# Advances 2002

## Advances in Breast Cancer Research

CALIFORNIA
Breast
Cancer
Research
PROGRAM

CALIFORNIA

# Breast Cancer Research PROGRAM

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# *Research Highlights*

A hand-held Laser Breast Scanner could detect breast cancer using near-infrared light. See "Non-Invasive Optical Characterization of Breast Physiology," page 51.

Asian women who ate tofu at least 4 times a week as teenagers had a 35% lower risk for breast cancer than those who ate tofu less often than once a month. See "Gene-Diet Tobacco Interactions in Breast Cancer in Asians," page 62.

Tibetan herbal medicine is being tested as a breast cancer treatment. See "Tibetan Medicine for Advanced Breast Cancer," page 88.

Women who have previously had breast cancer are taking a compound derived from vegetables such as broccoli and cabbage in an experiment to see if this will prevent a recurrence of the disease. "Dietary Indole Effect on Estrogen Urinary Metabolites," page 96.

Researchers are attempting to develop a way to use the fluorescent protein produced by fireflies and a type of video camera to externally detect very small tumors produced experimentally in living animals. See "Metastasis Suppressor Genes for Breast Cancer," page 116.

Exercise alone prevented tumors more effectively than exercise and Vitamin E together. See "Exercise, Hormones and Cancer Prevention," page 130.

Can Essiac tea, a widely-used herbal mixture, prevent tumors in mice and rats? See "Evaluation of Essiac Tea to Prevent Mammary Tumors," page 135.

Twenty-nine percent of women who had breast cancer surgery felt they were harassed on the job as a result. See "Perceived Support in the Work Place and Return to Work," page 141.

# Message from the Director

During 2001, the California Breast Cancer Research Program (CBCRP) awarded $18,369,080 for 66 single- and multiple-year research projects at 32 California institutions. Over our eight-year history, the CBCRP has awarded more than $100 million in research grants to investigators throughout the state.

This Annual Report is part of our wide-ranging efforts to make our research available to the public. On these pages, we give brief summaries of the studies we funded this year, along with summaries of studies we funded in previous years that were completed or made progress during 2001. We are one of the few research programs in the world to publish annual summaries of studies while they are still in progress.

We know that breast cancer is a varied and highly complex disease–a puzzle made up of millions of pieces. Much of the research we have supported to date has examined individual pieces of this puzzle, studying the molecular, genetic, and cellular mechanisms by which breast cancer arises and develops. As we examine the pieces, we will be able to put some of them together and use the picture that emerges to teach us how to prevent and cure breast cancer.

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

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

The purpose of the CBCRP's investment in breast cancer research is to speed the day when we can prevent the majority of breast cancer, and cure what we can't prevent. That day is coming.

*"The purpose of the CBCRP's investment in breast cancer research is to speed the day when we can prevent the majority of breast cancer, and cure what we can't prevent. That day is coming."*

Mel Kavanaugh-Lynch

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

## *Thanks, California Taxpayers!*

*Every year, California taxpayers have an opportunity to contribute to a variety of nonprofit organizations, including the California Breast Cancer Research Program, by checking a box on—and adding a donation to—their state income tax returns. Last year, the CBCRP was #1 in the state for tax check-off donations.*

*By the end of 2001, 62,238 taxpayers made donations with a total of $623,991.*

*Thanks, California taxpayers!*

# About the California Breast Cancer Research Program. . .

## Making California a Leader among States

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

The activists, most of them women who had survived or currently had breast cancer, were impatient with the slow pace of progress against the disease. With their allies, they wrote and won passage of statewide legislation to push breast cancer research in new, creative directions. The California Breast Cancer Act, sponsored by then-Assemblywoman Barbara Friedman, raised the tobacco tax by two cents per pack, with 45% of the proceeds going to what was then, and still is, the largest state-funded breast cancer research effort in the nation, the California Breast Cancer Research Program.

Funded primarily by the tobacco tax (a steadily declining source), supplemented with taxpayer donations selected on state income tax returns, and private contributions, the California Breast Cancer Research Program (CBCRP) has provided a total of $115,667,191 in research funds since 1995. In 2001, the CBCRP awarded $18,758,851 for 66 single- and multiple-year grants at 32 California institutions.

## Pushing the Research Boundaries

During our eight-year history, the CBCRP has established a record for filling gaps not covered by other research funders, jump-starting new areas of research, and fostering new types of collaboration. Three examples of CBCRP funding strategies illustrate how we push the boundaries of research:

- To tap the expertise of people most affected by breast cancer, the CBCRP has pioneered collaboration between research scientists and community-based organizations, including community clinics, organizations serving women with breast cancer, and organizations serving minority communities. The collaborations are available in even wider circles. "Not a Breast Cancer Researcher? Concerned

### The California Breast Cancer Research Program's Key Strategies

1 Support the best, most innovative research

2 Build the research talent pool by training new researchers

3 Encourage creativity by financing collaboration across research fields

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

Community Member?" say headlines on the cover of our call for research applications. Inside, the call invites Californians with promising research ideas to team up with professional scientists.

- Because the results of basic science research can sit on the shelf for years, with no one in the scientific community being aware of any possible implications for fighting breast cancer, the CBCRP also funds "translation" grants. These grants spark collaboration between basic research scientists and scientists who may be able to translate basic research into improvements in breast cancer prevention, detection, or treatment.
- Since the disease is still raging despite increasing research efforts, new breakthroughs are likely to come from thinking outside established patterns of scientific thought. So the CBCRP brings together scientists from different fields to develop creative ideas outside traditional research channels.

## A Structure that Encourages Public Input

The CBCRP's structure has set a standard for community involvement that has inspired similar changes in other research funding agencies around the nation. Breast cancer activists play a leading role in every aspect of our work, from setting research priorities to recommending grants for funding 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 16-member Breast Cancer Research Council includes scientists, clinicians, representatives of industry and non-profit health organizations, and five 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 that every proposal must pass to receive funding. The Council reviews research proposals for relevance to the CBCRP's goals, while teams of research scientists and breast cancer advocates from outside California also review all proposals for scientific merit.

In addition, all Californians concerned about breast cancer have opportunities to help set the research agenda via the CBCRP's statewide advisory meetings, which are open to the public. Our bi-annual research symposia, brings 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 (http://cbcrp.ucop.edu) and this Annual Report.

## Donations

Revenue from the California Breast Cancer Research Program's main source of funds, the tax on tobacco, decreases every year. You can support innovative breast cancer research in California by:

- Checking the donation line on your California Income Tax Return and adding a donation to the California Breast Cancer Research Fund
- Sending a check payable to The Regents of the University of California, with a letter designating the funds for the California Breast Cancer Research Program, to 300 Lakeside Drive, 6th Floor, Oakland, CA 94612-3550.

# *What They're Saying About the CBCRP*

## To End the Suffering

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

## The Envy of Many a Breast Cancer Researcher

"The CBCRP is the envy of many a breast cancer researcher elsewhere in the country. This program provides a competitive edge for innovative ideas to be developed into full-fledged research programs. I had the privilege of serving on the Pathogenesis Review Committee for the past three years. This participation was indeed a great learning experience for me. I enjoyed reading many high-quality proposals as well as the cordial, yet highly professional, atmosphere of the review meetings. During the meeting, each proposal was given sufficient time for thorough deliberations, instead of being tossed on the floor once it got triaged. It is the goal of the review committee to provide young investigators with constructive critiques to help their research. I wish the CBCRP program continued success."

