immediately after the mammary gland began to develop and that these tumors not only grew dramatically faster but also quickly produced new tumor blood vessels. Based on these findings, Dr. Oshima concluded that the increased blood supply that VEGF provides is important for large tumors and appears to play a critical role in the transformation of fast-growing cells into small tumors. Dr. Oshima's results were recently published in *Cancer Research* 64 (2004):169-79.

Defining a Role for Endothelial Precursor Cells in Breast Cancer.

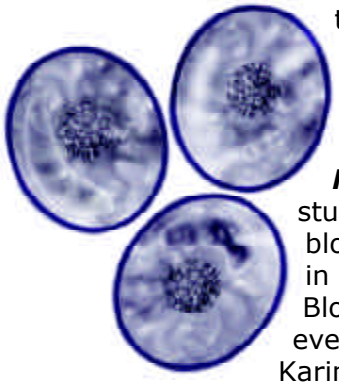
Blood vessels are lined with endothelial cells; new endothelial cells can come from existing blood vessels or from endothelial precursor cells that originate in the bone marrow and circulate in the blood. ***Longchuan Chen, Sc.D.,*** at

the ***La Jolla Institute for Molecular Medicine,*** investigated the role endothelial precursor cells play in both normal breast development and in breast tumors. Dr. Chen's team used mice with breast tumors to track the movement of the endothelial precursor cells from the marrow. They found groups of these cells in the tumor blood vessels, but they were only a small percentage of the total number of endothelial cells. Dr. Chen is going to continue to study the role that the endothelial precursor cells that come from bone marrow play when cancer begins to develop. He is also going to continue to study an antibody his team found that could stop the endothelial precursor cells from forming new blood vessels. This antibody could become a breast cancer treatment.

Research in Progress

A number of ongoing CBCRP grants in the topic of *Biology of the Normal Breast* reported substantial progress in 2003.

Role of IKKa in Mammary Gland Development.



In the tiny space between the cell's membrane (where information is received) and the cell's nucleus (where genes are regulated), there exist a multitude of signaling pathways. Collectively the study of "signal transduction" involves all areas of cancer biology. A particularly interesting pathway is called NF-κB, which plays an important role in the regulation of the immune response, cell death, inflammation, cell cycle progression, and cancer. Activation of NF-κB is thought to be part of a stress response induced by growth factors, cytokines, UV, and pharmacological agents. ***Michael Karin, Ph.D.,*** at the ***University of California, San Diego,*** is studying an NF-κB regulatory element, called IKKα. Dr. Karin has shown that blocking this enzyme decreases or delays the development of breast cancer in mice. Dr. Karin is now investigating how IKKα causes tumors to grow. Blocking this enzyme doesn't affect other tissues or organs, so it could eventually be a target for a treatment that would have few side effects. Dr. Karin and his colleagues have published numerous articles on this topic, which they recently reviewed in *Seminars in Cancer Biology* 13 (2003):107-114 and *Nature Reviews Cancer* 2002 Apr;2(4):301-10.

Steroid Receptor Coactivators in Mammary Gland Development.

Cells in normal breast tissue and in estrogen receptor (ER)-positive breast cancers need estrogen to grow. Breast cells that do not get estrogen stop proliferating and die. This is why ER-positive breast cancers are treated with drugs that block estrogen activity. ***Shi Huang, Ph.D.,*** at ***The Burnham Institute,*** La Jolla, and colleagues discovered a new tumor suppressor gene, RIZ1, and they are investigating this new gene and the protein it produces. They have found laboratory evidence that suggests that the breast needs RIZ1 to respond to the hormones estrogen and progesterone, and they are now exploring the relationship between RIZ1 and the estrogen receptor. This research could lead to the development of new drugs for the prevention and treatment of breast cancer.

Genetic Aspects of Physiological Response During Lactation.

When a clump of tumor cells grows too large, the level of oxygen in the tissue decreases (i.e., hypoxia). In response, a protein, HIF-1α, increases and activates genes that control new blood vessel growth. Recent studies have shown that high levels of HIF-1α have been found in a variety of tumors, including breast tumors. ***Randall S. Johnson, Ph.D.,*** at the ***University of California, San Diego,*** is investigating whether the HIF-1α response to lowered oxygen

levels contributes to mammary gland development and the production of milk in mice. These findings could lead to new ways to block blood vessel growth in breast tumors and to new breast cancer treatments. Results from this research were published in *Development* (2003) 130:1713-1724.

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, and much of this information is in publicly-accessible databases; however, statistical techniques to identify important and useful patterns in the data are not available. ***Saira Mian, Ph.D.,*** at the ***Lawrence Berkeley National Laboratory,*** is developing a variety of cutting-edge statistical techniques that can identify these patterns. This approach could make it easier to diagnose and treat breast cancer and may help explain why cancer treatments work on some people, but fail for others. Results from Dr. Mian's research were published in *Journal of Biological Chemistry* 278 (2003):3882-3890, *Signal Processing* 83 (2003):729-743, *Lancet* 362 (2003):440-445, and *Mechanisms of Aging and Development* 124 (2003):109-114.

Effect of Breast Cell Environment on Repair of DNA Damage.

Breast cells become cancerous when they no longer respond to signals that control their growth. Signals regulating cell growth come from both within and outside the cells. Within the breast tissue, cells contact other cells as well as the scaffold material, called the extracellular matrix (ECM) that surrounds them. ***Aylin Rizki, Ph.D.,*** at the ***Lawrence Berkeley National Laboratory,*** is investigating how communication between cells and the ECM affect a cell's ability to repair damage to its DNA. When the DNA is not repaired properly, it can accumulate genetic changes, which sets the stage for cancer to occur. She is also continuing to explore the finding that restoring proper communication between the cells and the ECM can turn cancer cells back into normal cells. Results from this research were published in *Differentiation* 70 (2003):537-46 and *Signal Processing* 83 (2003):729-743.

Rac/STAT5 Signaling.

Normal breast function depends on proper interactions between breast epithelial cells and the cells that surround them. These interactions regulate the responses of epithelial cells to hormones, like prolactin and estrogen, 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, and the theory that they function as a master switch that not only controls how the genes in the breast respond to prolactin and estrogen but also aids in the development of breast cancer and tumors that are drug resistant. His research on the role Rac and STAT5 play in both normal and breast cancer cells will provide important information about normal breast biology and cancer progression.

Role of Chromatin Regulator in Breast Cell Growth.

To grow, both normal cells and cancer cells need the information carried on their DNA to synthesize a large number of different proteins. Chromatin is the substance that forms chromosomes. It contains DNA, RNA, and various proteins. ***Hongwu Chen, Ph.D.,*** of the ***University of California, Davis,*** has found that one of the proteins that regulates chromatin is also present in elevated amounts in breast tumors. Dr. Chen is investigating how this protein controls normal breast cells and spurs breast tumor cell growth. This research has allowed Dr. Chen to develop a new model for why tumors stop responding to the hormonal treatment tamoxifen. It also has the potential to lead to new breast cancer treatments.

The Importance of Growth Inhibitory Signals in Normal Breast Cells.

HER-2 is a protein found in larger than normal amounts in about 30 percent of breast cancer cases. Scientists do not yet understand how having too much HER-2 promotes 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 in the breast that are the body's first line of defense against breast cancer. Dr. Wilson and her colleagues are also continuing to explore their finding that higher than normal levels of HER-2 can make cells less sensitive to a protein called transforming growth factor beta, which may control the growth of breast epithelial cells. This research could lead to the development of new treatments for women with HER2-positive breast cancer.

Telomere Clustering is Lost in Mammary Epithelial Tumors.

Paul Kaminker, Ph.D., of ***Lawrence Berkeley National Laboratory,*** is investigating a part of the nucleus associated with the telomeric protein, TIN2, called a "TIN2 cluster." The absence of these clusters has been shown previously to be an indicator that a tumor is malignant. Dr. Kaminker's research will provide more information about what types of proteins comprise these clusters, how likely it is that cells that do not have these clusters will become cancerous, and whether keeping the clusters together will affect whether tumors are formed. Dr. Kaminker and his mentor, ***Dr. Judith Campisi,*** recently reviewed their progress on this topic in *Oncogene* 21 (2002):503-11.

Understanding Aging Effects in the Breast.

As the body ages or senesces, the supporting stromal cells become less functional and this affects the overall biology of the breast. ***Ana Krtolica, Ph.D.,*** at the ***Lawrence Berkeley National Laboratory,*** is investigating a type of breast cell called a fibroblast. Fibroblasts do not usually become cancerous, but they are part of the structure that supports the cells that do.

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.

Why are epithelial cells the source of most cancers? An answer may come from the study of **stem cells**, which are immortal cells that persist in all organs where cell replacement activity is needed. Recent work from the **University of Michigan** has shed light on the role of stem cells in breast cancer. **Drs. Michael Clarke and Max Wicha** with their associates have developed novel ways of detecting and investigating the properties of breast stems cells. Importantly, they find that these cells persist in breast tumors in small numbers, and appear to be the source of the tumor growth and progression. Thus, the current therapeutic paradigm of killing tumor cells and shrinking tumors as a measure of efficacy may fail in practice, if tumor stem cells resist the therapy and persist to regenerate the tumor.

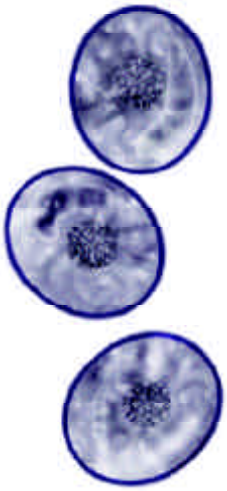
Dr. Krtolica is studying which mutations in breast cells make them sensitive to the senescent fibroblasts around them. What she learns about how cells in the breast age and how their aging affects nearby cells could lead to new advances in breast cancer prevention and treatment. Results from this research were published in *International Journal of Biochemistry and Cell Biology* 31 (2002):1401-1414 and *Cytometry* 49 (2002):73-82.

Genetic Alterations in MRI Screen-Detected Breast Lesions.

James Ford, M.D., and ***Sylvia Plevritis, Ph.D.,*** at ***Stanford University,*** are using Magnetic Resonance Imaging (MRI) screening in women with inherited BRCA1 and BRCA2 mutations who are at high risk for developing breast cancer. The tissue from breast lumps found through MRI will be analyzed for genetic changes that may be able to predict whether a benign lump later becomes cancerous. This research could lead to more extensive use of MRI for breast cancer screening and to new genetic tests for predicting who is at risk for breast cancer. Drs. Ford and Plevritis recently published their results in *Cancer* 100 (2004):479-89.

Understanding Telomere Dynamics in the Breast.

Telomeres, which cap the ends of chromosomes, shorten as we age, and when they get too short, a cell can no longer divide. Cancer cells learn how to keep the telomeres from getting too short, which allows them to divide indefinitely. ***Steven Artandi, Ph.D.,*** at ***Stanford University,*** is studying how normal breast cells respond to telomere shortening as they age. He is also investigating how telomeres are reactivated. This research on how breast cancer evolves could lead to new methods of prevention and treatment.



Research Initiated in 2003

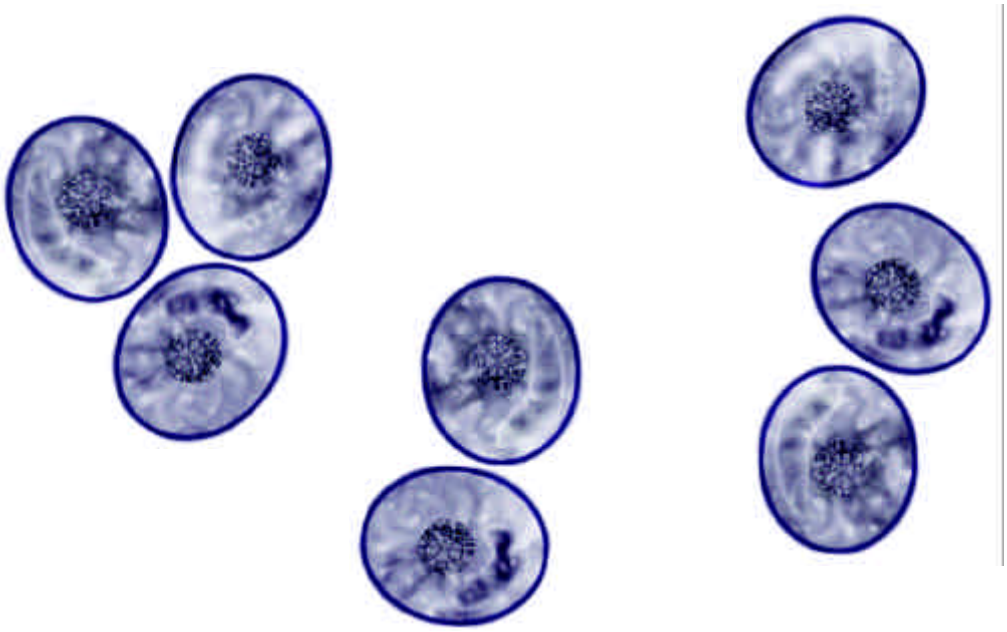
The CBCRP funded eight new individual grants in 2003 to pursue studies on *Biology of the Normal Breast.* The earliest stage of *embryonic breast development* involves the migration of the breast epithelial cells to the location on the body where the breast will eventually form. ***Saverio Bellusci, Ph.D.,*** of the ***Children's Hospital Los Angeles,*** received a three-year grant to investigate this process. He will study how the interactions between the growth factor FGF10 and WNT gene family direct breast epithelial cell migration. Ultimately this research may give us insights into the metastatic process of breast tumors.

Three investigators were awarded grants to study the *regulation of gene activation and inactivation in the normal breast cell*. ***John Conboy, Ph.D.,*** of the ***Lawrence Berkeley National Laboratory,*** will investigate the changes in cell behavior due to "alternate splicing"—when one gene produces different proteins from the same code. Dr. Conboy will study the mechanism for the determining which protein is produced under different cellular conditions. ***Peter Kaiser, Ph.D.,*** of the ***University of California, Irvine,*** will also use an IDEA to study the genetic regulation of the breast cancer susceptibility gene BRCA1 through a process of protein degradation, called ubiquitylation. ***Yuehai Ke, Ph.D.,*** at ***The Burnham Institute*** in La Jolla, was awarded a postdoctoral fellowship to determine the role of a set of proteins called tyrosine phosphatases, which are known to regulate the activation of other proteins, in the development and normal functioning of the mammary gland.

The *aging of breast cells and supporting stroma* result in changes that may contribute to breast cancer. Two newly-funded CBCRP grants will investigate the role of DNA integrity in the function of normal breast cells. ***Kimberly McDermott, Ph.D.,*** of the ***University of California, San Francisco,*** will undertake a postdoctoral fellowship to investigate the how the cellular struc-

tures that regulate DNA replication (centrosomes) function to protect it from mutations and chromosomal abnormalities. ***Paul Yaswen, Ph.D.,*** of the ***Lawrence Berkeley National Laboratory,*** will investigate a newly discovered gene, called BORIS, for its role in controlling the integrity of DNA and determine whether it plays a role in the early transformation of breast cells.