—Ching-Shih Chen, Ph.D.
Professor of Medicinal Chemistry
College of Pharmacy, The Ohio State University
Columbus, OH

## Having a Voice

"As a member of The Young Survival Coalition—an advocacy and outreach network for breast cancer survivors 40 and younger—it means a lot to me to have a voice as to how the CBCRP's research dollars get allocated. Pre-menopausal women are often times forgotten about in research studies. I think that my participation in the decision making process has made a significant impact with research scientists participating in the program."

—Joy Simha
Advocacy Officer, Young Survival Coalition
New York, New York

## Seed Funding for Innovative Ideas

"The CBCRP has a unique mission—to fund work that might not be supported by the more traditional funding agencies like the National Cancer Institute, but has the potential to advance the field. Our studies aim to rigorously study herbal medicine, but given the infancy of the field, we had to generate the preliminary data. Our early work on Tibetan Medicine for advanced breast cancer was funded by the CBCRP and has now been presented at the American Society of Clinical Oncology Annual Meeting. The CBCRP's seed funding for pilot projects such as these will serve as a basis for more definitive studies that can eventually address the value and limitations of alternative medicine and other innovative ideas to treat breast cancer."
—Debu Tripathy, M.D.
Associate Clinical Professor of Medicine
Director of Research
UCSF Breast Care Center
UCSF Comprehensive Cancer Center and Department of Medicine
University of California, San Francisco

## Challenging Current Dogma

"The fact that the state of California can put money into projects that are novel and challenge current dogma is very important. Many times national review panels stick to a conservative approach. The ability to fund new ideas and new investigators makes the California Breast Cancer Research Program crucial."
—Anne Hamburger, Ph.D.
Professor of Pathology, University of Maryland School of Medicine
Greenebaum Cancer Center
Baltimore, Maryland

## A Model for Other States

"It was an honor to be asked to serve as a consumer reviewer for the California Breast Cancer Research Program for the first time in April 2001, and I hope I will have other opportunities to serve. Bringing consumers, scientists, and clinicians together around a table to discuss research proposals has led to more innovative approaches to difficult research problems and engendered mutual respect for all involved in the difficult fight against breast cancer. The CBCRP is the only state program of its kind funded by the tobacco tax. It is an outstanding model I wish other states would adopt."
—Karin Noss
Board Member, Y-ME National Breast Cancer Organization
Vice President, Virginia Breast Cancer Foundation
Board Member, National Breast Cancer Coalition
Vienna, Virginia

## Funding for New Discoveries

"We're doing very basic research trying to identify proteins that might have roles in packaging of genomic DNA in breast cancer cells and test if there is any difference in the amount of these proteins between breast cancer cells and non-malignant cells. We have been able to identify such candidate proteins, which are much increased in breast cancer, and found that some of them are potentially good targets for breast cancer gene therapy. These discoveries have come as a result of funding from the CBCRP. Without the CBCRP, we could never have pursued this project."

—Terumi Kohwi-Shigematsu, Ph.D.
Senior Scientist
Lawrence Berkeley National Laboratory, University of California
Berkeley, California

## Helpful, Dedicated

"The CBCRP administrators and staff are always very helpful and responsive to my questions and suggestions, and they seem truly dedicated to the mission of the organization. CBCRP provided unique funding opportunities that allowed me to pursue my interest in breast cancer research as a postdoctoral fellow and that helped me develop my research program as a new investigator."

—Shelley M. Enger, Ph.D., M.P.H.
Research Scientist
Kaiser Permanente Medical Care Program, Southern California
Pasadena, California

## Well-Run

"My experience reviewing research proposals for the CBCRP has been very positive. Because the program is well-run, it gets the expertise of good reviewers from all over the country. I appreciate the input on the review panels from women who have had personal experience with breast cancer. They keep the focus on the patient. For a basic scientist like me, that's a big plus. I'm also really impressed with the generally high quality of the research proposals the CBCRP receives."

—Debra F. Skafar, Ph.D.
Associate Professor of Physiology
Wayne State University School of Medicine and
Barbara Ann Karmanos Cancer Institute
Detroit, Michigan

## Stimulating New Breast Cancer Research

"California's Breast Cancer Research Program has led the nation in innovation to stimulate new approaches to the detection, management and understanding of breast cancer. The program's integration of research in biology with research in community outreach and patient care has generated novel projects by established investigators and has attracted new investigators to the field. I have worked in breast cancer for 15 years, and I can speak to the impact the program has had on stimulating research in breast cancer at our institution. Investigators at Lawrence Berkeley National Laboratory have benefited from the program's emphasis on new ideas in basic biology, which supports research deemed too preliminary for funding by some federal funding agencies."

—Mary Helen Barcellos-Hoff, Ph.D.
Group Leader, Cancer and Tissue Biology
Cell and Molecular Biology Department
Life Sciences Division, Lawrence Berkeley Laboratory
Berkeley, California

## Extremely Pleased

"I am extremely pleased that the California Breast Cancer Research Program is encouraging cancer chemoprevention research on natural chemicals found in plants. Lack of stringently controlled pre-clinical studies on these relatively nontoxic phytochemicals represents a major limitation on documenting their potential for prevention and treatment of clinical breast cancer."

—Nitin Telang, Ph.D.
Associate Professor, Weil Medical College
Cornell University, and
Director, Division of Carcinogenesis and Prevention
Strang Cancer Research Laboratory
Rockefeller University
New York, New York

# CBCRP-Funded Research in the Media

## Breast Fluid May Mean Cancer Risk

WASHINGTON—Researchers who studied specimens from thousands of women suggest that the presence of abnormal cells in breast fluid may predict a doubled risk of breast cancer.

In a study appearing Wednesday in the *Journal of the National Cancer Institute*, the researchers said that analyzing fluids extracted from nonpregnant and nonlactating women showed that those with abnormal cells were twice as likely to develop breast cancer.

"Our study shows that if you can get fluid from a woman and there are abnormal cells in that fluid, then it is an indication of increased risk of breast cancer," said Margaret R. Wrensch, an epidemiologist at the University of California, San Francisco School of Medicine and first author of the study.

—From a December 4, 2001 Associated Press Report.

## Doc No Holiday

SAN FRANCISCO—Dr. Arthur Coleman is 81 years old and can't quit.

He is the only privately practicing family physician left in San Francisco's neglected Bayview-Hunters Point district, where the city's largest concentration of African Americans lives.

Coleman, a man who knows exactly how badly he's needed, still works seven days a week and even makes house calls, toting a black leather medical bag.

When Coleman leaves his practice—and he's not saying when—the neighborhood loses its first black doctor, a 50-year health care and civil rights advocate, and a relic of a bygone era when the family doctor would call after hours just to see how you're feeling.

—From a profile of Dr. Coleman in the *San Francisco Chronicle*, May 23, 2001. With funding from the CBCRP, Dr. Coleman added research to his 7-day-a-week medical practice. During 2000, he and a colleague completed a study on barriers African American women face in getting timely follow-up care after they have abnormal mammograms.

## Laser May Be Breast Cancer Tool

IRVINE—Researchers at the Beckman Laser Institute developed a painless scanner that they believe can better diagnose breast cancer in young women.

After 10 years of working out complicated equations and building a hand-held laser scanner, institute professor Bruce Tromberg and his team found that lasers similar to those in CD players can detect the kinds of subtle changes in tissue that lead to cancerous growths.

—From a February 2001 article in the *Orange County Register*.

## Medical Breakthroughs: Chinese Breast Cancer Therapy May Help Fight Disease

BAKERSFIELD—Chinese herbs. Some swear by them, while others scoff. Now, doctors at the University of California, San Francisco, are trying to find out, once and for all, if they work.

Oncologist Debu Tripathy, M.D., is studying 60 women with early stage breast cancer to see if herbal therapy can help reduce the unpleasant side effects of chemotherapy. He says, "All our patients ask us about this and we really don't have good information to give them."