The *early changes in the transition from a normal breast cell to a breast tumor* cell are subtle, but it is the goal of two studies funded this year to define the key genetic changes in this transition. ***Thea Tlsty, Ph.D.,*** of the ***University of California, San Francisco,*** developed an early precursor model of breast cancer, called the variant Human Mammary Epithelial Cell (vHMEC) that has specific genetic characteristics. Dr. Tlsty will determine whether these same characteristics can be found in early pre-cancer breast lesions, and therefore used to distinguish them from normal cells. Finally, the information age has opened new avenues for characterizing and understanding important changes to tissues at the protein level. One new technology is called proteomics, which is the simultaneous comparison of proteins in tissues under different physiological conditions. ***Drs. Dave Hoon, Armando Giuliano,*** and ***Lori Wilson*** (co-PIs) at the ***John Wayne Cancer Institute*** in Santa Monica will apply this new technology to the breast. The two major goals of the project are to: (1) determine whether it is possible to develop a proteomic profile signature of normal breast tissue during different stages of physiology, and (2) determine if proteomic profile signatures of various types of benign breast disease can be used for diagnosing early stages of pre-cancerous breast disease.



Pathogenesis: Understanding the Disease

Although cancer is often described simply as a genetic disease, there are many competing theories to explain the gene alterations and mutations that initiate cancer and those that promote disease progression. **W. Wayt Gibbs**, writing in the July 2003 issue of *Scientific American,* summarized this cancer confusion as, "…it is more useful to think of cancer as the consequence of a chaotic process, a combination of Murphy's Law and Darwin's Law: anything that can go wrong will, and in a competitive environment, the best adapted survive and prosper." In a more scientifically detailed fashion, **Dr. William Hahn** at Dana-Farber Cancer Institute in Boston and **Dr. Robert Weinberg** at MIT have pointed to six key cellular events that are "hallmarks of cancer" (recently reviewed in *New England Journal of Medicine* 348 (2003):674). Taken together these cellular events attempt to account for the sporadic nature of cancer; the biological and pathological heterogeneity seen in patients; immortality of cancer cells; numerous gene and chromosomal alterations; uncontrolled growth, motility, and metastasis events; and resistance to therapy.

Since no single approach can successfully explain cancer, researchers are employing a variety of technologies and methods. These range from cell and animal models; complex genomic and proteomic techniques to identify and relate multiple genetic changes in various forms of the disease; and the application to cancer of new discoveries in basic cell biology, DNA repair, cell cycle, growth signaling, and gene regulation processes. Still, in breast cancer the response to hormones, especially estrogen, remains a key underlying theme. Researchers now think that estrogen may operate in ways outside the classical estrogen response. New thinking is also emerging for the growth factor receptors, epidermal growth factor receptors (EGFR), and the Her oncogenes. There is much interest in cross-talk between the hormone response and growth factor signaling pathways, previously thought to be distinct. Finally, the inherited breast cancer risk genes, BRCA1 and BRCA2, are being studied in more advanced ways to better explain how DNA defects, repair processes, and cell growth/death pathways are interrelated and become defective in cancer.

Research Conclusions

Under the *Pathogenesis* priority topic 19 grants were completed in 2003.

A New Model for Inflammatory Breast Cancer.
Anti-E-Cadherin Apoptosis of Inflammatory Breast Carcinoma.
Inflammatory breast cancer is a relatively rare, fast-growing form of breast cancer usually not detected by mammograms or ultrasound. Unlike other

types of breast cancer, inflammatory breast cancer spreads locally in the breast via the lymphatic system just below the skin. To better understand how the inflammatory breast cancer cells enter the blood and lymphatic vessels, the CBCRP has funded ***Sanford Barsky, M.D.,*** and a postdoctoral fellow in his laboratory, ***Mary Alpaugh, Ph.D.,*** from the ***University of California, Los Angeles.*** Together they developed a method for getting an inflammatory breast tumor to grow in a mouse's lymph and blood vessels the same way it does in humans. They have used this transplantable tumor, called Mary-X, to look at how the protein E-cadherin (which is produced by normal breast cells) will allow the cells to attach in layers to other cells, functions in the inflammatory breast tumor, and how stopping this attachment affects these cells. They were also able to learn more about what makes inflammatory breast cancer cells resistant to chemotherapy and why these cells easily spread to other parts of the body. Future research with the transplantable tumor, Mary-X, may lead to new treatment options for inflammatory breast cancer. It also will allow researchers to study how all forms of breast cancer are able to spread through the blood and lymph system to other parts of the body. Research findings supported by CBCRP funding to Drs. Barsky and Alpaugh appeared in many publications, including *Cancer Research* 61 (2002):5231-41, *Oncogene* 21 (2002):3631-43, *Human Gene Therapy* 13 (2002):1245-58, and the *American Journal of Pathology* 161 (2002):619-28. Dr. Barsky has described his concept of tumor growth as the "ship in a bottle" to suggest that tumors (ship) induce the surrounding stroma and blood vessels to create the vascular "bottle" around themselves.

Role of MMPs in Breast Tumor Initiation and Aggressiveness.

Metalloproteinases (MMPs) are enzymes that normal cells secrete to allow cell movement, tissue remodeling, and healing processes. Breast cancer cells produce more MMPs than normal and this allows tumors to become invasive. ***Jimmie Fata, Ph.D.,*** of the ***Lawrence Berkeley National Laboratory,*** investigated how high levels of a specific MMP, called MMP-3, cause breast cancer in mice. He explored whether MMP-3 is able to split the endothelial protein E-cadherin, which attaches cells to one another. This splitting could lead normal breast epithelial cells (the type of cells where most breast cancer begins) 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. Dr. Fata created cells with EMT characteristics, and then inhibited the action of MMPs in these cells. He also developed cells with mutant forms of a cell-cell adhesion protein, called E-cadherin. Dr. Fata found forms of E-cadherin that were resistant to MMP splitting. Dr. Fata, his mentor ***Dr. Mina Bissell,*** and **Dr. Zena Werb** from the ***University of California, San Francisco,*** reviewed this topic in *Breast Cancer Research* 6:1-11.

Metastasis Suppressor Genes for Breast Cancer.

Are there cancer metastasis genes that have not yet been discovered, and do genes exist that work as tumor suppressors to effectively block cells from spreading? These two questions were addressed by ***Stanley Cohen, M.D.,*** at ***Stanford University*****.** Dr. Cohen and his laboratory are pioneers in gene cloning technology, and he used CBCRP funding to turn his attention to breast cancer. Using a technique called Random Homologous Knock Out (RHKO), Dr. Cohen has been able to isolate cancer cells with defective metastasis suppressor genes, which allow the cancer cells to spread. While doing this research Dr. Cohen found an oncogene, a gene that causes normal cells to change into cancerous cells, that is clearly associated with metastasis. Dr. Cohen also has begun working with a biotech company to develop ways to externally detect very small tumors in mice being used in cancer research. This external detection method would allow researchers to determine whether a tumor has

spread without killing or dissecting the mice, thereby allowing researchers to obtain more comprehensive analyses from their studies. Dr. Cohen's work with metastasis suppressor genes (MSGs), the oncogene he found, and the external detection system have the potential to contribute to the identification of new approaches to slowing or stopping breast cancer metastasis. Use of the technology to detect novel tumor suppressor genes was published by Dr. Cohen and his CBCRP-supported postdoctoral fellow, ***Dr. Quan Lu,*** in the *Proceedings National Academy Sciences USA* 100 (2003):7626-31.

Novel Enzymes Associated with Breast Cancer Angiogenesis.
Lasp-1 Signaling in Breast Carcinoma Cell Invasion/Migration.
Hox Transcriptional Regulation of Angiogenesis.

Three CBCRP grants were funded to study novel genes and processes in relationship to breast cancer angiogenesis. ***Steven Rosen, Ph.D.,*** of the ***University of California, San Francisco,*** studied two novel enzymes, Sulf-1 and Sulf-2. First, they cloned cDNAs and sequenced Sulf-1 and Sulf-2 proteins in both mice and humans. This allowed them to look closely at how the enzymes function and to confirm that they are involved in the angiogenesis process. Then, Dr. Rosen's lab demonstrated that there are large amounts of Sulf-2 in mice with breast cancer and in human breast cancer. These findings led Dr. Rosen to conclude that it is possible that the Sulfs play a role in promoting the creation of new blood vessels in tumors. Results from this grant were published in the *Journal of Biological Chemistry* 277 (2002):49175–185.

The Lasp-1 gene is associated with breast cancer invasion in humans. Clinical studies have found that the Lasp-1 gene is turned on in 8–12 percent of breast cancer cells. ***Yi Hsing Lin, Ph.D.,*** at the ***Scripps Research Institute,*** La Jolla, had already shown that overproduction of the protein produced by Lasp-1 was necessary for cells to move to other body parts. The next step was to determine which part of the Lasp-1 protein was responsible for the spread of breast cancer. Dr. Lin's team found that two types of proteins—growth factor proteins and extracellular matrix proteins—played a role in getting Lasp-1 to get cells to move to other areas.

Audri Charboneau, Ph.D., at the ***University of California, San Francisco,*** investigated two developmental genes, Hox D3 and Hox D10, which control the vascular endothelial cells and their role in angiogenesis. Her research explored whether sustaining high levels of the protein produced by the Hox D10 gene, which keeps the endothelial cells quiet, or stopping the protein produced by the Hox D3 gene, which makes these cells active, affects the development of new blood vessels. She also studied possible ways of preventing the migration of the endothelial cells, which would keep the cancer from spreading. By removing Hox D3 or introducing Hox D10 into endothelial cells, they were able to block new blood vessel development.

Molecular Characterization of ErbB2 Positive Breast Cancers.
The Role of SGK in Breast Cancer Cell Proliferation.

The ErbB2 (Her-2/neu) protein is present at high levels in 20–30 percent of all breast cancers, but is more common in more aggressive cancers, especially breast cancers that do not have estrogen receptors. Two completed CBCRP grants studied genes that are associated with ErbB2 (Her-2/neu) and could provide clues on its role in breast cancer. ***Richard Neve, Ph.D.,*** of the ***Buck Institute for Age Research,*** Novato, is trying to find a better way to classify ErbB2-positive breast cancers into distinct molecular subtypes, so that effective therapies could be developed for each subtype. He is studying a gene-regulatory transcription factor protein, called ESX that is found in cancer cells that are high in ErbB2. Dr. Neve's team analyzed ErbB2 and ESX levels in 45 primary breast cancer samples and explored how the proteins interact with

one another. They found that ESX caused significant changes in the epithelial cells in the breast where most cancer begins, and they identified a group of genes controlled by ESX and ErbB2. In addition, they found a group of proteases (a type of enzyme) that have the ability to help cancer cells spread and that respond in high levels to ESX. Dr. Neve has moved to the University of California, San Francisco, and he is pursuing work on ESX and ErbB2 to confirm theses findings. Results from his project were published in *Oncogene* 21:3934-8.

Masaaki Hayashi, M.D., Ph.D., at ***The Scripps Research Institute,*** La Jolla, explored how ErbB2 gets cancer cells to grow. He investigated two proteins that help ErbB2 send signals to cancer cells, glucocorticoid-inducible kinase (SGK), which is necessary for breast cancer cells to grow, and the protein, Big MAP Kinase (BMK1), which regulates SGK. He found that there was a specific part of the BMK1 protein that is activated by SGK in breast cancer cells, and he identified 12 other proteins that interact with SGK. He also found that when SGK is shut off in breast cancer cells, those cells stop reproducing, demonstrating that SGK is necessary for cancer growth. Dr. Hayashi also developed a special mouse model that can be used for additional research on the proteins BMK1 and SGK.

Genetic Analysis of ErbB Signaling in *C. Elegans.*
In mammals, the ErbB family of genes regulates the development of breast tissue, and corresponding (homologous) genes exist in lower organisms. Since fundamental cell processes (such as the cell cycle, DNA repair, and

Angiogenesis

Tumors cannot grow larger than the size of a small seed (1–2 millimeters) unless they co-opt the neighboring, normal cells to provide a blood supply. This process of tumor vascularization is called angiogenesis.

The implications of angiogenesis research are obvious. If the growth factors released by tumors to stimulate angiogenesis could be blocked, then the tumor should "starve to death." Initial work from **Dr. Judah Folkman's** laboratory indeed showed this was true. However, the development of endostatin and angiostatin as cancer-killers has been slow. As in other areas of cancer research, the tumor cells always seem to be one step ahead of researchers' attempts to find a cure. A major growth factor in angiogenesis, VEGF, is the target of the newly introduced cancer therapeutic, Avastin™.

From a future research perspective, success at understanding tumor angiogenesis will require new thinking. For example, work from **Dr. Mary Hendrix** and colleagues at the University of Iowa shows that tumors can create their own vascular network by "mimicking" endothelial cells. In addition, even Dr. Folkman suggests that anti-angiogenic therapy cannot be measured by traditional methods, and might best be applied in combination with other anti-cancer drugs.

Note: A decade ago, the work of **Dr. Folkman** was a beacon for further research in angiognesis. The fact that Dr. Folkman had difficulty convincing "traditional" funding agencies to support his pioneering work directly led to improved efforts to support innovative research.

development) are conserved in evolution, researchers find it instructive to step back to organisms with a simpler biology to study genes and proteins that are important in human disease. ***Nadeem Moghal, Ph.D.,*** at the ***California Institute of Technology,*** Pasadena, used a nematode worm, called *C. elegans*, as a model system to identify and analyze which genes interact with the ErbB genes and the proteins they produce. Dr. Moghal's mentor, ***Dr. Paul Sternberg,*** uses this approach to study behavior, cell spatial patterns, and organ formation. After injecting the worms with a chemical that causes mutations, Dr. Moghal studied what happened to the worms' pseudo-ErbB gene, called let-23. This allowed him to identify a gene (TRAP230) whose mutation might play a role in the development of breast cancer and to define new mutations that might make ErbB genes too active. He also demonstrated that abnormal gene activity in other tissue, like muscle, could affect how ErbB responds in the breast's epithelial cells. Dr. Moghal intends to conduct future research on ErbB proteins and the TRAP230 gene. His work was published in *Oncogene* 22 (2002):5471-80, *Development* 130 (2003):4553-66, *Experimental Cell Research* 284 (2003):150-9, and *Development* 130 (2003):57-69. Dr. Moghal is continuing his research in oncology and use of *C. elegans* at the University of Utah, Huntsman Cancer Institute.

Molecular Study of BAG Domains: A New Motif in Breast Cancer.

In cell signaling processes, proteins interact by binding to each other in structurally compatible regions. Essentially, they assemble into multi-protein, functional complexes like pieces of a puzzle. Structural biologists dissect these protein-protein binding events by such techniques as nuclear magnetic resonance (NMR) imaging and crystallography. This approach is ideal to study apoptosis, because the processes of programmed cell death involve a number of key protein interactions, and identifying the sub-domains involved could lead to a rapid development of cancer therapeutics. ***Klara Briknarova, Ph.D.,*** at ***The Burnham Institute*** in La Jolla, investigated proteins from the BAG protein family. The initially-described member of this family, BAG1, is present in elevated levels in many breast cancers, promotes tumor growth and spread to other body parts, and makes tumors resistant to anticancer drugs such as tamoxifen. All of the BAG proteins have their activity directed by the BAG domain. Working with her mentor, **Dr. Kathryn Ely**, Dr. Briknarova was able to determine the molecular structure of the BAG domain and to closely study how the BAG1 and BAG4 proteins operate. Results from this project were published in the *Journal of Biological Chemistry* 277 (2002):31172-8.

Overcoming Drug Resistance in Breast Cancer.

Breast cancer cells can sometimes avoid being killed by chemotherapy, and researchers are studying the underlying biological reasons for this resistance. It is believed that most chemotherapy drugs work by triggering cell death, called apoptosis, and the adhesion status of the cell may influence this process. Exploring this hypothesis, ***Kristiina Vuori, M.D., Ph.D.,*** from ***The Burnham Institute,*** La Jolla, found that there are certain molecules on the cell surface, known as integrins, that not only keep cancer cells from getting the signal that they should die, but may even make cancer cells resistant to chemotherapy. Dr. Vuori found that she was able to use anti-integrin antibodies to stop the integrins from blocking the message telling the cell to die. She also learned more about the integrins' ability to turn on an enzyme called PI3-kinase, which helps send the "do-not-die" message. Dr. Vuori's continued research in this area could lead to new ways of increasing the benefits of chemotherapy. Results from this research were published in *Oncogene* 20 (2001):4995-5004.

The Role of BRCA1 in Nucleotide Excision DNA Repair.
Nucleotide excision repair (NER), a type of DNA repair pathway, corrects DNA damaged from many environmental toxins, including cigarette smoke and ultraviolet radiation. The tumor suppressor gene, p53, and the breast cancer hereditary gene, BRCA1, are both involved in NER, and NER is subdivided into two pathways—global genomic repair (GGR)—which targets and removes lesions from the whole genome, and transcription-coupled repair (TCR), which preferentially removes lesions from the transcribed strand of expressed genes. ***Anne-Renee Hartman, M.D.,*** at ***Stanford University,*** addressed the question of how BRCA1 affects NER and whether this effect is independent of p53. She found that BRCA1 plays a role in maintaining the NER pathway in the cell. This effect is very significant when the p53 tumor suppressor gene is not functioning in the cell, which occurs in more than 50 percent of human cancers and more than 80 percent of BRCA1-associated breast cancers. Dr. Hartman demonstrated that BRCA1 affects NER through transcriptional regulation of NER genes. These findings could support the development of clinical trials for women with BRCA1 mutations using specific chemotherapy drugs, like cisplatin, that specifically target the DNA repair process. Results of the study were published in *Nature Genetics* 32 (2002):180-4 and the *Journal of Molecular Medicine* 81 (2003):700-7.

Grant follow-up report—Where they are now

Dr. Anne-Renee Hartman recently completed her CBCRP-funded fellowship in the laboratory of **James Ford, M.D.,** at **Stanford University**. Dr. Hartman has continued her career in medicine and research as both a medical oncologist at **Dana Farber Cancer Institute** and as an Assistant Professor of Medicine at **Harvard Medical School**. In these dual roles, her career involves both clinical and laboratory research. On the clinical side she focuses on early detection of breast cancer and pre-cancerous breast lesions in high risk women using novel technologies and imaging modalities, such as MRI. The goal is to identify early molecular and genetic changes that cause a normal breast cell to turn into a cancer cell. On the basic research side, Dr. Hartman works with **Dr. Alan D'Andrea's** laboratory to study the BRCA/Fanconi Anemia DNA repair pathways. It is anticipated that these studies will identify mutations and other influences on cell behavior early in the transition from normal breast cell to cancer cell. It is important to note that Dr. Hartman's clinical and basic science goals are integrated. Thus, she says the long term goals of her work, "…are to identify molecular targets for early detection and prevention and to develop localized preventative therapies using a delivery system involving ductal lavage and molecular imaging." Dr. Hartman recently published her research "Breast magnetic resonance image screening and ductal lavage in women at high genetic risk for breast carcinoma" with CBCRP-funded investigators Drs. Ford, Plevritis, and colleagues at Stanford University in *Cancer* 100 (2004):479-89.

DNA Packaging Defects in Breast Cancer.

If unraveled, the chromosomal DNA from a *single cell* would stretch about three meters. Obviously, there are structural solutions that cells use to package this DNA into a nucleus that is only a few microns (10^{-6} M) in diameter. ***Terumi Kohwi-Shigematsu, Ph.D.,*** from the ***Lawrence Berkeley National Laboratory,*** studied the differences in the DNA structure and packaging between breast cancer cells and normal cells. She identified a protein called poly (ADP-ribose) polymerase (PARP) that binds to a specific stretch of DNA, called the matrix attachment regions (MARs). Dr. Kohwi-Shigematsu's research demonstrated that the PARP protein, which plays a role in DNA repair, is found in high levels in breast cancer cells but at very low levels in normal cells. She also found that when PARP is removed from aggressive human breast cancer cells that are being studied in the lab, the breast cancer cells change back into the type of cells that are less likely to invade other tissues. To investigate this further, Dr. Kohwi-Shigematsu used microarray technology—a technique that allowed her to simultaneously check 20,000 genes—to look for the specific genes that were turned on in both the aggressive breast cancer cells and those that had had PARP removed. This revealed several genes that play a role in cancer development. In addition, Dr. Kohwi-Shigematsu studied mice that had been genetically engineered to spontaneously form breast cancer but to not produce PARP. Preliminary data from this research suggests that mice are less likely to grow tumors when PARP is not present. Taken as a whole, this research suggests that PARP helps cancers grow and that targeting PARP may be beneficial for cancer treatment. Dr. Kohwi-Shigematsu received a new CBCRP grant in 2002 to study this further. Publications based on this research appeared in the *Journal of Cellular Biochemistry* 35 (2001):36-45 and *Critical Review Eukaryotic Gene Expression* 10 (2000):63-72.

TGF-b3 and Small GTPases in Invasive Breast Cancer.

Vesa Kaartinen, Ph.D., of the ***Children's Hospital Los Angeles,*** investigated proteins involved in the epithelial-to-mesenchymal transdifferentiation (EMT) process, and focused on two GTPases called Rac and Rho. GTPases are proteins that can control a chain of chemical reactions within a cell. Some GTPases tell a cell to divide and grow; others tell a cell to move from one location to another. Dr. Kaartinen found that the protein TGF-β3 changes the locations and amounts of two adhesion molecules (integrins) in mouse mammary epithelial cells. The team also found that Rac3, a protein involved in a chain of chemical reactions within these cells, plays a role in the growth of mammary epithelial cells and in the formation of cells that are in transition from normal to cancerous. Dr. Kaartinen intends to continue to study the role of TGF-β3 and GTPases in invasive breast cancer. Results of this study were published in *International Journal of Molecular Medicine* 9 (2002):563-70 and the *Journal of Biological Chemistry* 277 (2002):8321-8.

Immortalization of Human Mammary Epithelial Cells by ZNF217.

Amplification of the ZNF217 gene, meaning that more than two copies are present, has been found in many different types of tumors, including some 40 percent of human breast cancer cell lines. ***Paul Yaswen, Ph.D.,*** at the ***Lawrence Berkeley National Laboratory,*** found that higher than normal levels of ZNF217 not only helps keep cells alive but also may make the cells resistant to chemotherapy and radiation treatments. Dr. Yaswen and collaborators will continue to study ZNF217 to determine if there is a relationship between how active a woman's ZNF217 gene is and her risk for breast cancer or her prognosis after she is diagnosed with breast cancer. If ZNF217 is found to be involved very early on when breast cancer develops, then this research could lead to the development of new drugs that could prevent the disease from occurring. Results from this research were published in the *International*

Journal of Biochemistry and Cell Biology 34:1382-94 and *Cancer Letters* 194 (2003):199-208.

Rodent Model for Human Ductal Carcinoma *in Situ.*

Mammography has greatly increased the detection of two types of pre-cancers: ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS). Although almost all breast cancer begins as DCIS or LCIS, not all DCIS or LCIS will become breast cancer. Currently, however, there is no way to tell which pre-cancers will progress and become cancers. To help unravel some of the questions about DCIS and LCIS, ***Satyabrata Nandi, Ph.D.,*** of the ***University of California, Berkeley,*** developed a method to induce a large variety of DCIS and LCIS in rats. Dr. Nandi then demonstrated that it is possible to use a cancer-causing chemical to make the DCIS and LCIS become breast cancer. This research will allow Dr. Nandi to conduct further studies on DCIS and LCIS and how hormones influence their growth. These studies could ultimately lead to better ways of determining which DCIS and LCIS will progress to cancer and how DCIS and LCIS should be treated.

Role of PTEN/Akt Pathway in Invasion in Human Breast Cancer.

Ductal carcinoma *in situ* (DCIS) is considered a pre-cancer and not true cancer because the altered cells are confined to the breast duct. It is known that about 25–30 percent of DCIS lesions will eventually progress to become invasive cancer, but it is not known how to predict which cases have the

BRCA genes and DNA repair

It is generally accepted that a cancer arises and progresses due to the accumulation of genetic changes in a target cell. It is a combination of genetic damage (e.g., UV radiation, free radicals, environmental toxins) and a failure in DNA repair processes that drives cancer progression. All the functions of the hereditary breast cancer susceptibility genes, BRCA1 and BRCA2, have not yet been completely detailed, but research on them is providing important insights into key events in cancer biology. BRCA1 and BRCA2 are very large proteins and interact with numerous other proteins to monitor DNA integity, direct repair processes, and signal these events to other places in the cell. In total, BRCA genes are associated with several forms of DNA repair, the cell cycle, apoptosis, and protein turnover (ubiquitination) pathways.

BRCA1 functions more in the surveillance of DNA, signaling damage, and directing its repair by homologous recombination (HR), nucleotide-excision repair (NER), and possibly non-homologous end-joining (NHEJ). BRCA2 has a more specific role in DNA repair, regulating the activity of RAD51, which is required for HR. In the clinical setting, it is the association with the tumor suppressor p53 that seems most relevant. BRCA1 and -2 mutations are frequently linked to inactivation of p53.

Watson and Crick's structure for DNA, now 50 years old, elegantly showed how DNA could be duplicated with great fidelity; however, it seems that cells invest as much effort in monitoring and repairing damage to DNA as they do in replicating it. The rationale for robust and diverse DNA repair processes is that the world inside and outside the cell is a dangerous place for the double-helix.

Progression: Breast cancer is a slowly-developing and **progressive disease**. By the time a tumor is detected through mammography or self-exam, it may have been present for 8–10 years. The earliest phase of breast cancer development involves a process called epithelial-to-mesenchymal transdifferentiation (EMT). These events are associated with a loss of responsiveness to transforming growth factor-beta (TGF-β), the transition to a fibroblast-like phenotype, loss of cell-cell adhesion characteristic of the ductal epithelial layered structure, and a gain in the ability of cells to migrate. Early cancer development also is associated with cell immortality, which is the capacity for continued cell divisions beyond normal limits (50 to 100 cell division limits are normal for most adult cells). For cancers to continue to progress there needs to be loss, mutation, or functional changes in key tumor suppressor genes, such as p53 and PTEN. This opens the door for the accumulation of other mutations.

potential to become invasive. ***Shikha Bose, M.D.,*** at ***Cedars-Sinai Medical Center*** in Los Angeles, believes that there are underlying genetic differences in DCIS that might be used to predict which DCIS cases would progress to invasive cancer. This research has focused on PTEN, a recently identified tumor suppressor gene that is located in a part of chromosome 10 and that is frequently lost in invasive breast cancer. When PTEN becomes lost or altered because of changes to chromosome 10, it creates the possibility for invasive breast cancer to occur. The team's research focused on surveying the global genetic changes that link PTEN with breast cancer invasion and progression. By cDNA array comparisons they will be able to catalog and compare genetic changes in women with DCIS to those with invasive breast cancer. The goal is to validate genetic markers that physicians could use when making treatment decisions. These genetic markers might also provide insight into which proteins and genes could be investigated for new drug development. Dr. Bose is continuing this research with additional CBCRP funding that began in 2003.

Studies of Telomere Capping Dysfunction in Breast Cancer.

Protective caps, called telomeres, keep chromosomes in working order. ***David Gilley, Ph.D.,*** at the ***Lawrence Berkeley National Laboratory,*** tested the hypothesis that breast cancer begins when problems with the telomeres lead the chromosomes to become uncapped. This uncapping could allow chromosomes that should be separate to fuse together, leading to genetic mistakes that can result in the development of breast cancer. His team found that an important telomere protein, called TRF2, is found at higher levels in breast cancer. This suggests that TRF2 may play a role in the development of breast cancer. Dr. Gilley intends to continue to study TRF2 to learn more about its role in breast cancer. This work could lead to a better understanding of how breast cancer begins. Dr. Gilley resigned his New Investigator CBCRP award after one year to accept a faculty position at Indiana University.

Role of p53 in Irradiated Stroma and Mammary Carcinogenesis.

Ionizing radiation, such as x-rays, can cause changes in breast cells that lead them to become cancerous. Most studies concentrate on the changes in epithelial cells, where breast cancer begins. ***Mary Helen Barcellos-Hoff, Ph.D.,*** at the ***Lawrence Berkeley National Laboratory,*** pursued the hypothesis that radiation may cause changes in the stromal cells that are part of

the framework that supports epithelial cells. These changes, in turn, may create an environment that makes the epithelial cells more likely to become cancerous. Working with Dr. Joseph Jerry at the University of Massachusetts, Amherst, Dr. Barcellos-Hoff's team used mouse mammary epithelial cells that lack a gene, p53, which normally suppresses tumors, to determine the exact radiation exposure that would lead to cancer development. They found that a radiation dose of 4 Gy did not change the length of time it took tumors to develop or how often they developed, but that it did change the characteristics of the tumors that did develop. They also made the surprising observation that doses of radiation less than 4 Gy actually reduced the number of tumors that developed. This research on how radiation alters normal mechanisms that stromal cells use to keep epithelial cells from turning cancerous may provide new strategies for enhancing these mechanisms to prevent or reverse cancer. She has published her work in the *Journal of Mammary Gland Biology and Neoplasia* 2001 Apr; 6(2):213-21.

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.

Research in Progress

A number of ongoing CBCRP grants in the topic of *Pathogenesis* reported substantial progress in 2003.

Profiling Enzyme Activities in Models of Human Breast Cancer.
Benjamin Cravatt, Ph.D., from ***The Scripps Research Institute,*** La Jolla, has developed a novel technique called activity-based protein profiling (ABPP) that is able to detect, measure, and purify *active* breast cancer-associated enzymes. This proteomic-based approach is significant, because the traditional, biochemical approach to investigate proteases could not reliably detect active forms from those present as precursors (zymogens) or bound to inhibitors. Five papers on Dr. Cravatt's research were published, including articles in the *Journal of the American Chemical Society* 125 (2003):4686-4687 and *Proceedings of the National Academy of Sciences USA* 99 (2002):10335-10340.

The Detailed Structure of a Model Breast Cancer Genome.
Locating Novel Breast Cancer Genes Using DNA Microarrays.

Two ongoing CBCRP-funded grants are aiming to apply novel technologies to map and catalog the chromosomal changes in breast cancer cells and tumor samples. ***Colin Collins, Ph.D.,*** at the ***University of California, San Francisco,*** is using a new technique called End Sequence Profiling that has the potential to identify *all* the genetic differences between breast cancer and normal cells. End Sequence Profiling uses some of the same methods that were used to map the human genome. Dr. Collins begins by creating a bacterial artificial chromosome (BAC) library for the tumor being studied. He then compares the BAC with a reference library of chromosomes, which allows him to quickly see if there are extra genes or missing ones. Results from Dr. Collin's CBCRP project were published in the *Proceedings of the National Academy of Sciences USA* 100 (2003):7696-7701 and *Bioinformatics* 1 (2003):1-12.

Jonathon Pollack, M.D., Ph.D., at ***Stanford University School of Medicine,*** is using the more established method of DNA microarrays (gene-chips) that can look simultaneously at more than 26,000 genes from human tumor samples to find extra and missing genes. In collaboration with CBCRP-funded investigators, such as ***Dr. Stefanie Jeffrey*** at Stanford, Dr. Pollack's laboratory can directly compare expression data (i.e., messenger RNA assays) with chromosomal data to determine whether genetic alterations associated with gene deletion or duplication result in a corresponding change in the gene transcription. This research could lead to new genetic tools that will help oncologists assess how aggressive a cancer is and improve treatment options. Genetic approaches to classifying breast cancers were reviewed by Drs. Pollack and Jeffrey in *Breast Cancer Research* 5 (2003):320-8.