—From a February 7, 2002 segment on KGET 17 TV News in Bakersfield. Dr. Tripathy's research on Tibetan herbal medicine for breast cancer was also profiled on January 1, 2001, on the NBC program *Dateline*.

# Breast Cancer in California

Every two hours, on average, a California woman dies of breast cancer.

During 2001, an estimated 20,000 California women were diagnosed with the disease. Nearly 200,000 women in the state are living with a past or present diagnosis of breast cancer. While many are long-term survivors, some are battling a recurrence and others are fighting for their lives. Today, no woman who has survived breast cancer can be guaranteed that it won't return.

Because of early detection through widespread mammogram screening, a California woman diagnosed with breast cancer today has a better chance of surviving than in the past. Since 1973, the breast cancer death rate in the state has dropped 20%. However, California women are more likely to get breast cancer today than in 1973. The breast cancer rate for California rose alarmingly until 1988. It has gone down only slightly since, and last year, the state's breast cancer rate actually rose slightly.

## Not an Equal Opportunity Killer

*When it comes to breast cancer in California, ethnicity makes a difference. White women are most likely to get the disease, followed closely by black women, then Asian/Pacific women, with the lowest rate among Hispanic women.*

*Although the death rate has dropped in the last 12 years, most of the gains have come for white women. Black women have the highest death rate, even though they are less likely than white women to get the disease. Death rates for Asian/Pacific and Hispanic women, although they were lower to begin with, have not improved in recent years.*

*Income level also matters. Low-income women are less likely to survive breast cancer, because their tumors are more likely to be caught later, when treatment is less successful.*

# 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 the California Breast Cancer Research Program when we decide which research to fund. We answer it by applying our research dollars to meet two broad goals: funding the most creative new research ideas, and moving the larger world of breast cancer research toward innovation. Each year, the Breast Cancer Research Council sets the priorities for research funding. These priorities are based on the Council's judgment of what critical research the CBCRP can add to move most rapidly to the prevention and cure of breast cancer.

## Funding Creative New Research Ideas

We encourage research in new directions in several ways. One is by earmarking funds for subjects we know need more research. During 2001, we set aside up to $5.5 million for new research in Health Policy and Health Services; Racial and Ethnic Differences in Breast Cancer; Sociocultural, Behavioral, and Psychological Issues Relevant to Breast Cancer; and the Biology of the Normal Breast.

However, the CBCRP has found that even when we identify under-researched areas and make research funds available, we can't always fund the type of research we'd like to see. We still don't receive enough proposals for research that meet our high standards for scientific merit and innovation. That's why we make extra efforts to build up new areas of research. A case in point is our efforts to encourage the women most affected by breast cancer to become more active in doing research.

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

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

The CBCRP did outreach to find more potential researchers. We worked with research teams whose proposals hadn't been strong enough, and helped them improve the design of their studies so we could fund them in the future. We interviewed research teams we'd already funded and used their suggestions to make our Community Research Collaboration Award process more user-friendly.

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

To change this situation, the CBCRP is attempting to publish articles about our own experience with Community Research Collaborations in scientific journals and other publications. We want to pave the way, so the community-based researchers we fund will also be able to get their research published. What's more, we want to inspire the larger research world and community organizations to think seriously about making it possible for the women most affected by breast cancer to actively do research on the disease. We hope this will move other breast cancer funding agencies toward this innovative area of research.

## Moving Other Breast Cancer Funding Agencies toward Innovation

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

An example is our funding for research that has a high potential for scientific payoff—and also a high potential for failure. When the CBCRP began funding breast cancer research in the mid-1990s, less than 10% of research proposals submitted to the nation's funding agencies were getting funded. This led the people who decided what got funded—panels of research experts—to look for proposals that seemed most likely to succeed. Research scientists had to have done a significant portion of the research, and have strong preliminary data, before they could even get a grant. This made it hard for anyone to get funding in order to try out a high-risk idea; however, high-risk ideas are often the source of scientific breakthroughs.

That's why we started our IDEA Awards, grants specifically designed to encourage scientists to investigate high-risk questions. If the research succeeds, the researcher may well be able to get another research funding agency to fund the next step. For example, the CBCRP gave Robert Debs, M.D., an IDEA Award in 1997 to investigate gene therapy for breast cancer. When the idea showed promise,

### Including Minority Women in Research

*In all the research studies the CBCRP funds that have women or human tissues as subjects, we make it a practice to include minority women. In addition, some of the studies we fund are focused solely on minority women. We also make it a practice to include low-income women, lesbians, older women and other groups who don't have equal access to health care and are often left out of research.*

*California is a very diverse state, with many different ethnic groups, immigrant groups, and a mix of urban and rural dwellers. Some of the research the CBCRP funds takes advantage of this diversity. A number of the studies we fund—such as research with Samoan American or Hmong American women—could only be done in our state.*

he was able to get funding from the federal government's National Institutes of Health (NIH) to pursue the research on a much larger scale. Alex Strongin, Ph.D., received a grant from the CBCRP in 1996 to study the role of enzymes in breast tumors developing the ability to spread to other parts of the body. The CBCRP award led to grants from the NIH, the Susan Komen Foundtion, and funding from private industry to develop this line of research.

To get creative new research going through our IDEA Awards, we've also needed to influence the larger research world. We had to encourage and train researchers in California to submit exciting new ideas. In addition, we had to train scientific experts from outside California, who review our research proposals for scientific merit, to identify promising new research concepts. We developed a new scoring system to help reviewers read proposals with a perspective toward rewarding high-risk research.

## Our Research Categories

Every piece of research we fund must fit into two separate sets of categories: our Priority Subject Areas and our Types of Awards. The CBCRP's Subject Areas are broad, which allows us to have an impact across a wide spectrum of breast cancer research. Our Types of Awards, which include the IDEA and Community Research Collaborations discussed above, are narrowly targeted. The narrow targeting is designed to jump-start under-funded areas of research, encourage creative new thinking, and bring new investigators into the fight against breast cancer.

Priority Subject Areas:

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

Award Types:

- Collaboration Awards
  - Scientific Perspectives Research Collaboration (SPRC) Awards
  - Community Research Collaboration (CRC) Awards
  - Translational Research Collaboration (TRC) Awards
  - Joining Forces Conference Award
- Targeted Awards (RFAs)
  - Biology of the Normal Breast
  - Racial and Ethnic Differences in Breast Cancer
  - Health Policy and Health Services
  - Sociocultural, Behavioral, and Psychological Issues
- Training Awards
  - New Investigator Awards
  - Postdoctoral Fellowship Awards
  - Training Program Awards
- Innovative Research Awards
  - Innovative Developmental and Exploratory (IDEA) Awards
  - STEP Awards

On the following pages, we explain our eight Priority Subject Areas and provide statistics on the 66 projects we funded in 2001 by subject. Then we explain our Award Types and provide statistics on the 66 projects by award type.

## Priority Subject Areas

**Biology of the Normal Breast**

Number of projects funded in 2001: 7

**Funds awarded: $1,847,959**

Percentage of total projects funded: 11%

Percentage of total funds awarded: 10%

Types of awards: 3 Postdoctoral Fellowship Awards, 2 New Investigator Awards, 2 Targeted Awards.

### The Starting Point
### The Biology of the Normal Breast

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

**Earlier Detection**

Number of projects funded in 2001: 9

**Funds awarded: $2,338,830**

Percentage of total projects funded: 13%

Percentage of total funds awarded: 12%

Types of Awards: 2 Innovative Developmental and Exploratory (IDEA) Awards, 3 STEP Awards, 1 Postdoctoral Fellowship Award, 2 Translational Research Collaboration (TRC) Awards, 1 Community Research Collaboration (CRC) Award.