Cyclin E Affects Growth Arrest in Breast Cancer Cells.
Caspase-mediated Apoptosis Mechanisms in Breast Cancer Cells.
Regulation of the Rad1 Checkpoint Complex in Breast Cancer.

Three CBCRP dissertation grants to support graduate students achieved breakthrough findings in 2003. ***Navdeep Dhillon,*** at the ***University of California, Davis,*** is investigating the cell cycle regulatory protein, called cyclin E, and the role it plays in breast cancer and programmed cell death (apoptosis). Dhillon and colleagues found that cells that contain high levels of cyclin E do not respond as well to tamoxifen. They also found that elevated levels of cyclin E result in a severe decrease of a protein that prevents cell death. This has led Ms. Dhillon and her mentor, **Dr. Maria Mudryj,** to propose a novel function for the cyclin E protein as an "effector" for cell death. Results from their research were published in *Genes and Immunity* 4 (2003):336-342.

Kelly Boatright, from the ***Burnham Institute,*** La Jolla**,** has developed a technique for studying the key apoptosis cell death enzymes, called caspases. Her methods allow the comparison of caspase function in normal cells versus cancerous breast cells. She is also investigating whether cancer cells are more likely to respond to an anti-tumor agent called TRAIL (TNF-related apoptosis-inducing ligand) when it is combined with the chemotherapy drug doxorubicin (Adriamycin). This work could lead to new ways of inducing cancer cells to respond better to cancer treatments. Results from this research in the laboratory of **Dr. Guy Salvesen** were published in *Molecular and Cellular Biology* 11 (2003):529-541 and the *Journal of Biological Chemistry* 278 (2002):10458-10464.

Cells are constantly exposed to agents that can damage their DNA. Checkpoint proteins in cells sense and respond to DNA damage and slow cell growth

until the damage is repaired. The risk for cancer increases when these checkpoint proteins fail to work. ***Patrick Lupardus,*** at ***Stanford University School of Medicine,*** is investigating how two checkpoint proteins, ATR and Rad1, interact to start the DNA repair process. Greater understanding of these checkpoint proteins and how they work may provide new opportunities to prevent or treat breast cancer in ways that—unlike chemotherapy—do not harm normal healthy cells. Results from this research performed in the laboratory of CBCRP-funded investigator ***Dr. Karlene Cimprich*** were published in *Genes and Development* 16 (2002):2327-2332.

Structure and Function of the Bax Apoptosis Regulator.

The Bcl-2 family includes some proteins that can activate the process of cell death (apoptosis) and others that can stop it in normal cells and breast cancer cells. ***Francesca Marassi, Ph.D.,*** at ***The Burnham Institute,*** La Jolla, is investigating two members of the Bcl-2 family, Bc1xL and Bax. Bc1xL keeps cells from dying while Bax promotes cell death. Dr. Marassi's hypothesis is that these proteins play a role in controlling whether breast cancer cells die. The information gained from this research will provide new information about the normal breast and breast cancer, and may be useful for developing new approaches to breast cancer treatment. Results from this research were published in five journals, including *Biochemica et Biophysica Acta* 1645 (2003):15-21, *Journal of Magnetic Resonance Imaging* 161 (2003):64-69, and *Protein Science* 12 (2003):403-411.

Genes That Modulate Dioxin-Induced Breast Cancer.

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,*** searched for genes that either promote or suppress breast cancer initiated by dioxin. The research team used two techniques. The first, RHKO, has been used to discover genes that inhibit tumor growth. The second, microarrays, is a technology that allows a researcher to study thousands of genes simultaneously. These techniques allowed Dr. Lu to identify several previously unknown genes that are involved in cancers caused by dioxins. Use of the technology to detect novel tumor suppressor genes was published by Dr. Lu and his mentor ***Dr. Stanley Cohen*** in the *Proceedings National Academy Sciences USA* 100 (2003):7626-31.

BRCA1-Dependent Ubiquitin Ligase Activity in Breast Cancer.

The BRCA1 gene is gaining an established role in DNA repair, but it also functions in the regulation of cellular protein turnover. BRCA1 has "ubiquitin ligase" activity, and ***Yan Xia, Ph.D.,*** at the ***Salk Institute for Biological Studies,*** La Jolla, is studying this function of this BRCA1-regulated process. Results from this research were published in the *Journal of Biological Chemistry* 278 (2003):5255-63.

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

Vitamin A compounds, called retinoids, are being studied for their ability to prevent or treat cancer. Research has shown that one of these compounds, called AHPN, can cause breast cancer cells to die, and that a protein called TR3 plays an important role in this process. ***Nathalie Bruey-Sedano, Ph.D.,*** at ***The Burnham Institute,*** La Jolla, is investigating what chemical reactions within cells are necessary for TR3 to trigger cell death. Her team has already found that breast cancer cells die more quickly when they are exposed to both vitamin A compounds and chemotherapy than when they are exposed to either one alone. These findings could lead to a new approach for treating breast cancer.

Regulation of Estrogen Response by Corepressors.

Breast development is regulated by interactions between hormones and growth factors. The hormone estrogen is one of the most important in this process. It binds to the estrogen receptor, which is regulated by proteins called corepressors. ***Martin Privalsky, Ph.D.,*** at the ***University of California, Davis,*** is investigating chemical interactions between corepressors and other proteins called kinases, and how this affects the estrogen receptor. This research will provide new information on what happens when breast tumors stop responding to the hormonal treatment tamoxifen, and may lead to the development of new breast cancer treatments.

Role of Id-2 in Breast Cancer and its Relationship to Id-1.

For a cancer cell to spread, it has to be able to move from its original site and then grow and divide in a new environment. ***Pierre-Yves Desprez, Ph.D.,*** at the ***California Pacific Medical Center Research Institute,*** San Francisco, is studying two proteins, Id-1 and Id-2, that are produced in normal and cancerous breast cells and are believed to play a role in this process. Desprez and his colleagues found that invasive breast cancer cells in mice and cancer cells in human breast tissue have high levels of Id-1. Dr. Desprez is now investigating the Id-2 protein, which, in contrast to Id-1, is present in low levels in invasive cancer cells. His studies in mice and in human tissue have shown that high levels of Id-2 are more likely to be found in non-aggressive breast cancer cells. This research is providing important insights into how the Id-1 and Id-2 proteins interact and how breast cancer grows and spreads.

Genetics and Proteomics

The study of cancer-related genes, the completion of the Human Genome Project, and the associated widespread use of advanced genetics techniques (e.g., cloning, knock-out mice, array analysis) has raced ahead of more biochemical, protein-based research. However, in recent years, the discipline of "proteomics" has made great strides. Proteomics involves the applications of techniques, such as mass spectrometry, to simultaneously analyze the protein content of complex cell, tumor, tissue, and organ samples. For example, researchers are looking for the fingerprint of cancer in blood samples, both in the context of detection and diagnosis of disease characteristics.

It was a little surprising when the Human Genome Project showed the total number of genes to be about 35,000. This number is 2–3 times lower than predicted earlier. In contrast, each gene product, or protein, might have an average of five functional regions. These protein-based structural regions allow such things as enzyme activity and protein-protein binding to be contained as discrete portions in a larger protein molecule. Thus, the proteome of an organism, which is the sum total of all protein structural-functional units, might be five times larger than the number of genes. In terms of a contribution to cancer research, proteomics is in its infancy. Will the mystery of cancer be eventually understood at the genetic level (i.e., the computer's operating system) or the phenotypic level (i.e., software "bugs")? And whether humans, at the level of disease processes, are more advanced at the genetic or protein level than the favorite animal model in cancer research, the mouse, is an issue yet to be resolved.

Research Initiated in 2003

The CBCRP funded 12 new grants in 2003 to pursue new studies on the pathogenesis of breast cancer. ***Min-Ying (Lydia) Su, Ph.D.,*** from the ***University of California, Irvine,*** was funded to use a magnetic resonance imaging (MRI)-based approach to study angiogenic markers in the earliest phases of breast cancer progression—from hyperplasia through DCIS. Dr. Su and colleagues hope to identify and classify the early cancers that are most likely to undergo formation of new blood vessels (angiogenesis) and progress to life-threatening stages. ***Verena Kallab, M.D.,*** from the ***University of California, San Francisco,*** was awarded a postdoctoral fellowship to study circulating tumor cells (CTCs) from patients with advanced disease. Dr. Kallab will study the cytotoxic effects of breast tumor therapy on CTCs and how key cancer biomarkers on CTCs correspond with the primary tumor. ***Nadim Jessani,*** from the ***Scripps Research Institute,*** La Jolla, is a graduate student in the lab of CBCRP-funded investigator, ***Dr. Benjamin Cravatt.*** Mr. Jessani was awarded a dissertation grant to apply a novel proteomics (i.e., study of the whole protein component profile of a cell or tissue) method to detect the active proteases present in human tumors grown in mice. Proteases, such as metalloproteinases, are key modulators of cell invasion, so knowing the active proteases is much more useful than cataloging them at the gene level.

Tsui-Ting Ching, Ph.D., at the ***University of California, San Francisco,*** was funded for a postdoctoral fellowship to study gene variation and gene methylation patterns in cell samples from patients with elevated Her-2. Dr. Ching hopes to identify gene/methylation patterns that underlie Herceptin resistance, since only about 30 percent of patients respond well to this therapy. On the same general theme of drug resistance, ***Kristiina Vuori, M.D., Ph.D.,*** from ***The Burnham Institute,*** La Jolla, was awarded a grant to investigate why about 40 percent of the patients treated with tamoxifen have tumors that don't respond well to this therapy. Dr. Vuori and colleagues are focusing on a docking protein called Cas that may function as an assembly point for anti-estrogen resistance signaling pathways. ***Nola Hylton, Ph.D.,*** at the ***University of California, San Francisco,*** was funded to study the role of p53 as a regulator of radiation-induced cell death in a mouse cancer model.

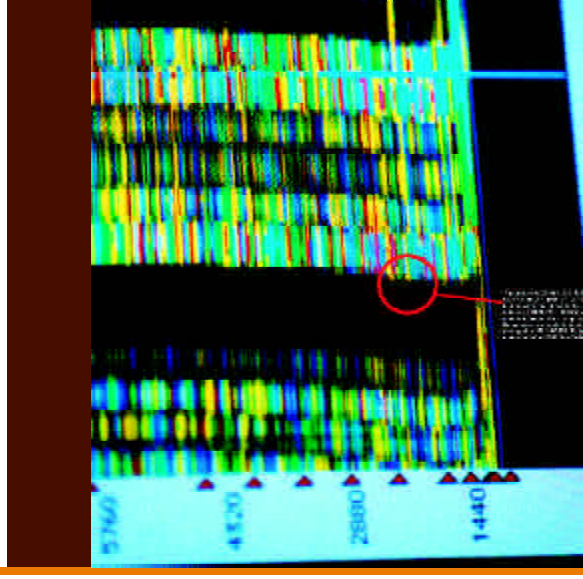
Research on Metastasis, the Spread of Breast Cancer

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 on 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 are likely to represent a huge advance in reducing deaths from breast cancer.

Dr. Hylton will be trained in the techniques of basic science and transfer this knowledge to her current expertise in MRI and radiology. ***Steven Martin, Ph.D.,*** from the ***University of California, Berkeley,*** received an award to investigate how an oncogene, called Src, regulates cell signaling though growth factors to influence the breast tissue architecture associated with early malignant events. Loss of cell polarity is a key morphological change in cancer development, and Dr. Martin will study the connection to Src by using specific inhibitors and a 3-D tissue culture system in the laboratory of his colleague, ***Mina Bissell, Ph.D.,*** at the ***Lawrence Berkeley National Laboratory.***

When breast cancer is detected clinically, it has already been present for many years; first in a pre-cancerous stage and then in small, developmental stages. We have too little information on what is happing at the etiological (i.e, causative) and biological (i.e, genetic) levels during breast cancer progression. ***Paul Henderson, Ph.D.,*** at the ***Lawrence Livermore National Laboratory,*** was funded for a novel approach to measure oxidative damage to DNA. While the ability to repair DNA eventually becomes defective in cancer, cancer etiology is believed to be driven to a large extent by the generation of oxygen-derived free radicals. Using breast cancer cell lines and tumors in animals, Dr. Henderson can feed cells or animals an oxidative damage-reporting marker for detecting and measuring DNA damage. This approach will enable the measurement of the ability of cells to either develop lesions or repair the damage. In recent years the role of the BRCA1 gene in DNA repair has become better defined, but we still need more information on its multiple roles in coordinating the cell cycle, protein degradation, and gene regulation. ***Quan Zhu, Ph.D.,*** at the ***Salk Institute for Biological Studies,*** La Jolla, is a postdoctoral fellow in the laboratory of **Dr. Inder Verma**. Dr. Zhu will use new gene expression vectors to enable the many BRCA1 functional domains to be studied independently in a mouse model of breast cancer. A paradox in breast cancer biology and the clinic is why about one third of patients at diagnosis are estrogen receptor negative (ER-). ***Keon Wook Kang, Ph.D.,*** has been awarded a postdoctoral fellowship to study the ER+ to ER- transformation using a special mouse model in **Dr. Eva Lee's** lab at the **University of California, Irvine.** Another perplexing issue in breast cancer is how to associate DCIS, both for the odds of clinical progression and biologically, to invasive cancer. ***Ruria Namba, Ph.D.,*** from the ***University of California, Davis,*** is funded as a postdoc in the laboratory of ***Jeffrey Gregg, M.D.,*** to study DCIS-like hyperplasic outgrowths from pre-malignant mouse mammary tumors for the expression of altered genes and biomarkers of breast cancer. ***Euan Slorach, Ph.D.,*** from the ***University of California, San Francisco,*** was awarded a postdoctoral fellowship to study a novel gene called Melb1 which is associated with embryonic and mammary development. Dr. Slorach will study this gene for its role in breast tumor development in the context of knockout mice lacking Melb1.



Diagnosis and Treatment: Delivering Clinical Solutions

Early detection does not guarantee a cure, and the limitations of mammography require women to undergo sometimes unnecessary biopsies and emotional strain. Patients and physicians have too few options for treatment, so the CBCRP encourages research into new methods of detection and treatment of breast cancer.

We divide research in this area into two Priority Issues:

· Earlier Detection

· Innovative Treatments

Earlier Detection: Improving the Chances for a Cure

As more California women have regular mammograms, examine their own breasts, and receive breast exams from their physicians, breast cancer is being detected at earlier stages. Earlier detection combined with improvements in treatment has led to a 25 percent drop in the rate of death from breast cancer in the state. However there's still room for improvement. Women need detection methods that can find breast cancer at its earliest stage and distinguish harmless breast abnormalities from cancer. Mammograms don't provide diagnostic information, such as tumor aggression.

Research Conclusions

Four CBCRP grants under the *Earlier Detection* topic were completed in 2003. Three of these grants supported research that would involve the establishment of biomarkers, and one grant involves a novel imaging technology.

3rd Symposium on the Intraductal Approach to Breast Cancer.
Susan Love, M.D., is a pioneer in breast cancer and women's health issues. In addition, Dr. Love supports a novel research topic that might someday give physicians a new avenue for detection, prognosis, and even treatment of breast cancer. The CBCRP funded the ***Susan Love MD Breast Cancer Research Foundation,*** Santa Barbara, to bring together scientists, physicians, and breast cancer advocates from California and throughout the world. They discussed research into detecting breast cancer by examining the fluids and cells in the lining of the milk ducts of the breast, the place where 95 percent of breast cancers begin. The intraductal approach provides direct access to the inside of the lining of the breast. A typical scenario is to collect nipple aspirate fluid (NAF), which contains cells and secreted proteins. Another approach is routine operative breast endoscopy (ROBE), which can directly visualize abnormal regions with tiny video cameras. Solutions can be introduced through the nipple opening and recovered so the protein constituent can be analyzed for biomarkers of cancer. The CBCRP was interested in funding this meeting because of the high potential to develop new collaborations between basic scientists and clinicians.

Two-Dimensional Magnetic Resonance Spectroscopy of Breast Tumors.
Nathaniel Wyckoff, Ph.D., at the ***University of California, Los Angeles,*** investigated whether a new technology, a variation of the widely used MRI (Magnetic Resonance Imaging) test, can be used to detect breast cancer. Dr. Wyckoff investigated two-dimensional magnetic resonance spectroscopy, a technique that detects the presence of various chemicals in tissue. The research team used the technique to create a chemical profile of the breasts of 30 healthy women, 13 women with invasive breast cancer, and two women

with benign breast tumors. Magnetic resonance imaging worked well to tell the difference between breast cancer tissue and healthy breast gland tissue. It also worked well to tell the difference between breast cancer tissue and benign breast tumor tissue, although the number of women in this study with benign tumors was so small that more research needs to be done to confirm this. The technique worked less well to tell the difference between breast cancer tissue and healthy breast fatty tissue.

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, M.D.,*** at the ***University of California, Davis,*** investigated whether measuring the level of a fat found in the blood, lysophosphatidlycholine (LPC), can be used to detect breast cancer. The research team is also investigating whether LPC blood levels can be used to detect a recurrence of the disease, or reveal whether treatment is working against breast cancer that has spread to other body parts. They have recruited 98 women; 57 are recently diagnosed and under treatment, 19 have had breast cancer that has not recurred, 9 women are being treated for breast cancer that has spread to other places in their bodies, and 12 women have not had breast cancer. The research team has

Biomarkers

In terms of detection and treatment, cancer biomarker research involves the discovery and validation of telltale proteins from either the cancer itself or body fluids that can expose a malignant tumor. A breakthrough in this area was the PSA test for prostate cancer, but the benefits of this test are still being debated. A better approach would be the use of a panel of biomarkers, and this is where advances of proteomic technology are playing a critical role. The most promising effort to date has been the work at the NCI, headed by **Dr. Lance Liotta** and at the FDA, headed by **Dr. Emanuel Petricoin**. However, the primary target is ovarian cancer, which is usually detected at a late stage of disease progression and is not amenable to imaging technologies, such as mammography. Many researchers work on ovarian and breast cancer in parallel, since there is a strong overlap in hormone responsiveness, growth factor receptors, and hereditary gene involvement (i.e., BRCA genes). For breast cancer, promising work is coming from Pacific Northwest National Laboratory in Washington with **Dr. Richard Zangar** as the lead investigator. This group studies protein in Nipple Aspirate Fluid (NAF). Both in NAF and blood, one group of proteins, the proteases, stand out as promising biomarkers. These are key proteins for cell invasion, are secreted from cells, and are fairly stable components.

On the DNA-gene side of the biomarker effort, there has emerged a breast cancer molecular taxonomy that has been most advanced through the work of **Dr. David Botstein** and colleagues at Stanford University. This research was published with **Dr. Charles Perou**, now at the University of North Carolina, as the first author in the *Proceedings National Academy Sciences USA* 96 (1999):9212-9217. The Stanford group identified five major sub-types of breast cancer, and this is based on the clustering of key gene biomarkers.

collected blood samples from some of the women and will finish this research with funding from another research funding agency.

Discovery and Study of Breast Cancer Secreted Proteins.

Elizabeth Williamson, Ph.D., at ***Cedars-Sinai Medical Center,*** Los Angeles, originally tried to identify proteins breast tumors secrete into the bloodstream that could become the basis for a blood test to detect the disease. She was unable to find any. However, she discovered a protein, $p27^{Kip1}$, which is present in cells with normal BRCA1 genes, but barely present, or even absent, in cells that have the BRCA1 mutation that, which leads to a higher chance of breast cancer. Further research showed that lack of this protein in cells may contribute to those cells developing breast cancer. A therapy based on stimulating cells to produce this protein could prevent the development of breast cancer. Results of her study were published in *Oncogene* 21 (2002): 21, 3199-3206.

Research in Progress

A number of ongoing CBCRP grants in the topic of *Earlier Detection* reported substantial progress in 2003.

Breast CT for Much Earlier Detection of Breast Cancer.

Young women and women whose breast tissue looks dense on a mammogram are at higher risk for having tumors missed when they have a mammogram. These women, in particular, need a more accurate and sensitive detection method. ***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, more comfortably than a mammogram, because there would be no breast compression. This year, the team will complete the construction of the scanner and then test it on volunteers who have and do not have breast cancer. A recent article was published in the *American Institute of Physics Conference Proceedings* 682 (2003):308.

Non-Invasive Optical Characterization of Breast Physiology.

Bruce Tromberg, Ph.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 device 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 hemoglobin, a component of blood. In the past year, the team tested the instrument on 17 women, many of them breast cancer patients, at UC Irvine and UC San Francisco. The scanner has potential for earlier detection of breast cancer and also for monitoring whether therapy is shrinking a tumor. It could also lead to a reduction in biopsies. The CBCRP first funded Dr. Tromberg to test this innovative idea in 1996, and again in 2000. As a result, the National Institutes of Health recently provided UC Irvine with a $7 million grant to continue this technology across a range of medical uses. This is an example of start-up funds from the CBCRP leading to much greater funding from larger funding institutions. The optical detection basic science underlying this technology was recently published in the *Journal of Biomedical Optics* 7 (2002):60-71.

Clinical Utility of Breast Cancer DNA Markers in Plasma.

David Hoon, Ph.D., of the ***John Wayne Cancer Institute,*** Santa Monica, has shown that DNA specific to breast cancer can be detected in the blood and bone marrow of breast cancer patients. The team has found that DNA

markers, parts of the DNA that are specific to the tumors, 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 is evaluating how the presence of these markers compares with other ways to test the progress of a breast tumor. They have developed a more efficient method for testing blood for levels of multiple DNA markers, and are developing software to aid in analyzing the results of the test. 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. This research led to a publication in *Cancer Research* 63 (2003):1884-7.

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, has found that when a woman's tumor has the protein LEA.135 on the surface of at least some cells, her cancer is less likely to recur and she is more likely to survive. The team developed a method for measuring LEA.135 and used it to test tissue samples from biopsies of 387 patients. However, measuring LEA.135 does not help predict whether chemotherapy or preventive therapy with the drug tamoxifen will be effective against a particular tumor. This research resulted in a publication in *Anticancer Research* 22 (2002):2933-7.

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 measure 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. However, current methods of measuring breast density aren't accurate enough to be useful. The research team has adapted two techniques already used to measure bone density, called dual (DXA) and single (SXA) x-ray absorptiometry, and have succeeded in accurately measuring breast density with both. They believe these methods can become part of a routine mammogram exam to better identify a woman's breast cancer risk. This research resulted in a publication in *Radiology* 223 (2002):554-7.

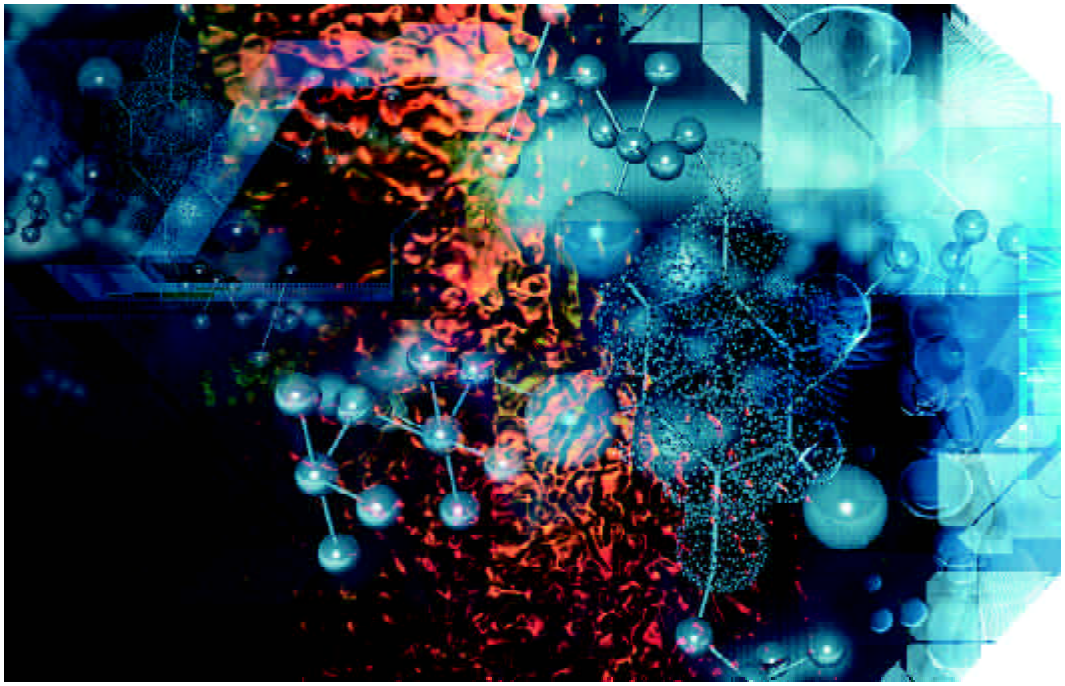
Research Initiated in 2003

Combined Optical and Ultrasound Imaging for Breast Cancer.

Sean Merritt, working in the laboratory of ***Dr. Bruce Tromberg*** at the Beckman Laser Institute at the ***University of California, Irvine,*** is developing and testing a possible new device to detect breast tumors more accurately than mammograms. The portable, hand-held device combines ultrasound with diffuse optical tomography (DOT). DOT uses light to measure the amounts of water, fat, and hemoglobin (a part of blood) in breast tissue. This research grows out of another CBCRP-funded project (see "Non-Invasive Optical Characterization of Breast Physiology," described above, in this section under "Research in Progress.")

Innovative Treatments: Search for a Cure

The clinical translation of promising cancer laboratory discoveries is a time consuming, costly, and inefficient process. Patient advocates often ask why drug discovery and development cannot be improved and why researchers aren't more cognizant of the human issues of the disease. **Mr. Clifton Leaf,** writing in the March 22, 2004, issue of *Fortune* magazine, has thrown down the gauntlet to the federal cancer funding agencies, drug companies, and researchers through his article, "Why we're losing the war on cancer (and how to win it)." Mr. Leaf and many others have noted a series of fatal flaws in our shortsighted search for the cure. Perhaps the key underlying research issue is the pre-clinical model, which often uses human cancer cell lines grown in special strains of mice. This approach is riddled with problems that are not being solved. The human breast cancer cell lines themselves do not represent common forms of breast cancer, and they often vary from lab to lab. When grown as tumors, these "xenograft mouse models" lack the cellular heterogeneity seen by clinical pathologists when they examine human tumor biopsies. The mice themselves often have defective immune systems, so the drugs to be tested are working in an abnormal setting. The most troubling issue in pre-clinical testing is that *metastatic disease* is **not** the focus. Researchers typically measure drug efficacy in xenograft mouse models by *tumor shrinkage*, which is not an accurate predictor of benefit for the patient. Taken together, the pitfalls of pre-clinical drug testing and breast tumor modeling in mice has resulted in the development of drugs that extend survival by merely *months*.



Fortunately the NIH is taking steps to address the issues of animal models of cancer. The NCI's **Mouse Models of Human Cancers Consortium (MMHCC)** is "a collaborative program designed to derive and characterize mouse models, and to generate resources, information, and innovative approaches to the application of mouse models in cancer research." Still, there is a critical need for pre-clinical research work on better representation of the human disease in the cell lines chosen for study, and for new approaches that focus on metastatic disease, the real killer.

In the *Innovative Treatment* research settings supported by the CBCRP, there are continued efforts in key topics. For immunotherapy, researchers are developing new types of antibodies to target the key proteins in breast cancer. As the key growth signaling and apoptosis (cell death) pathways are identified and dissected by researchers, there are parallel efforts to evaluate each new protein and its functional domain as potential new targets for therapy. Alternative medicines based on plant compounds and herbs are being considered in the context of both therapy and chemoprevention. Researchers continue to revisit angiognenesis and other topics with novel technologies. Advances in gene therapy and targeted drug delivery become refined and inch towards clinical translation. Research is being funded that originates from non-cancer disciplines, such as blood clotting and inflammation, because they may have unexplored applications to breast cancer.

At the CBCRP we strive to link new ideas, collaboration, and translation into a synergistic strategy to attract researchers and fund new approaches in the topic of *Innovative Treatments.*

Research Conclusions

Eighteen grants in the *Innovative Treatments* priority issues were completed in 2003.

Cell-Based Immunotherapy for Breast Cancer.

Nabila Jabrane-Ferrat, Ph.D., was funded as a New Investigator at the ***University of California, San Francisco,*** to develop a method of getting immune-response genes to alter tumor cells and create a "danger signal" in the tumor that will activate the immune system. Her team created tumor cells that produce one of three proteins, CIITA, IFN-gamma, or B7.1, which signal the immune system to attack the tumor cells. They injected these tumor cells into mice that were genetically engineered to produce tumors. Dr. Jabrane-Ferrat's team found that when the virus carrying CIITA or CD80 was inte-

Immunotherapy:

The immune system protects us from illness by recognizing and attacking cells that are infected with viruses and invading bacteria. But the Achilles' heel is that the immune system does not efficiently recognize defects in the body's own cells, such as seen in cancer. Thus, researchers are looking for ways to entice the immune system to better fight cancer. For immunotherapy to become useful, a key challenge is to (1) identify tumor antigens that can be recognized by the immune system, and (2) stimulate immune cells to attack the antigen-bearing cells. In an ideal therapy, people could be vaccinated against tumor antigens to prevent disease progression or recurrence.

grated into tumors and the tumors were transplanted into animals, they caused an immune response and grew much more slowly than uninfected tumor cells. This research provides clues that could lead to new breast cancer treatments. Results of this research were published in *Molecular and Cellular Biology* 22 (2003):5616-25.

A New Genetic Vaccine Therapy for Breast Cancer.

Breast cancer can recur after many years in which there has been no sign of a tumor. This suggests that there are a small number of tumor cells that remain alive after standard treatments. ***Edward Nelson, M.D.,*** at the ***University of California, Irvine,*** is trying to develop a vaccine that could eventually be used after treatment for breast cancer to stimulate the immune system to kill any remaining cancer cells and prevent a recurrence. This vaccine would stimulate the immune system's most potent cells, the dendritic cells. Dr. Nelson and his team investigated the effectiveness of a method of getting the vaccine to the dendritic cells called VEE Replicon particles (VRP). They found that when they used the VRP approach to immunize rats against portions of

Targets for Therapy:

New drug development is initiated as researchers dissect each new piece of the puzzle in breast cancer. They consider whether there is the opportunity for each new gene or protein to become a target for therapy. The laborious method of gene "knock-out" in mice is often being substituted by the new technology of RNA-interference (RNAi or si-RNA), which allows quick verification of gene function. RNAi itself might become the drug of the future. Next, the initial stages of pre-clinical development typically involves treating simple cell and animal models of breast cancer with existing vs. investigational drugs to determine the effects on gene-protein expression patterns, growth, cell death, and metastasis-angiogenesis processes. Existing technologies, such as phage display, continue to be employed as information from other areas offer new opportunities to analyze and test possible leads.

rat neu, which is like the cancer gene Her-2/neu in humans, the vaccine was successful in getting the immune system to wipe out the tumor. Dr. Nelson is going to continue to study rat neu and the VRP approach to stimulating dendritic cells to fight breast cancer. Dr. Nelson and colleagues presented their results at the *American Association for Cancer Research* annual meeting in 2003.