### Improving the Chances for a Cure
### Earlier Detection

Since there is still no effective way to prevent breast cancer, early detection remains the best line of defense. Present methods of detection are far from perfect. Mammograms miss some tumors, falsely indicate cancer in some cases, and expose women to ionizing radiation. Low-income and minority women are also less likely to have their cancer detected early, when treatment is most likely to succeed. The CBCRP concentrates funding for detection in areas not well addressed by other funding agencies. These include new detection technology, potential new detection methods (such as blood or urine tests) that may detect cancer earlier than methods now in use, and ways to improve detection for women for whom current technology is less accurate, including women under 50.

**Etiology**
Number of projects funded in 2001: 4
**Funds awarded: $2,842,467**
Percentage of total projects funded: 6%
Percentage of total funds awarded: 15%
Types of awards: 1 STEP Award, 3 Targeted Awards.

## Finding the Causes
## Etiology

Discovering the causes of breast cancer can lead to strategies to prevent, treat, or cure it. The CBCRP emphasizes research in areas that haven't received enough study, including possible environmental causes, environment-gene interactions, as-yet-undiscovered genes that affect breast cancer risk, and finding the biological basis behind factors—such as early pregnancy or socio-economic status—that affect risk. We encourage research into the possible causal role of lifestyle, hormones, and nutrition. We also fund studies into the biological mechanisms that could account for some women being at higher- or lower-risk for breast cancer; for example, studies into the biological mechanisms behind the increased risk for women with higher estrogen levels.

**Health Policy and Health Services**
Number of projects funded in 2001: 5
**Funds awarded: $3,526,106**
Percentage of total projects funded: 7%
Percentage of total funds awarded: 19%
Types of awards: 2 Community Research Collaboration Awards, 3 Targeted Awards.

## Serving Women's Needs
## Health Policy and Health Services

In California, as in the nation and in the world, inequality increases the suffering breast cancer causes. Low-income women and women from some minority groups have less access to early detection, are less likely to get treatment, are less likely to survive, or all three. We encourage more study on how to address the often lethal problem of unequal access to the best in prevention, detection, and treatment. We also encourage more work on ethical and legal issues surrounding breast cancer and on finding the most effective and supportive ways to deliver health care. In addition, we encourage research into new ways to deliver breast cancer care.

**Innovative Treatments**
Number of projects funded in 2001: 14
**Funds awarded: $3,031,380**
Percentage of total projects funded: 21%
Percentage of total funds awarded: 16%
Types of awards: 1 Innovative Developmental and Exploratory (IDEA) Award, 8 STEP Awards, 2 New Investigator Awards, 2 Postdoctoral Fellowship Awards, 1 Translational Research Collaboration (TRC) Award.

## Search for a Cure
## Innovative Treatments

Rather than fund more studies on new combinations of standard chemotherapy, the CBCRP puts our research dollars into novel medical approaches that hold potential to improve treatment or even point toward a cure. These include new therapies based on blocking breast cancer's ability to hijack blood vessels and investigations of alternative medicine and nutritional factors. We encourage research to evaluate non-conventional alternative treatments and to develop methods to better manage the side effects of current treatments.

**Pathogenesis**
Number of projects funded in 2001: 21
**Funds awarded: $3,502,288**
Percentage of total projects funded: 32%
Percentage of total funds awarded: 19%
Types of awards: 4 Innovative Developmental and Exploratory (IDEA) Awards, 2 STEP Awards 5 New Investigator Awards, 10 Postdoctoral Fellowship Awards.

## Understanding the Disease
## Pathogenesis

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

**Prevention and Risk Reduction**

Number of projects funded in 2001: 1

**Funds awarded: $185,642**

Percentage of total projects funded: 2%

Percentage of total funds awarded: 1%

Type of award: Innovative Developmental and Exploratory (IDEA) Award

## Ending the Danger of Breast Cancer
## Prevention and Risk Reduction

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, environment, and lifestyle. So changing our environment or lifestyle has great potential to prevent cancer; however, the question is, which changes? The CBCRP funds research into promising areas, including diet, potential vaccines, and safer alternatives to environmental substances already known to cause breast cancer. Although we were only able to fund one Prevention study during 2001, we are actively encouraging researchers to submit more proposals in this area.

**Sociocultural, Behavioral, and Psychological Issues**

Number of projects funded in 2001: 5

**Funds awarded: $1,484,179**

Percentage of total projects funded: 8%

Percentage of total funds awarded: 8%

Types of awards: 3 Community Research Collaboration (CRC) Awards, 1 New Investigator Award, 1 Scientific Perspectives Research Collaboration (SPRC) Award.

## The Human Side
## Sociocultural, Behavioral and Psychological Issues

California women with breast cancer, and those at high risk, get treatment or don't get treatment, make decisions or miss their chance to make them, and cope with the disease—all in a social and cultural context. This context has great impact on well-being and even survival. So the CBCRP encourages research on the human side of the disease, including studies on enhancing quality of life for women with breast cancer, on improving doctor-patient interaction, and on non-medical factors leading to long-term survival. We also fund studies on how to increase the number of women with breast cancer taking part in the testing of promising treatments.

## Award Types

## Collaboration Awards

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

**Scientific Perspectives Research Collaboration (SPRC) Awards**
Number of projects funded in 2001: 1
**Funds awarded: $129,000**
Percentage of total projects funded: 2 %
Percentage of total funds awarded: <1%
Subject area: Sociocultural, Behavioral, and Psychological Issues.

### Scientific Perspectives Research Collaboration (SPRC) Awards

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

**Community Research Collaboration (CRC) Awards**
Number of projects funded in 2001: 6
**Funds awarded: $2,775,621**
Percentage of total projects funded: 9%
Percentage of total funds awarded: 14%
Subject areas: 2 Health Policy and Health Services,
4 Sociocultural, Behavioral, and Psychological Issues.

### Community Research Collaboration (CRC) Awards

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

**Translational Research Collaboration (TRC) Awards**

Number of projects funded in 2001: 3

**Funds awarded: $773,458**

Percentage of total projects funded: 5%

Percentage of total funds awarded: 4%

Subject areas: 2 Earlier Detection, 1 Innovative Treatments.

## Translational Research Collaboration (TRC) Awards

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

**Joining Forces Conference Award**

Number of projects funded in 2001: None, but we hope to fund more conferences of this type and are actively encouraging the submission of proposals for next year.

## Joining Forces Conference Award

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

**Targeted Awards**

Number of projects funded in 2001: 8

**Funds awarded: $5,760,935**

Percentage of total projects funded: 12%

Percentage of total funds awarded: 31%

Subject areas: 2 Biology of the Normal Breast, 3 Etiology, 3 Health Policy and Health Services.

## Targeted Awards

Each year, the CBCRP selects under-researched areas that are crucial to progress against breast cancer, and we make a special effort to encourage more research in these areas. In 2001, $1 million to $1.5 million was set aside to encourage creative research in each of the following areas:

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

## Training Awards

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

### New Investigator Awards

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

**New Investigator Awards**

Number of projects funded in 2001: 10

**Funds awarded: $2,889,338**

Percentage of total projects funded: 15%

Percentage of total funds awarded: 15%

Subject areas: 2 Biology of the Normal Breast, 2 Innovative Treatments, 5 Pathogenesis, 1 Socio-cultural, Behavioral and Psychological Issues.