Targeted Delivery of an Anti-Breast Tumor Agent.

Continuing research that the CBCRP funded from 1995–2000, ***Francis Markland Jr., Ph.D.,*** and ***Noriyuki Kasahara, M.D., Ph.D.,*** from the ***University of Southern California,*** Los Angeles, teamed with ***Gary Fujii, Ph.D.,*** from ***Molecular Express,*** Los Angeles to explore how a Copperhead snake venom protein, called contortrostatin (CN), could be used in breast cancer treatment by blocking the formation of tumor blood vessels. Dr. Markland had demonstrated previously that CN could block both blood vessel formation and the spread of breast cancer cells. In addition, he had identified the specific breast cancer and blood vessel "integrin" adhesion receptors that CN blocks. Integrin adhesion receptors, which are found on all types of cells,

serve to anchor cells to their surrounding protein matrix. The next step was to use mice to test methods of getting CN to the tumor site when it is injected into the bloodstream. To that end, the collaborative team explored two drug delivery methods, one in which CN is delivered in protein form, the other in which CN is delivered as DNA (also known as gene therapy.) Both methods proved successful in inhibiting tumor growth. Dr. Markland intends to continue to study the possibility of using CN snake venom protein to treat breast cancer. Several publications resulted from this research, including articles in *Biochemistry & Biophysics Research Communications* 267 (2000):350, *Breast Cancer Research & Treatment* 61 (2000):249, and *Acta Crystallographica* D58 (2002):2122-2124.

Targeting the EphB4 Receptor to Inhibit Breast Tumor.
Novel Anti-Angiogenic Agents for Breast Cancer Therapy.
PPARd Ligands for Inhibition of Breast Cancer Progression.

Three completed CBCRP-funded grants explored non-conventional connections between angiogenesis and cell growth processes. First, EphB4 is a "receptor tyrosine kinase" that is found at high levels in breast cancer cells that spread to other parts of the body. ***Elena B. Pasquale, Ph.D.,*** of ***The Burnham Institute,*** La Jolla, investigated whether the portion of EphB4 that is exposed on the cell surface stimulates the formation of blood vessels that allow a tumor to grow. Dr. Pasquale's team found that EphB4 signaling activity does not promote tumor cell growth, like other receptor tyrosine kinases do. Instead, EphB4 proteins actually inhibited tumor growth; however, the presence of EphB4 on tumor cells may still promote the growth of blood vessels that feed the tumor. These findings could lead to the development of breast cancer treatments that target EphB4 to inhibit cancer growth. Dr. Pasquale published some of her findings in *Oncogene* 19 (2000):5614-9.

The connection between angiogenesis inhibition and a group of drugs called selective estrogen receptor modulators (SERMs) was studied by ***Keith Laderoute, Ph.D.,*** at ***SRI International,*** Menlo Park. SERMs, like tamoxifen, are already used to treat breast cancer tumors that are estrogen receptor (ER) positive. Dr. Laderoute found that a novel compound developed by SRI, called SR 16234, not only blocks tumor cell growth in mice, but also blocks the growth of blood vessel cells and the formation of new blood vessels. SR 16234 is now being studied in a Phase I breast cancer clinical trial.

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor family of ligand-activated transcription factors. PPARs regulate a wide array of biological processes, from cell differentiation to metabolic homeostasis. ***Brian Murphy, Ph.D.,*** also at ***SRI International,*** demonstrated that a protein called PPARδ is not only present in breast cancer cells but is found at higher levels in some of the breast cancer cells that have the ability to spread to other body parts. Dr. Murphy interpreted this as an indicator that PPARδ helped promote breast tumor growth and spread, and was an opportunity for a new treatment intervention. He studied a drug, called SR 13904, which could attach to and inhibit the PPARδ protein and thereby stop breast cancer progression. Dr. Murphy intends to conduct further studies on SR 13904 in animal models. Toxic side effects from a drug like SR 13904 should be minimal because it selectively targets the PPARδ protein, which has no known critical role in normal tissue.

Blood Vessel Markers in Breast Cancer.

Erkki Ruoslahti, M.D., Ph.D., at ***The Burnham Institute,*** La Jolla, has developed a novel technology called "phage display" to distinguish blood vessel proteins that are associated only with breast cancers. The identification of such a homing peptide could be the basis of directing the therapeutic drug

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Grant follow up report—Where they are now

Successful anticancer therapy requires that a drug have the ability to selectively kill cancer cells without causing normal cells to become ill or die. To accomplish this objective, biological testing in cell and animal models of cancer needs to be linked to modern chemistry and computer modeling advances. From 2000–2002 the CBCRP funded a collaborative project, "Computer-Aided Discovery of Novel Breast Cancer Therapeutics". **Danni Harris, Ph.D.,** a computational chemist from the **Molecular Research Institute,** Mountain View, and **Marcia Dawson, Ph.D.,** a medicinal chemist and cancer researcher, from **The Burnham Institute**, La Jolla, combined their talents to develop a new approach to find primary compounds to induce breast cancer cell death. In earlier work, Dr. Dawson had synthesized and tested a set of vitamin A-related compounds (i.e., retinoid-like), which are called AHPNs. The novel element of the CBCRP project was to computationally expand this effort to create a pharmacophore, which is a conceptual template for drug design. To accomplish this Dr. Harris developed a specific, three-dimensional map of the chemical and physical properties common to all active conformations of a set of APHNs that exhibited a particular biological activity, namely, the ability to kill cancer cells. Thus, in practice a pharmacophore becomes an association of the three-dimensional chemical structures with biological activity. Establishment of a pharmacophore allows primary compounds to be identified and complex chemical libraries to be analyzed to discover new compounds having the desired biological features that had been previously thought to be structurally unrelated. The APHN-pharmacophore project between Drs. Dawson and Harris had five fundamental goals: (1) to identify the features in these molecules crucial for effectively inducing breast cancer cell apoptosis; (2) to identify the molecular features associated with their ability to induce the expression of vitamin A-sensitive genes, which is associated with their binding and activating retinoid receptor proteins and vitamin A's adverse effects; (3) to develop techniques to accurately predict anticancer activity or systemic toxicity as a function of these molecular features; (4) to refine the computational techniques of virtually screening databases of molecules using the information gathered in steps 1 through 3 to identify similar compounds that would have similar anticancer activity; and (5) to validate their apoptotic (cell death) activity in breast cancer cells.

This research, published in the *Journal of Medicinal Chemistry* 47 (2004):3518-36, should provide a rational approach to the design of more efficacious APHN compounds. The therapeutic aim is to cause breast cancer cell apoptosis and simultaneously avoid the side effects that prevent retinoids from clinical development to treat this disease. In addition, the new pharmacophore was also used to identify novel compounds in databases for purchase and testing against breast cancer cell growth. The problems in this approach, identified during the CBCRP research, are now being corrected via "virtual screening" refinement techniques, including the development of better chemical libraries. Such collaborative efforts, partnering investigators with complementary expertise and a common passion, accelerate advances in discovery linked to human health by eliminating bottlenecks in research by implementing multifaceted, parallel approaches. Drs. Harris and Dawson are continuing their collaboration, and the CBCRP funded a follow-up grant to Dr. Dawson in 2002 to focus on the biological testing of new APHN drugs.

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to a tumor and avoiding side effects to the rest of the body. To date, the group has identified a five-amino acid peptide, which only attaches to the blood vessels of human breast tumors grown in mice. They are in the process of patenting and publishing these findings.

Dietary Indole Effect on Estrogen Urinary Metabolites. Novel Agents for Treatment of Advanced Breast Cancer.

Two CBCRP-funded projects examined compounds derived from natural sources. Research has shown that diets that include large amounts of foods from the *Brassica* family, such as cabbage, broccoli, and Brussels sprouts can reduce breast cancer risk. One of the main substances found in these vegetables is Indole-3-carbinol (I3C), which has been shown in the lab to inhibit the growth of human breast cancer cells. The human body converts I3C to Diindolymethane (DIM). In the first project, ***Gary Firestone, Ph.D.; Leonard Bjeldanes, Ph.D.;*** and ***Kathie Dalessandri, M.D.,*** at the ***University of California, Berkeley,*** studied what effect DIM capsules, which have been shown to be safe when taken orally, would have on postmenopausal women with early stage breast cancer (Stages 0–2). Nineteen women completed their study. Ten women took DIM capsules daily for 30 days; the other nine received a placebo. The research team tested the women's urine before and after they took the pills. They found that the women who took DIM had changes in certain chemicals in their urine that could be associated with a reduced risk for breast cancer. This pilot study could lead to future research on the use of DIM supplements for breast cancer prevention and treatment.

Medicinal chemists strive to develop more active, stable, and specific derivatives of existing compounds to begin clinical development. ***Ling Jong, Ph.D.,*** at ***SRI International,*** Menlo Park, explored the therapeutic potential of a new class of compounds derived from indole-3-carbinol (I3C). Dr. Jong developed a new drug, called SR13668. When tested in tumors grown in mice and in cells in culture, SR13668 appears able to inhibit both estrogen receptor-positive and estrogen receptor-negative types of breast cancer as well as tumors that no longer respond to the SERM tamoxifen. Successful development of SR13668 for clinical use may bring a new, safe, improved weapon to combat cancer. Dr. Jong was funded by the CBCRP in 2003 to continue this line of research.

Novel Technologies to Identify Tissue-Selective Estrogens.

A critical issue in the clinical development of SERMs, like tamoxifen, are the unwanted estrogen-promoting effects in other organs, like the uterus. Thus, researchers are trying to fine-tune SERMs and develop tests that better distinguish SERM effects in various cells and body organs. ***Fred Schaufele, Ph.D.,*** at the ***University of California, San Francisco,*** is using novel technology to speed the identification of drugs that are organ-specific for breast cancer prevention and treatment. Dr. Schaufele uses a unique fluorescence resonance energy transfer (FRET) technique that allows him to see how a drug affects living cells from tissue (like the uterus) that may respond to estrogen-like drugs.

Role of p14ARF in Metastatic Breast Cancer.

A protein found in normal cells and tumor cells, p53, triggers a cell's death after it has been damaged by chemotherapy or radiation. Another protein normally found in the cell nucleus, p14ARF, binds to and stabilizes p53 to allow maximum function. Some breast tumors have defective p53, but many of those with normal p53 appear to be missing p14ARF. And when the p14ARF protein is not present, the cancer cells lack the ability to trigger their own death. ***Ruth Gjerset, Ph.D.,*** at the ***Sidney Kimmel Cancer Center,*** San Diego, found that p14ARF is generally missing from breast cancer specimens. She explored whether restoring p14ARF with gene therapy would make cells

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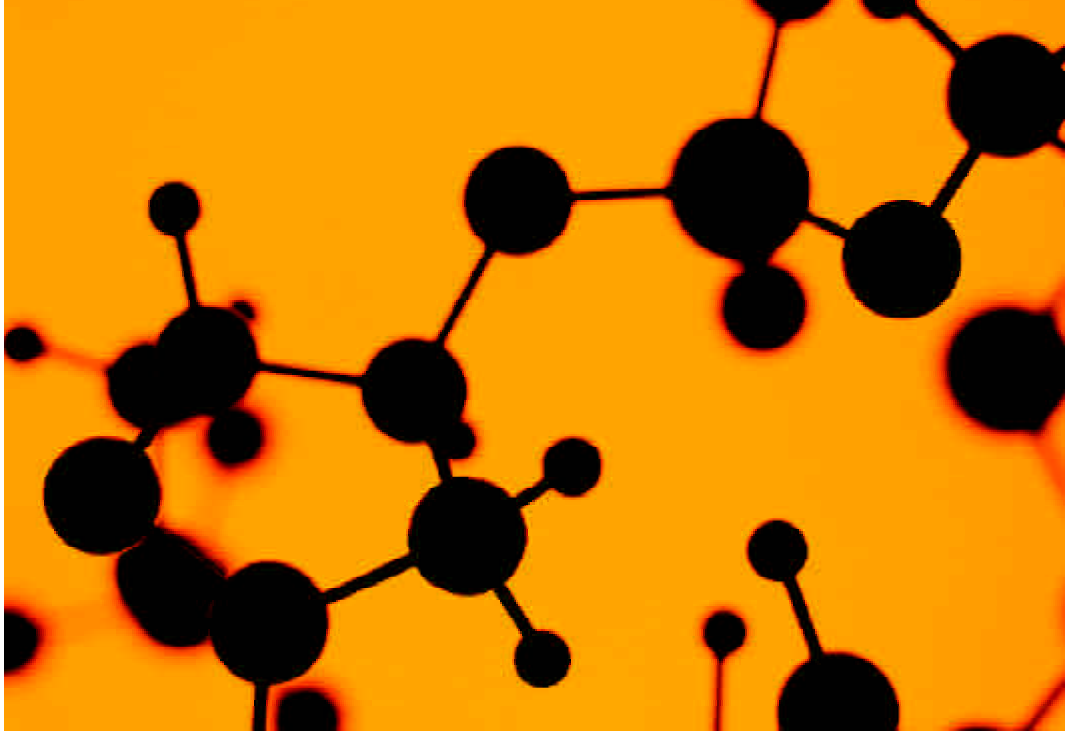
Grant follow-up report—Where they are now

Gene therapy is attractive in principle but has proven extraordinarily difficult in practice. In an idealized world, physicians might use gene therapy to replace a defective gene with a normal copy. This has been the "Holy Grail" for cystic fibrosis, where the defective gene for epithelial chloride transport was identified back in 1989. In the context of cancer, gene therapy might be used to restore the function of a critical cell pathway that becomes defective. This is the strategy with ONYX-15, which is a virus genetically engineered to work only in cancer cells lacking p53, but not in normal cells. Although gene therapy suffered a major setback in 1999 with the death of an 18-year-old patient by a severe immune response, both the technology and the concept hold promise.

The CBCRP funded **Dr. Robert Debs,** a physician-scientist at the **California Pacific Medical Center Research Institute,** San Francisco, in 1997 for a project, called "Gene Therapy for Breast Cancer." Dr. Debs developed his research in a collaborative setting, which was advanced through the pioneering work of the late **Dr. Demetrios Papahadjopoulos.** Dr. Debs along with his many colleagues and collaborators at CPMC and the University of California, San Francisco, have used the approach of encapsulating the therapeutic genes in small, microscopic fat particles, called liposomes. The liposome angle allows two developmental strategies. First, the liposome greatly increases the biological stability and circulation time in the blood, so the therapeutic effect is extended. Second, the liposome can be "decorated" with antibodies or other targeting molecules. This has the potential to direct the liposome to specific cells, such as tumor cells. In addition, the liposome technology is not restricted to gene therapy; it can be used to deliver chemotherapeutic drugs, for example. Finally, the technology spin-off from gene therapy has broad application for asking basic cancer research questions.

Using CBCRP funding from 1997–1999, Dr. Debs found that the delivery of genes that block blood vessel formation in tumors, such as VEGF, could effectively suppress the spread of breast cancer in animals. Dr. Debs used these results as the basis for several scientific papers, including a key article in the *Journal of Biological Chemistry* 274 (1999):13338-13344. Dr. Debs was able to leverage his CBCRP funding to obtain more substantial support though the NIH/NCI (1R01CA082575). Thus, the CBCRP grant allowed five additional years of research on breast cancer. Wanting to do more innovative work, Dr. Debs was able to use preliminary results from his NIH-sponsored studies to obtain a second CBCRP innovative research grant ("Molecular Pathogenesis of Metastatic Breast Cancer") in 2001. The aim of this project is to identify specific genes responsible for the ability of breast cancers to spread (metastasize). Recently, work from this second CBCRP grant appeared in the *Proceedings National Academy Sciences USA* 100 (2003):14253-8. In summary, using gene therapy technology and access to innovative research funding, Dr. Debs and colleagues have now discovered specific sets of genes, **the FKBP gene family,** whose abnormal expression at least in part appears responsible for the metastatic spread of breast cancers. These studies are particularly important, since it has become clear that multiple genetic errors, rather than a single genetic alteration, are responsible for the development and lethal spread of human cancers.



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more sensitive to therapy that depends on the action of the p53 protein. She found that re-introducing p14ARF to cells slowed breast cancer cell growth, even when p53 is not present, and that it added to the effectiveness of chemotherapy. In addition, p14ARF had a "bystander effect"; adjacent cells were affected even if they didn't take up the gene therapy treatment. These findings could lead to the development of gene therapies that could be useful in treating women with metastatic breast cancer. Results from this research were published in *Cancer Gene Therapy* 9 (2002):830-9.

A Patient Decision Support Framework for Breast Cancer.

Physicians seek better methods of predicting successful treatments for breast cancer. ***C. Anthony Hunt, Ph.D.,*** from the ***University of California, San Francisco,*** is developing a computerized process called a "decision support framework" to help physicians choose the dose of chemotherapy that will provide the greatest benefit with the least amount of harmful side effects. Working with collaborators at the University of Michigan Cancer Center, Dr. Hunt has been exploring the role of the Erythromycin Breath Test (EBT) in determining individual chemotherapy dosage. The EBT, which is quicker and easier than taking a blood sample, measures how quickly the antibiotic erythromycin is metabolized in the body by an enzyme called CYP3A4. Dr. Hunt has found that measuring this patient-specific rate of metabolism, combined with other standard dose selection procedures, is an improvement over the current method, which determines dosage based on a woman's body size. He is continuing to fine-tune his informatics/computer software approach for choosing the best chemotherapy dosage, with the goal of providing women with individualized breast cancer treatment.

Can Molecular Markers Predict Response to Adjuvant Therapy?

Tumor-related biomarkers are genes or proteins that may provide information on the best choices for therapy and likely clinical outcome. ***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, investigated whether some of the markers that can be found in tumor tissue—including estrogen receptors (ER), Her-2/neu, p53, BCL-2, and BAX—could be used to predict whether a patient is likely to respond to various treatments. If these markers could predict response, then they might be used to determine

the best treatment options. Drs. Enger and Press completed medical reviews of 1,465 breast cancer patients. They found that women whose tumors were ER-negative or HER2/neu-positive had a greater risk of dying of their disease than did women whose tumors were ER-positive or Her2/neu-negative. However, a woman's risk of death did not appear to be influenced by whether her tumor contained p53, BCL-2, or BAX, and preliminary data suggest that expression of HER2/neu molecules may be associated with risk of death mainly among patients who did not receive doxorubicin as part of their initial treatment. Drs. Enger and Press will continue to follow these patients so that they can examine long-term outcomes associated with these different tumor markers. These findings have the potential to lead to more personalized and effective treatment regimens.

New Radiation Therapy for HER-2-overexpressing Breast Cancer. ***Richard Pietras, M.D., Ph.D.,*** of the ***University of Southern California,*** Los Angeles, explored what happens at the molecular level when Herceptin and radiation therapy are combined. Studies have shown that tumors are able to survive radiation by stimulating DNA to repair the damage that has occurred. Dr. Pietras found that Herceptin appears to keep this from happening by interfering with the DNA repair mechanism by altering a protein, p21WAF1, that plays an important role in DNA repair. Noting that recent studies have found that combining Herceptin with new treatments that keep tumors from developing new blood vessels also appears to make radiation more effective, Dr. Pietras concluded that understanding precisely how

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Her-2

Her-2, also known as Her-2/neu and ErbB2, was first appreciated for its role in breast cancer by **Dr. Dennis Slamon** at UCLA in the 1980s. The story of how the biology of Her-2 lead to the development of Herceptin® (Trastuzumab) by Genentech is a compelling tale documented in the 1998 book by **Robert Bazell,** *Her-2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer.* Her-2 is increased in abundance and there is an underlying tumor cell gene amplification in about 25–30 percent of breast cancer patients. Her-2 is a member of a family of growth factor receptors, collectively called receptor tyrosine kinases (RTKs). In addition to Herceptin, another RTK inhibitor, called Tarceva™ (erlotinib) is under FDA fast track clinical development by OSI Pharmaceuticals, Genentech, and Roche. Tarceva blocks a Her-2 related growth receptor, called EGFR and also known as Her-1. Tarceva is being tested on lung cancer. Perhaps the most interesting recent development in the Her-2 and RTK field has been the appreciation that there is cross talk between the Her-2 growth signaling and estrogen receptor signaling pathways. This is thought by some researchers to account for much of the inherent and acquired drug resistance by some patients to Tamoxifen and other SERM treatments. Thus, patients with high Her-2 levels and resulting growth stimulation pathways can circumvent the therapeutic effect of SERMs, and this can lead to either a failure of the therapy or recurrence the disease. The ER-RTK cross talk topic was recently reviewed by CBCRP-funded researcher **Dr. Richard Pietras** in *The Breast Journal* 9 (2003):361-73.

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Herceptin and other cancer treatments work together at the cellular level may lead to new treatments for women whose tumors make too much of the HER2/neu protein. Results of the study were published in *Endocrine* 2001 Apr;14(3):417-27.

Wnt Signaling in Breast Cancer: Translational Studies.

Wnt proteins are a family of evolutionarily conserved, secreted signaling molecules that regulate cell-to-cell interactions during embryogenesis. In cancer, they are of interest because of their connection with catenin proteins that regulate the cell-cell associations that are critical for forming the epithelial monolayer structure of the breast ducts. ***Randall Holcombe, M.D., Marian Waterman, Ph.D.,*** and ***Lawrence Marsh, Ph.D.,*** from the ***University of California, Irvine,*** explored the role of the Wnt proteins and ligands that are part of its signaling system in breast cancer. They found that there was less of the family member Wnt7b and more of LEF1 protein in breast cancer tissue than there was in normal tissue. And they found that the amount of the LEF1 protein was influenced by estrogen in breast cancer cells. They also showed that high levels of the LEF1 protein were not linked to high levels of the Her2/neu protein, and that abnormalities in the Wnt signaling pathway were separate from abnormalities in the Her-2/neu signaling pathway.

Stress Protein and Drug Resistance in Human Breast Cancer.

In solid tumors, such as breast cancer, there are regions of low oxygen concentration (hypoxia). Low oxygen starves cell metabolism and leads to the production of response proteins. These so-called "stress proteins" may influence the sensitivity of the tumor cells to chemotherapy. ***Amy Lee, Ph.D.,*** at the ***University of Southern California,*** Los Angeles, established that when cancer cells produce a lot of a stress protein, called GRP78, they become more resistant to certain types of chemotherapy drugs, such as doxorubicin (Adriamycin) and cisplatin. To see if this holds true for human breast cancer cells, Dr. Lee is studying whether decreasing the production of GRP78 will make breast cancer cells more likely to respond to (and be killed by) chemotherapy treatments. She is also looking at whether the tumor's estrogen receptor or p53 status influences the effect that GRP78 has on breast cancer cells. This research was published in *Journal of Biological Chemistry* 278 (2003):20915-24.

Clotting Breast Cancer.

Thrombosis for Anti-angiogenic Therapy of Breast Cancer.

Anyone who has watched a cut heal notes the inflammatory redness, which is associated at the cellular level with cell growth, division, differentiation, and healing. But as noted in the February 23, 2004, issue of *Time*, "The Secret Killer: the surprising link between inflammation and heart attacks, cancer, Alzheimer's, and other diseases," there is much to be learned about the link between healing and cancer. Is cancer a result of an injury that does not heal? Two CBCRP-funded projects examined blood clotting, immune mast cells, and angiogenesis events in breast cancer. ***Michael Samoszuk, M.D.,*** from the ***University of California, Irvine,*** noted that tumors had endogenous anti-clotting mechanisms in place to prevent clots from blocking their blood supply. Dr. Samoszuk wanted to see what would happen if these anti-clotting mechanisms were blocked. Using four different drugs—sodium cromolyn, which is used to treat allergies; heparinase enzyme, which is being tested as a treatment for people who overdose on blood thinner; gabexate mesylate, which is used in Europe to treat patients with bleeding disorders; and imatinib mesylate (Gleevec), which is approved for the treatment of chronic myelogenous leukemia—he found that all of the treated mice had evidence of blood

clotting in their tumors while none of the untreated mice had blood clotting occur. He also found that the tumors in the treated mice were larger than those in the untreated mice. Thus, Dr. Samoszuk concluded that allergic cells may play an important role in regulating blood clotting in breast cancer and promoting the growth of breast cancer, that drugs that stop the allergic cells can lead to blood clotting in breast cancer, and that this blood clotting is associated with increased tumor growth and decreased oxygen levels in tumors. Results from this research were published in *International Journal of Cancer* 107 (2003):159-63, *International Journal of Cancer* 106 (2003):647-52, and *Thrombosis Research* 25 (2003): 109:153-6.

A colleague of Dr. Samoszuk was funded independently to study this process in animal models using magnetic resonance imaging to visualize the tumor vasculature during drug treatments of tumors grown in mice. ***Min-Ying (Lydia) Su, Ph.D.,*** from the ***University of California, Irvine,*** explored the possibility of using blood clotting as a novel way to treat breast cancer. Using mice and rats, her group tested two drugs that stimulate blood clotting and are intended to stop tumors from creating blood vessels or to damage those that have already been created. This treatment, however, was not successful: tumors grew at the same rate in the mice and rats treated with the drug as they did in the untreated mice and rats. Even so, the techniques developed in this study can be applied in future studies of drugs now in development. These results were published in the *American Journal of Pathology* 159 (2001):245 and *NMR in Biomedicine* 15 (2002):106.

Research in Progress

A number of ongoing CBCRP grants in the topic of *Innovative Treatments* reported substantial progress in 2003.

PPARg Modulators as Apoptosis Sensitizers for Breast Cancer.

Every cell contains a suicide mechanism that tells it when it is time to die. This programmed cell death is called apoptosis. Cancer results, in part, from a cell not getting its suicide message. ***John Reed, M.D., Ph.D.,*** of ***The Burnham Institute,*** La Jolla, is investigating a class of plant compounds called triterpinoids (there are over 5,000 triterpinoids in nature) to see if they can restore apoptosis functions in breast cancer cells. Dr. Reed is focusing on the ability of triterpinoids to bind to and activate a gene modulator called PPARγ, which can get the suicide message to cancer cells. Results from this research were published in the *Journal of Biological Chemistry* 277:22320-22329. This research is being conducted in collaboration with **Michael Sporn, M.D.,** at **Dartmouth University**.

Regulation of SXR and Drug Resistance in Breast Cancer.

A major problem in the treatment of advanced breast cancer is that, at some point, the tumor will become resistant to the chemotherapy drug that is being used. ***Jennifer Murray,*** at the ***Beckman Research Institute of the City of Hope,*** Duarte, is studying the SXR protein as well as the proteins—called coactivators and corepressors—that control its activity. This research could lead to a greater understanding of drug resistance and a new way to predict if it will occur. Ms. Murray, who is a graduate student in the laboratory of **Dr. Susan Kane**, presented her research at the *American Association of Cancer Research* annual meeting in 2003.

Retinoids in Combination Therapies against Breast Cancer.

Compounds derived from vitamin A (retinoids) have been shown to have the ability to kill cancer cells; however, high doses of vitamin A may cause severe side effects. ***Francisco Javier Piedrafita, Ph.D.,*** at the ***Sidney Kimmel***

Cancer Center, San Diego, is testing whether combining retinoids with medications that choke off a tumor's blood supply or stimulate the body's immune system would create a more effective breast cancer treatment. These experiments are being done in breast cancer cells grown in cultures and in animals. If this combination is found to be effective, it will allow the use of lower doses of retinoids, which would minimize potential side effects.

Potential New Drug Therapy for Breast Cancer.

New drugs are needed to treat breast cancer patients whose tumors do not respond to traditional treatments. ***Jack Youngren, Ph.D.,*** at the ***University of California, San Francisco,*** is testing compounds that block the action of IGF-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. One compound they have tested, small molecules known as diarylureas (DAU), has been found to be effective in blocking IGF-IR. The team also demonstrated that these small molecules stop another known target in breast cancer cells, and that they are not toxic in mice. Their future research will explore how these compounds affect breast cancer cells, how they stop cell growth, and their potential to be developed as new cancer treatments.

Patient-Individualized Chemotherapy in Breast Cancer.

Not all tumors will respond to all types of chemotherapy. Using a form of positron emission tomography (PET) scanning, called microPET imaging, ***Daniel H. Silverman, M.D., Ph.D.,*** at the ***University of California, Los Angeles,*** is developing a test that would show if an individual patient's tumor will respond to a particular chemotherapy drug. His team is currently exploring whether the PET scans can detect very small, non-toxic amounts of chemotherapy as it enters and passes through human breast tumors and normal tissues in mice. The hypothesis is that the way the small doses of the drugs distribute themselves in the tissues will predict which chemotherapy will work most effectively against a particular tumor. If this technique is successful, women could be pre-tested with small amounts of chemotherapy drugs to see which drugs would work and which would be ineffective.

Chemotherapy-Induced Ovarian Damage: Prevention and Impact.

When young women with breast cancer receive chemotherapy, it can damage their ovaries, leaving them unable to have children. Their chemotherapy treatment also typically puts them into early menopause, which can cause accelerated bone loss, hot flashes, and vaginal dryness. ***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 GnRH-analogue called triptorelin which stops estrogen production and induces temporary menopause and may protect the ovaries during chemotherapy. They gave this treatment to 32 women ages 35–44 before and during chemotherapy. They are also surveying 130 young women with breast cancer about chemotherapy, fertility, and how their breast cancer treatment affected their quality of life. This research will raise awareness of the impact chemotherapy has on young women and may motivate development of new treatments that are less damaging to the ovaries.

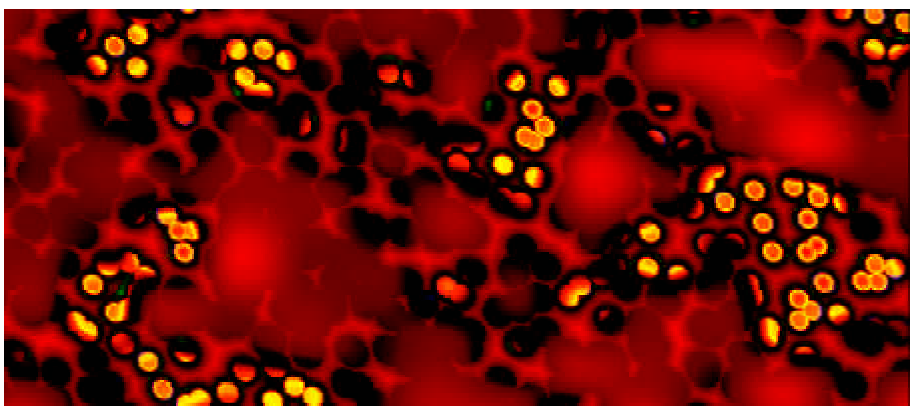
Research Initiated in 2003

The CBCRP funded nine new grants that focus on *Innovative Treatments*. Seven of our newly funded grants focus in two areas that have attracted advocacy attention: (1) less toxic treatments that might also be useful in chemoprevention and (2) harnessing the immune response. ***Christine Brew,***

Ph.D., and her mentor ***Dr. Gary Firestone*** at the ***University of California, Berkeley,*** were funded though separate grants to study I3C's (indole-3-carbinol) role in regulation of metalloproteinase genes and to identify the cellular target for the I3C derivative DIM, respectively. ***Ling Jong, Ph.D.,*** from ***SRI International,*** received an award to evaluate novel I3C derivatives using assays for cell signaling pathways associated with apoptosis (programmed cell death) and angiogenesis. Many natural compounds have potential as anti-cancer therapeutics, but the mechanism of action and cellular targets need identification prior to clinical development. Next, there is the concern that widespread use of alternative and complementary therapies might alter the effectiveness of Western medicines. ***Michael Campbell, Ph.D.,*** at the ***University of California, San Francisco,*** was awarded a grant to investigate how Chinese medicinal herbal preparations work in combination with the traditional chemotherapeutic drugs, doxorubicin and paclitaxel. Dr. Campbell's study will be done in cell culture systems, but promising results might quickly be translated to human trials.