### Postdoctoral Fellowship Awards

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

**Postdoctoral Fellowship Awards**

Number of projects funded in 2001: 16

**Funds awarded: $1,356,800**

Percentage of total projects funded: 24%

Percentage of total funds awarded: 7%

Subject areas: 3 Biology of the Normal Breast, 1 Earlier Detection, 2 Innovative Treatments, 10 Pathogenesis.

### Training Program Awards

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

**Training Program Awards**

Number of projects funded in 2001: None; however, we currently fund two training programs through 3-year grants made in previous years.

## Innovative Research Awards

### One-Year Innovative Developmental and Exploratory (IDEA) Awards

Number of projects funded in 2001: 8

**Funds awarded: $973,617**

Percentage of total projects funded: 12%

Percentage of total funds awarded: 5%

Subject areas: 2 Earlier Detection, 1 Innovative Treatments, 4 Pathogenesis, 1 Prevention and Risk Reduction.

### Innovative Developmental and Exploratory (IDEA) Awards

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

### STEP Awards

Number of projects funded in 2001: 14

**Funds awarded: $4,100,024**

Percentage of total projects funded: 21%

Percentage of total funds awarded: 22%

Subject areas: 3 Earlier Detection, 1 Etiology, 8 Innovative Treatments, 2 Pathogenesis.

### STEP Awards

STEP Awards fund innovative developmental research in exceptionally promising topics. The research team needs to have some preliminary data in breast cancer, but not enough to get funding from a major research agency for a full-scale study.

# *Sharing Our Research With Scientists and the Public*

Funding good research isn't enough. If the research is going to have an impact in the fight against 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 shape the fight against the disease. 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 the 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 our research widely, in print and over the Internet. We are one of the few research funding programs in the world to publish annual summaries of research while the studies are still in progress. The CBCRP does this so that scientists and other interested people can make use of the information as soon as possible. We get out the word about our research results and research in progress in a variety of ways:

**Research Symposia:** Every other year, we hold a Research Symposium, a statewide conference presenting the results of the research we fund. Our Symposium draws more breast cancer advocates and members of the public than is usual for such a scientific meeting. Our researchers present their findings in language geared toward the general public, and the meeting creates an opportunity for dialog between research scientists and breast cancer activists. Our 2001 symposium, with the theme, "From Research to Action," was postponed from September after the events of September 11 made travel difficult. The rescheduled symposium was held in Oakland during March 2002.

**Web site:** Our Web site (http://cbcrp.ucop.edu) is open to the public. It has summaries of all completed research projects and annual progress reports for ongoing projects, all in language accessible to the general reader. For anyone who wants a more detailed description, our summaries are linked to PubMed Abstracts, a public access Web site for all published scientific studies. Our Web site also contains a list of each year's awards and information on applying for grants.

**Annual Reports:** Our Annual Report, available free of charge to the public, contains summaries of all ongoing and completed research for the year. Multiple copies of our Annual Reports are available free of charge to organizations; the 1999 Annual Report was used during 2000 as a college text in a class for future health care professionals.

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

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

**Special Outreach:** The CBCRP makes special efforts to share its research results; during 2001, we continued and expanded these efforts by getting timely information on research to staff members of the statewide California Breast Cancer Early Detection Program. This state government program provides breast cancer screening to low-income women in California and is funded by the same tax on tobacco that provides the majority of funding for the CBCRP. Staff members at local early detection sites requested more information on research progress in early detection.

**Serving the Media:** When reporters from TV, newspapers, magazines, or other media need information on breast cancer research, the CBCRP links them with appropriate experts.

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

"We publish and distribute our research widely, in print and over the Internet."

# 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 a greater voice for the people breast cancer affects most, and we still set the standard for including advocates at all levels of leadership.

## Breast Cancer Advocates in Leadership

We developed our current funding strategy from recommendations made at our statewide Public Advisory Meeting in 1996, which are reviewed and modified annually by the Council. That meeting brought together research scientists from universities and the biotech industry, health care providers and health educators, and breast cancer activists and survivors. Together, they set the course for CBCRP grant making.

Breast cancer advocates constitute one-third of our highest leadership body, the Advisory Council. The Council recommends the research proposals that best fit our funding strategy. Throughout our eight-year history, an advocate has served as the Council's Chair or Vice-Chair. In addition, out-of-state panels of research scientists review all our research proposals for scientific merit. Out-of-state breast cancer advocates are full voting members of these review panels and a California advocate observes each one.

Advocates also exhibit their work at our bi-annual Symposia.

Involving 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.

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

## Advocates Doing Research

Breast cancer advocates are also investigators on a rising number of the CBCRP's research projects. In 1997, we pioneered a new type of research grant that allows breast cancer advocacy organizations to team up with experienced scientists for a research project. These Community Research Collaboration Awards are open to non-profit 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.

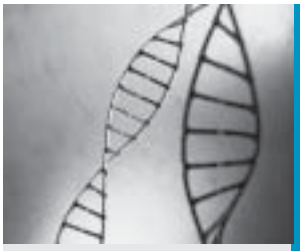
Projects we've funded over the years include:

- 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

## Community-Based Research Increased in 2001

During 2000, we conducted a formal evaluation of our Community Research Collaboration Awards. As a result of the evaluation, we decided to do more outreach to let potential researchers know about this opportunity, and we also made several changes to make the grants more user-friendly. We now provide community members with more training, support, and information. We've added smaller grants to help community researchers develop promising ideas by building a better research team or designing better research. We've also corrected some problems with timing and payments.

These improvements inspired members of more California communities to team up with scientists and send us good research proposals this year. As a result, during 2001, we funded a lot more community research, with 14% of our funds going for Community Research Collaborations, compared to 1% the year before. This means more California communities of women affected by breast cancer now have the power to conduct research on questions that concern them.



# Unmet Need

Although the California Breast Cancer Research Program allocates research to speed progress against the disease, we don't have enough funds to do all that needs to be done. We're unable to make grants to meet the following needs:

- **Clinical Trials.** In a clinical trial, some patients receive a promising new therapy and the outcome is compared to a group receiving standard therapy. Clinical trials are the way science discovers which treatments work. Currently, almost every child with cancer in the U.S. is treated through a clinical trial, compared to only 3% of women with breast cancer. With California's diverse population, statewide clinical trials here could lead to the discovery of information that would not be discovered elsewhere.

- **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 histories, 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 funding.

*With California's diverse population, statewide clinical trials here could lead to the discovery of information that could would not be discovered elsewhere.*

- **Grant Proposals the CBCRP Does Not Fund.** During 2001, the CBCRP turned down 105 grant applications requesting a total of $27.6 million. 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.

Since the CBCRP's major source of funding—the state tobacco tax—is decreasing every year, it is unlikely that we will be able to meet these critical needs, or continue to fund the broad range of projects we have funded in the past.

# *Improving our Program through Evaluation*

California taxpayers deserve to have the funds they provide for breast cancer research spent wisely. At the CBCRP, we're committed to evaluating our program to make sure we're doing the best job we can. We're planning a major evaluation of our entire program over the coming years. During 2001, we got started in two ways. First, we evaluated an important component of our work by taking a close look at one type of grant we make, our Postdoctoral Fellowship Awards. Second, we completed work on a survey of out-of-state experts who review our research proposals.

*Our primary goal for the Postdoctoral Fellowship Awards is to draw new researchers into the breast cancer field. Our survey indicates we are succeeding.*

## Evaluating CBCRP Postdoctoral Awards

The CBCRP's Postdoctoral Fellowships go to scientists in training who work under a mentor on breast cancer research. The grants—up to $80,000 for as long as two years—are designed to prepare researchers for a long-term professional research career. The CBCRP has invested almost $6.4 million in 94 postdoctoral awards since 1995. They make up 20–25% of the grants we award.

To evaluate the Postdoctoral Fellowship Awards, we surveyed researchers who were CBCRP postdocs during the first four years of the program.

Our primary goal for the Postdoctoral Fellowship Awards is to draw new researchers into the breast cancer field. Our survey indicates we are succeeding. Forty-four percent of our former postdocs used the CBCRP Award to gain first-time experience in breast cancer research. Of these, 70% have stayed in the field, and 27% say they would not be involved in breast cancer research today without the CBCRP's support. Moreover, 62% of the CBCRP's former postdocs say the grant helped them stay in the breast cancer field.

Another goal for our Postdoctoral Fellowship Awards is encouraging high-quality researchers from a variety of disciplines. We are meeting the first part of this goal well. Our survey turned up a number of indications that we funded high-quality researchers. As a result of research at least partly funded by the CBCRP fellowship, 39 former postdocs published a total of 108 articles in scientific journals, gave 78 presentations at scientific conferences, and received four

patents. Seven former postdocs received a total of nine awards for this work. However, the CBCRP fell short on another part of this goal—encouraging research from a variety of disciplines. The majority of Postdoctoral Fellowships went to researchers in the field of pathogenesis. The CBCRP is taking steps to increase postdoctoral fellowship training in other fields.

When we began making Postdoctoral Fellowship Awards, we hoped the awards would help develop the careers of new researchers. We seem to be succeeding here. More than half of our former postdocs told us the fellowship helped them gain a higher-level job, recognition, self-confidence, and skills to become a better researcher. We also hoped the Postdoctoral Fellowships would help launch promising new breast cancer research, and they appear to be doing so. Our first four years of Postdoctoral Fellowships have led to various funding agencies providing over $36 million in grants to continue avenues of research begun with our funding.

Along with letting us know that Postdoctoral Fellowships are generally succeeding, our former postdocs also made a number of suggestions for improving the program. These included making grants to researchers who want to work part-time, offering training in grant writing to postdocs, and getting the word out about these awards so more researchers will apply. The CBCRP is investigating ways to put these and other suggestions from former postdocs into practice. We plan to evaluate the awards again in four or five years.

### Surveying Our Reviewers

Every grant the CBCRP makes must pass a review by out-of-state research scientists and breast cancer advocates. Together, these reviewers make up a pool with a high level of expertise and knowledge about breast cancer. During 2001, we tapped this talent pool with a survey that asked these out-of-state reviewers their opinions on what the CBCRP has achieved and on how we should move forward.

In general, the people who review our proposals agreed with the CBCRP's approach to funding breast cancer research. There was no agreement on the need for any major changes.

This survey's most striking finding is strong support for including advocates—generally women who have or have had breast cancer—in decisions about which research to fund. The advocates told us they learn a tremendous amount. The scientists said advocates keep them focused on the human side of the disease. As one scientist commented, "Most advocates have important and significant information to convey. They may not know the science, but they remind us all of what our end point should be."

### More Evaluation Next Year

Over the coming year, we plan to evaluate more of our program, as part of our continuing effort to target our research dollars in the way that will do the most to make breast cancer a disease of the past.

*This survey's most striking finding is strong support for including women who have or have had breast cancer in decisions about which research to fund.*

# *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 2001. We also present summaries of research in progress, and of new research started this year.

We have organized the Research Progress and Results by the CBCRP's eight priority subject areas:

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

# Biology of the Normal Breast

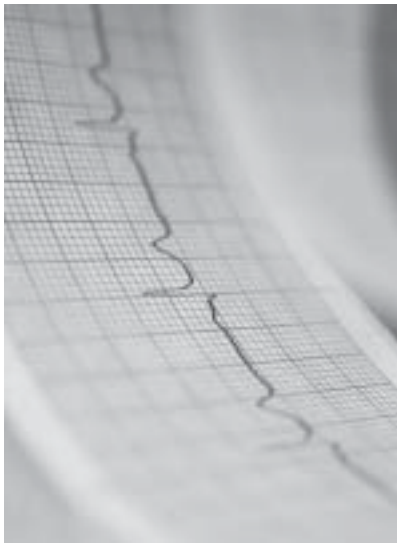

Biology of the Normal Breast:
The Starting Point

# Biology of the Normal Breast

## The Starting Point

As any woman who performs her monthly breast self-examinations knows, the normal breast is a constantly changing organ. The breast's normal changes can obscure the more ominous changes associated with cancer. Researchers have worked hard to determine what constitutes a cancerous change in the breast, but the lack of a thorough understanding of the normal breast makes this work more difficult. Because a relatively small amount of research is being done in this area, the California Breast Cancer Research Program earmarks funds especially for it. In 2001, we funded researchers who are studying the development, structure, hormonal regulation, and genetic control of the normal breast. Our hope is that these studies will provide a strong foundation for distinguishing the difference between benign and malignant breast changes.

# Research Conclusions



**A Novel Gene Associated with an Altered Risk of Breast Cancer.**
A full-term pregnancy reduces a young woman's lifetime risk of breast cancer by about 30%. ***Satyabrata Nandi, Ph.D.,*** from the ***University of California, Berkeley,*** investigated the hypothesis that pregnancy leads to changes in genes that are responsible for reducing the risk. Dr. Nandi's previous research showed that pregnancy will protect rats from substances used to cause mammary tumors (the rat equivalent of human breast cancers) in laboratory experiments. Using a special cloning method, his lab identified a gene called Rat Mammary Tumor-1 (RMT-1). This gene is present mainly in the mammary gland, at higher levels in breast cancer, but is less evident in older rats and in rats that have completed a full-term pregnancy. A higher level of activity of the gene seems to be associated with sensitivity to mammary cancer induced in the lab with a cancer-causing substance. The presence of RMT-1 appears also to be associated with higher levels of estrogen receptors, proteins within breast cells that bind with the hormone estrogen. This research was published in *Cancer Letters* 174:45-55 (2001).

**Regulation of Breast Epithelial Cell Motility by Proteases.**
***Vito Quaranta, M.D.,*** of ***The Scripps Research Institute***, La Jolla, investigated molecule-level interactions that underlie the ability of cells to move to a new location within the body. In the human breast, epithelial cells–the cells where most cancer arises–are surrounded by a complex structure containing support components and other types of cells. The structural components of the breast include proteins called laminin. To move around and reorganize when the breast goes through normal changes–such as the start of milk production–the epithelial cells need to digest the structural proteins surrounding them. Cancerous cells do the same thing when they migrate to other parts of the body. Dr. Quaranta found that an enzyme produced by epithelial cells, MT1-MMP, digests a laminin protein, Ln-5, by splitting it in two places. The resulting fragments may have a function. Another enzyme, MMP2, may increase the efficiency of cell migration. In mice that genetically lacked MT1-MMP, splitting of the Ln-5 molecule was lacking or greatly reduced. Their tissues also showed abnormal

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

organization of epithelial cells. The results of this study may point to ways to block cell migration as a way to limit or prevent breast cancer cells from spreading to other parts of the body. Publications resulting from this research appeared in *Journal of Cell Biology* 2000 148(3):615-24, 2000 149(6):1167-70, 2001 153(3):465-78; and *Cell Adhesion and Communications*, 2001 8:29-44.