Three newly-funded CBCRP awards focus on research questions related to immunotherapy of breast cancer. ***Joseph Lustgarten, Ph.D.,*** at the ***Sidney Kimmel Cancer Center,*** San Diego, was funded to study a novel group of "non-self" protein fragments (peptides) for their potential to establish immune responses against the Her-2 oncogene. The normal immune response to Her-2 is weak, so Dr. Lustgarten's approach of directly activating T-cells might circumvent the immune tolerance exhibited by most patients. ***Edward Nelson, M.D.,*** at the ***University of California, Irvine,*** received an award to explore a novel immunophototherapy approach. This is based on the injection of a precursor molecule, uptake by tumor cells, and metabolic production of a photosensitive killer compound. The "photo" element involves activation by laser list focused on the tumor. Dr. Nelson is evaluating whether marrow-derived dendritic cells might work to enhance this therapy. ***Margaret Huflejt, Ph.D.,*** also from the ***Sidney Kimmel Cancer Center,*** received an award to explore how best to neutralize immunosuppressive galectins produced by tumor cells. Galectins are carbohydrate-rich cell surface proteins that are thought to mask tumor cells from immune detection.

Two newly-funded CBCRP projects focus on novel drug development and a special conference to explore better pre-clinical models for breast cancer. ***Peter Vogt, Ph.D.,*** from the ***Scripps Research Institute,*** La Jolla, will explore a new approach to screen drugs targeting Myc, an oncogene that is elevated in most breast cancers and serves to de-regulate many genes that are associated with aggressive tumors. Dr. Vogt is searching for compounds that block the key Myc-Max protein interaction, and he plans to evaluate lead compounds by their potential to block anti-estrogen resistance in cultured cells. ***Robert Cardiff, M.D., Ph.D.,*** at *the* ***University of California, Davis,*** received a Joining Forces Conference Award to partially support a special conference on improving animal models in pre-clinical research on breast cancer.



California Breast Cancer Research Program Staff

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Laurence Fitzgerald, Ph.D.

Katherine McKenzie, Ph.D.

Walter Price, Dr.P.H.

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Director

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Biomedical Research Administrator

Katherine McKenzie, Ph.D.
Biomedical Research Administrator

Walter Price, Dr.P.H.
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Senior Artist

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Assistant to the Director

Sharon Simms, M.P.A.
Grant Analyst

The 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

Chair | Advocate

Debra Oto-Kent, M.P.H. (07/01/03—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.

Chair | Scientist

Anna M. Wu, Ph.D. (07/01/02—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.

Council Members

Vice Chair | Scientist

Elaine Ashby, M.D. (07/1/03 - 06/30/04)

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.

Vice Chair | Advocate

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 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.

Council Members

Advocate

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

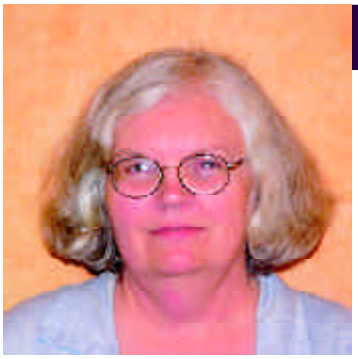
Janet Howard-Espinoza is a member of the Women of Color Breast Cancer Survivors Support Project, Los Angeles, which provides support in a nurturing environment through community outreach, encouragement, and support. She conducts an hundreds of motivational seminars and workshops each year, reaching diverse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

Advocate

Kim Pierce (07/01/03—06/30/06)

As Executive Administrator for the University of California, Los Angeles, Kim Pierce is responsible for all the administrative functions of six campus departments, including four departments within the School of Medicine. In addition, she is the Executive Director for the Academy of Molecular Imaging, a 1500-member nonprofit international professional society for physicians, scientists, technologists, and professionals in the field of molecular medicine; the Chair of the Imaging for Hope Patient Advocacy Committee; and a member of both the National Breast Cancer Coalition and the Los Angeles Breast Cancer Alliance. She has a solid, extensive management experience in research and clinical administration, and her range of accomplishments include developing long range plans for patient care and developing strategies for maintaining high-quality patient care in the UCLA Hospital System.

Council Members



Advocate

Kathy Walters, J.D. (07/01/03—06/30/06)

Community Breast Health Network

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.

Council Members

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.

Council Members

Industry

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

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.

Scientist/Clinician

Carol D'Onofrio, Dr.P.H. (07/01/03—06/30/06)

Carol D'Onofrio, Dr.P.H., is professor emerita at the School of Public Health, University of California, Berkeley. She is an active research scientist in breast cancer, prostate cancer, and tobacco-related diseases. Her breast cancer research includes collaborative research with community organizations to improve breast screening access for women with disabilities, and to increase quality-of-life for survivors, as well as for patients nearing the end-of-life. She is the author of multiple peer-reviewed publications, including Health Education Quarterly, Topics in Health Information Management, Health Education & Behavior, and Journal of Palliative Medicine. She has consulted for numerous national and California state agencies over the years, including the Northern California Cancer Center, National Cancer Institute, several units of the Centers for Disease Control, Veterans Administration, National Center for Health Services Research, American Red Cross, National Center for Health Education, the World Health Organization, and US Agency for International Development. Dr. DOnofrio is the recipient of several honors, including the 2001 Jill Ireland Award for Volunteerism from the Susan G. Komen Breast Cancer Foundation.

Council Members

Industry

Christine White, M.D. (07/01/03—06/30/06)

Dr. White is a medical oncologist, hematologist, and Sr. Vice President, Global Medical Affairs at Biogen Idec, where she has been employed since 1996. She served as Director, Clinical Oncology Research 1994-1996 at the Sidney Kimmel Cancer Center in San Diego. At Scripps Memorial Hospitals, La Jolla and Encinitas, she served as Medical Director, Oncology Research from 1989-1994, and Dept of Medicine Chair, in 1994. She was an Assistant Professor at UCSD/VA Hospital from 1983-1984 and a research associate at the Salk Institute from 1982-1992. She has been a member of the Board of Directors of the San Diego Regional Cancer Center (1990-1991) and the Hospice of North Coast, (1984-1988) serving one term as Vice President at the latter. She also served on the North Coast Regional Advisory Board at American Cancer Society in San Diego (1986-1989), the Scientific Advisory Committee to San Diego-Imperial Counties Organization for Cancer Control (1989-1991), was a member of the Medical Ethics Committee at Scripps Member Hospital, Encinitas, (1985-1990) and chaired the Investigational Review Board at San Diego Regional Cancer Center (1990-1996). She serves on numerous medical journal editorial boards.

Scientist/Clinician

James M. Ford, M.D. (07/01/03—06/30/06)

James M. Ford, M.D., is Assistant Professor of Medicine (Oncology Division), Genetics, and Pediatrics (Medical Genetics Division) at Stanford University School of Medicine; Director of the Stanford Program for Applied Cancer Genetics and the Breast Cancer Genetics Clinic; and Director of Stanford's Oncology Fellowship Training Program. He graduated in 1984 *magna cum laude* from Yale University where he later received his M.D. from the School of Medicine. He performed a residency in Internal Medicine and clinical fellowships in Medical Oncology at Stanford University Medical Center, and was a research fellow in Biological Sciences at Stanford from 1993-1997. Dr. Ford is an internationally recognized expert in the fields of DNA repair and the genetics of solid tumors. His laboratory and clinical research programs focus on the genetics and genomics of familial breast and GI cancers, and the use of new technologies for cancer diagnosis, prevention, and treatment. He is a member of numerous professional societies, is currently the chairman of the Human Genetics and Tumor Biology section of the American Society of Clinical Oncology and is an associate editor for *Cancer Research*.

Council Members

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.

Scientist/Clinician

Kathryn Phillips, Ph.D., M.P.A. (07/01/03 - 06/30/04)

Kathryn A. Phillips, PhD, is Professor of Health Economics and Health Services Research (tenured) in the Department of Clinical Pharmacy at the University of California, San Francisco. She leads the Program in Pharmacogenomics and Population Screening at UCSF.

Kathryn's research focuses on the application of quantitative tools to policy issues, and she has published over 60 peer-reviewed articles in policy and clinical journals, including JAMA, New England Journal of Medicine, Health Affairs, Health Services Research, American Journal of Public Health, Journal of Health Economics, Medical Care, and the Annals of Internal Medicine. She has served on several national and international panels, including study sections (for the National Institutes of Health, National Cancer Institute, Agency for Healthcare Research and Quality, Department of Defense, and the American Heart Association) and committees (for the Institute of Medicine, Centers for Disease Control and Prevention, National Center for Health Statistics, National Institutes of Mental Health, and the European Commission). She was recently appointed to a four-year term on the NIH Health Services Organization and Delivery Study Section. She serves on the editorial board of the *American Journal of Preventive Medicine* and is a reviewer for 30 journals.

Scientist/Clinician

Robert Kaplan, Ph.D. (07/01/02—06/30/03)

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.

Council Members

Medical Specialist

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

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.

Nonprofit Health 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.

Council Members

Nonprofit Health 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."

Nonprofit Health Organization

John Morgan, Dr.P.H. (07/01/03—06/30/06)

John W. Morgan, Dr.P.H., is a Professor of Epidemiology and Biostatistics at Loma Linda University and the Cancer Epidemiologist for Region 5 of the California Cancer Registry. Dr. Morgan is a member of the Board of Professional/Scientific Advisors for the American Council on Science and Health and is a member of the board of directors for the California Division of the American Cancer Society. His interests include epidemiologic research that identifies control and prevention strategies for cancer.

Summary of Research Funded in 2003

INSTITUTION/PI	DUR	DIRECT COSTS	INDIRECT COSTS	TOTAL COSTS
Breast Friends, Long Beach				
Michele Rakoff	1	$10,000	$0	**$10,000**
Children's Hospital Los Angeles				
Saverio Bellusci	3	$300,000	$146,400	**$446,400**
Guam Communications Network, Inc., Long Beach				
Lola Sablan-Santos	1	$10,000	$0	**$10,000**
John Wayne Cancer Institute, Santa Monica				
Dave Hoon, Lori Wilson, and Amando Giuliano (co-PIs)	1.5	$100,000	$88,800	**$188,800**
Korean Health, Education, Information & Research Ctr. Los Angeles				
Soo-Young Chin	1.5	$29,057	$7,264	**$36,321**
Lawrence Livermore Natl. Laboratory				
John Conboy	1.5	$75,000	$47,542	$122,542
Paul Yaswen	2	$149,998	$114,023	$264,021
				$386,563
Lawrence Livermore Natl. Laboratory				
Paul Henderson	3	$300,000	$292,586	$592,566
Kristen Kulp	2	$199,971	$163,789	$363,760
				$956,326
Long Beach Memorial Medical Ctr.				
John Link	1	$10,000	$0	**$10,000**
Northern California Cancer Ctr., Union City				
Christina Clarke Dur	3	$262,516	$104,481	$366,997
Sally Glasser	2	$231,156	$44,408	$275,564
				$642,561
Northern Sierra Rural Health Network				
Speranza Avram	1	$6,667	$0	**$6,667**

INSTITUTION/PI	DUR	DIRECT COSTS	INDIRECT COSTS	TOTAL COSTS
Salk Institute for Biological Studies, San Diego				
Quan Zhu	2	$80,000	$6,400	**$86,400**
Scripps Ressearch Institute, La Jolla				
Nadim Jessani	2	$60,000	$0	$60,000
Peter Vogt	2	$150,000	$129,919	$278,919
				$338,919
Sierra College, Nevada City				
Marry Anne Kreshka	1	$3,333	$3,333	**$3,333**
Sidney Kimmel Cancer Center, San Diego				
Margaret Huflejt	1	$100,000	$92,600	$192,600
Joseph Lustgarten	2	$200,000	$175,600	$385,200
				$577,800
SRI International, Menlo Park				
Ling Jong	2	$200,000	$188,491	**$388,491**
Stanford University				
Kate Collie	2	$79,758	$6,380	$86,138
Janine Geise-Davis	1.5	$100,000	$57,576	$157,576
Cheryl Koopman	1	43,333	$0	$3,333
				$247,047
Susan Love MD Breast Cancer Foundation, Santa Barbara				
Susan Love	1	$25,000	$0	**$25,000**
The Burnham Institute, La Jolla				
Yuehai Ke	2	$80,000	$6,400	$86,400
Kristiina Vuori	2	$150,000	$136,500	$286,500
				$372,900
University of California, Berkeley				
Christine Brew	2	$80,000	$0	$80,000
Gary Firestone	2	$150,000	$0	$150,000
Steven Martin	1	$75,000	$0	$75,000
				$305,000

Summary of Research Funded in 2003

INSTITUTION/PI	DUR	DIRECT COSTS	INDIRECT COSTS	TOTAL COSTS
University of California, Davis				
Robert Cardiff	1	$25,000	$0	$25,000
Michael DeGregorio	1	$99,708	$0	$99,708
Ruria Namba	2	$80,000	$0	$80,000
				$204,708
University of California, Irvine				
Peter Kaiser	1.5	$75,000	$0	$75,000
Keon Wook Kang	1	$39,086	$0	$39,086
Sean Merritt	2	$58,304	$0	$58,304
Edward Nelson	1	$99,834	$0	$99,834
Susan Neuhausen	3	$422,467	$0	$422,467
Min-Yang (Lydia) Su	2	$250,000	$0	$250,000
				$944,691
University of California, Los Angeles				
Catherine Carpenter	3	$533,527	$0	$533,527
Beth Glenn	2	$80,000	$0	$80,000
Annette Maxwell	1.5	$70,943	$0	$70,943
Helen-Rebecca Rausch	2	$250,000	$0	$250,000
				$934,470
University of California, San Francisco				
Michael Campbell	2	$200,000	$0	$200,000
Tsui-Ting Ching	2	$80,000	$0	$80,000
Rami Eversley	1.5	Collaborative Award		Coll. Award
Nola Hylton	1	$155,409	$0	$155,409
Verena Kallab	2	$80,000	$0	$80,000
Celia Kaplan	3	$774,174	$0	$774,174
Wendy Max	3	$315,198	$0	$315,198
Kimberly McDermott	2	$80,000	$0	$80,000
John Park, Morton Lieberman	1	$100,000	$0	$100,000
Euan Slorach	2	$80,000	$0	$80,000
Rebecca Smith-Bindman	3	$583,287	$0	$583,287
Thea Tlsty	2	$199,999	$0	$199,999
				2,648,067
University of Southern California, Los Angeles				
Christopher Haiman	3	$462,925	$0	$462,925
Brian Henderson	1.5	$162,311	$0	$162,311
Anna Wu	3	$1,050,751	$0	$1,050,751
				$1,675,987
Women's Cancer Resource Center, Oakland				
Diane Estrin and Linda Wardlaw	1.5	$125,000	$0	**$125,000**
TOTALS 50 GRANTS (including collaborative awards)				**$11,571,451**

California Breast Cancer Research Program
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