**Hox Genes in Normal Breast Development and Breast Cancer.**
The loss of control of cell growth and cell specialization is a hallmark of cancer. Understanding genes that control these processes can lead to new candidates for anti-cancer drug development. ***Carmen Hagios, Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, studied the role of Hox genes in breast cancer, because these genes regulate cell growth and specialization in the developing embryo. Breast cancer cells also have abnormally high amounts of the proteins these genes produce. Dr. Hagios designed cell cultures that reproduced the conditions in the body, where epithelial cells (the source of most cancers) are surrounded by a collagen-based support structure (the basement membrane). The team found that levels of the Hoxa-1 protein produced by the Hoxa-1 gene were higher in two mouse mammary tumor cell lines (Scg6 and TC-1) compared to normal mouse mammary epithelial cells. The tumor cells formed irregular structures, while the normal cells formed organized spheres. When the team experimentally decreased the level of Hoxa-1 protein in the tumor cells, the cells adopted more organized cell structures, similar to those of normal cells.

**Identification of Novel Id-1 Regulated Genes in Breast Cells.**
Id-1 is a gene that plays a role in the normal growth and development of breast epithelial cells, the cells where most cancer arises. The gene also helps epithelial cells continue to grow, which is one of the characteristics of cancer cells, and triggers the process where cells migrate to other parts of the body. ***Jarnail Singh, Ph.D.***, at the ***California Pacific Medical Center, San Francisco***, investigated genes involved in the normal growth and functioning of the breast that Id-1 turns on or off. The research team found that Id-1 causes another gene to produce more of a protein called clusterin. Clusterin tends to be high in cells that are producing milk in a laboratory culture and in mice. Clusterin may play a role in the process epithelial cells go through to produce milk. The team also found five more genes that Id-1 turns on or off. One is involved in cell death and another is turned on in breast cancer cells that have the ability to spread to other body parts.

# Research in Progress

**Breast Development**

**Hormonal Regulation of TGF-beta1 During Mammary Development.** The reproductive organs of female mice go through the estrus cycle, where fertile periods, when pregnancy is possible, alternate with infertile periods, when it isn't. Levels of the hormones estrogen and progesterone rise and fall in a pattern during the mouse estrus cycle, as they do during the human menstrual cycle. ***Mary Helen Barcellos-Hoff, Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, is investigating how changes in hormone levels interact with a protein, transforming growth factor beta1 (TGF-beta1) found in a small proportion of breast cells. Dr. Barcellos-Hoff's hypothesis is that the hormones estrogen and progesterone cause some cells to produce TGF-beta1, and that TGF-beta1, in turn, plays a role in the growth of new cells and replacement of worn-out cells during normal breast development. The team has shown that when mouse mammary cells (the equivalent of breast cells in humans) produce more TGF-beta1, they multiply more slowly. However, during puberty, the fertile periods, and early pregnancy, cells that produce more TGF-beta1 multiply more quickly. TGF-beta1 also stimulates the normal process of cell death, but only during the mouse fertile period. During the coming year, the team intends to identify more characteristics of TGF-beta1. Discovering the function of TGF-beta1 in the normal breast can lead to defining its role in breast cancer.

**Other Processes in Breast Biology**

**Method for Measuring Breast Epithelial Turnover in Humans.** Epithelial cells in the breast produce milk and deliver it to the nipple, and are also the source of most breast cancers. Breast cancer cells divide more rapidly than normal cells. Each time a normal cell divides, the chance of a genetic mutation goes up, and so does the risk that the mutation will lead to cancer. Therefore, it is important to have a reliable way to measure the division rate of cells in the

breast. ***Marc Hellerstein, M.D., Ph.D.***, at the ***University of California, Berkeley***, is investigating further a technique developed in his laboratory to measure cell division rates directly, without using radioactivity or toxic substances. His team has used the technique successfully to measure the cell division rate in women using breast tissues from core biopsies. They have also found that genistein, a substance found in soybeans, decreases the cell division rate in rats. They are working on establishing normal rates of breast cell division and factors that might be associated with variations of this epithelial turnover rate in women, such as age, weight, ethnicity, and diet.

**Genetic Changes in Normal Epithelium of the Cancerous Breast.** ***Shanaz Dairkee, Ph.D***, of the ***California Pacific Medical Center Research Institute***, San Francisco, is investigating genetic changes that occur in normal-appearing breast cells. The goal is to identify changes that indicate a propensity to become breast cancer. The team is looking at four genes–p53, ATM, BRCA1, and BRCA2. The normal version of all these genes suppresses tumors. Women can inherit a mutation on each of these genes that makes them more likely to get breast cancer. Many researchers believe that mutations in these genes play a role in non-inherited breast cancer, and that something other than an inherited mutation turns off these genes. One common way genes get turned off is by losing an actual part of the gene when the cell reproduces itself. This process is called loss of heterozygosity (LOH). Dr. Dairkee's team analyzed 40 tissue samples of ductal carcinoma in situ (DCIS, a pre-cancerous breast condition that can develop into cancer). The team found LOH at p53 in more than 50% of the samples. For 11 of these samples, they examined normal-looking adjacent breast tissue and found LOH in 2. This suggests that mutations in p53, which are commonly found in later stages (III and IV) of non-inherited breast cancer, begin with partial loss of the gene at a much earlier stage. The team found LOH at the BRCA1 gene in 29% of the samples and at the ATM gene in 11%. They could not detect any LOH at these two genes in the nearby normal-appearing tissue. During the coming year, the team will analyze a spectrum of breast cells ranging from normal to invasively cancerous to establish at what point during the course of breast cancer these four genes get inactivated.

**A Vascular Restriction of Mammary Tumor Progression.** The mouse mammary gland is equivalent to the breast in humans. ***Robert G. Oshima, Ph.D.***, at ***The Burnham Institute***, La Jolla, is developing mice with genes altered so they are prone to mammary gland tumors and also so they have higher levels of two substances in the mammary gland cells where most tumors arise. The two substances are VEGF and Ang1, proteins called growth factors that are normally found in cells. VEGF and Ang1 normally stimulate the growth of blood vessels in situations such as a wound. Dr. Oshima will investigate whether mice with higher levels of these two growth factors in their mammary glands produce new tumor blood vessels more quickly, and have a faster rate of tumor formation. The team hopes to discover whether the process of forming new blood vessels is the crucial step that determines how big a tumor can grow.

# Research Initiated in 2001

**Breast Development**

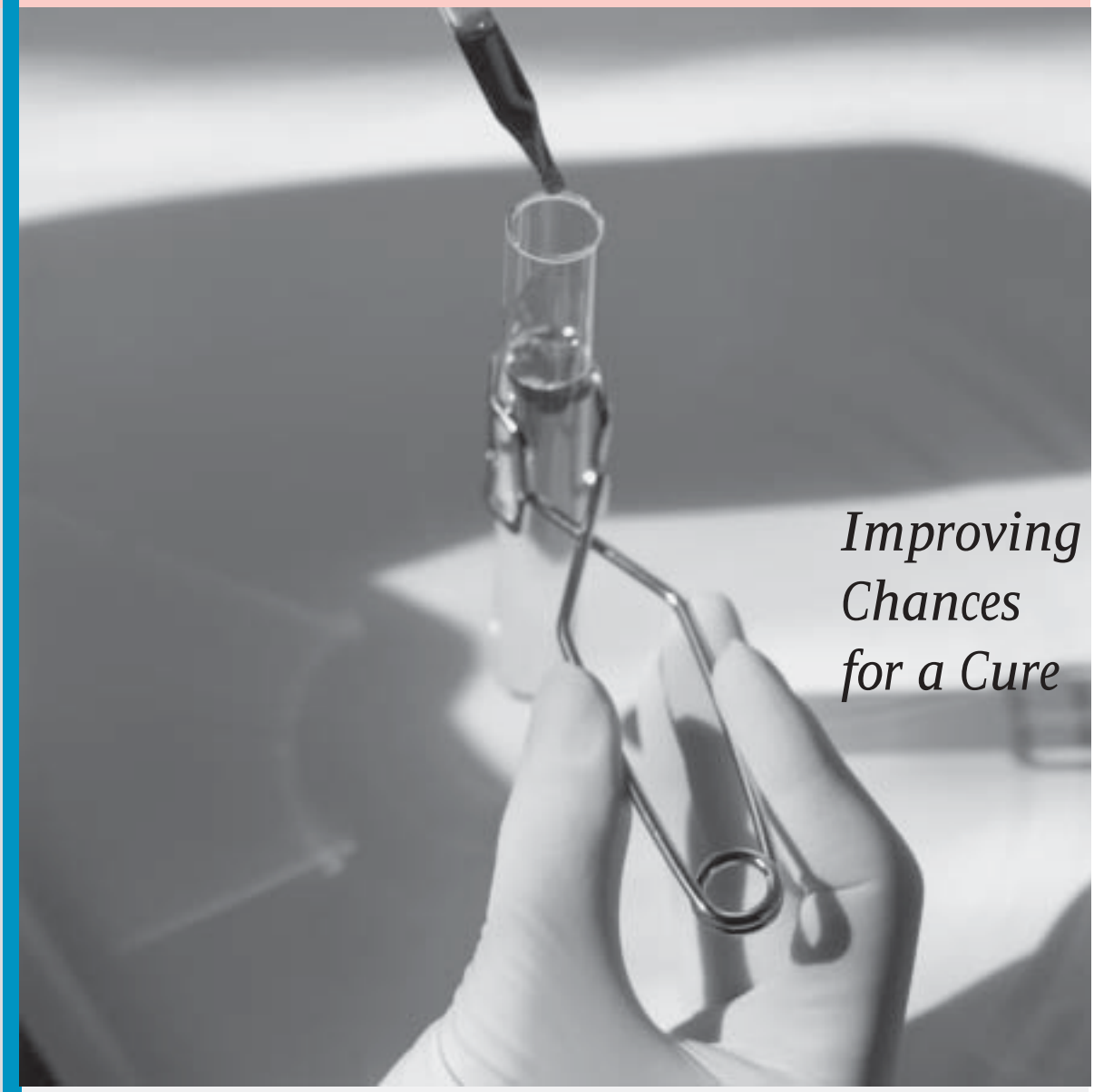
- **Telomere Dynamics During Breast Development.** Telomeres are composed of DNA and proteins located at the end of human chromosomes. They play a role in normal breast development and are also linked to both aging and cancer. ***Sahn-Ho Kim, Ph.D.***, of the ***Lawrence Berkeley National Laboratory***, is investigating the role of TIN2, a protein associated with telomeres, in normal breast development.
- **Analysis of a Protease Involved in Mammary Development.** ***Rana Zahedi, Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, is hunting for a protease (a type of enzyme) involved in the changes in the breast during pregnancy that lead to milk production. The goal is to shed light on cellular specialization and reorganization in the normal breast, and how these processes may go wrong in cancer.
- **Genetic Aspects of Physiological Response During Lactation.** Scientists believe that when tissue grows too large for its existing blood vessel network, the level of oxygen in the tissue drops. In response, a protein, HIF-1alpha, increases and activates genes that control new blood vessel growth. ***Randall S. Johnson, Ph.D.***, at the ***University of California, San Diego***, is investigating whether the HIF-1alpha response to lowered oxygen levels contributes to mammary gland development and the production of milk in mice. The goal is to generate information that will lead to better therapies to regions of tumors with lower oxygen levels, which are often resistant to treatment.

- **Role of IKKa in Mammary Gland Development.** ***Michael Karin, Ph.D***., at the ***University of California, San Diego***, is investigating an enzyme called IKK$\alpha$. Inactivating this enzyme prevents the extensive growth in breast cells that normally occurs during pregnancy. There is some evidence that the enzyme may also be involved in stimulating the growth of breast cancer cells and in protecting them from being killed by anti-cancer drugs. Inhibiting 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.

### Other Processes in Breast Biology

- **Role of Chromatin Regulator in Breast Cell Growth.** To grow, normal cells and cancer cells must synthesize a large number of different proteins using information carried on their DNA. DNA in human cells is organized into a structure called chromatin. The flow of information from DNA to make cellular proteins is highly controlled at the chromatin level by a group of proteins. ***Hongwu Chen, Ph.D.***, of the ***University of California, San Francisco***, has found that one of these proteins can increase the growth of breast cancer cells and prolong the life of normal breast cells. It is also present in elevated amounts in breast tumors. Dr. Chen will investigate how this protein controls normal breast cell life span and spurs breast tumor cell growth.
- **Telomere Clustering is Lost in Mammary Epithelial Tumors.** Telomeres–structures of DNA and proteins that cap the end of chromosomes–play a role in normal breast development, aging, and cancer. ***Paul Kaminker, Ph.D.***, of ***Lawrence Berkeley National Laboratory***, is investigating whether disrupting the structure of telomeres in cells leads to the formation of breast cell tumors.
- **Coactivators in Mammary Development and Tumorigenesis.** ***Zhiyong Wang, Ph.D.***, at ***The Salk Institute for Biological Studies***, La Jolla, is studying a protein, p/CIP, to see whether and how it causes cancer. The team will compare mammary gland and tumor development in mice with no p/CIP and mice with excessive p/CIP in the mammary glands.

# *Earlier Detection:*



## *Improving Chances for a Cure*

Earlier Detection:
Improving the Chances for a Cure

# *Earlier Detection:*

## *Improving Chances for a Cure*

The effectiveness of screening mammography has recently come under question and is being debated in both the lay and scientific press. However, the underlying rationale behind detecting cancers at an earlier stage of progression is strong. As more California women have regular mammograms, examine their own breasts, and receive breast exams from their physicians, breast cancer is being detected at earlier stages. Earlier detection combined with improvements in treatment has led to a 25% drop in the rate of death from breast cancer in the state. However there's still room for a lot of improvement. Women need detection methods that can find smaller tumors and distinguish harmless breast abnormalities from cancer. Mammograms don't provide diagnostic information, such as tumor aggression.

Areas of research the CBCRP funds include:

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

# Research Conclusions

**Novel Screening Approaches**

**Radiographic Densities and Breast Cancer Prevention.**
When a white woman's mammogram shows a lot of dense tissue, it means she's at higher risk for breast cancer. However, little research has been done about whether this is also true for African American and Asian American women. ***Malcolm C. Pike, Ph.D.***, at the ***University of Southern California, Los Angeles***, compared breast density in mammograms of 1,203 white, African American and Asian American women, 706 of whom had breast cancer. Asian American women had the highest percentage of dense breast areas and African American women the lowest. However, the risk of getting breast cancer was not the same for women with dense breasts from the three ethnic groups. The research team compared women with dense breasts (60% or more of the breast tissue appeared dense on the mammogram) with women with low-density breasts (10% or less tissue appeared dense on the mammogram). White women with dense breasts had a breast cancer rate 3.7 times that of white women with low-density breasts. For Asian American women with dense breasts, the breast cancer rate was 2.3 times higher than for Asian American women with low-density breasts. For African American women, dense breasts led to a rate of breast cancer only 1.7 times that of African American women with low density breasts.

**Protease Fingerprinting to Diagnose Breast Cancer.**
Breast cancer cells secrete proteins called proteases that break down other proteins and allow the cells to move. These proteases are also part of the process cancer cells use to recruit the body's blood vessels in order to grow. If there were a way to detect these proteases in blood, it could be the basis for a test that could detect tumors or predict whether a tumor is likely to spread. ***Jeffrey Smith, Ph.D.***, at ***The Burnham Institute***, La Jolla, explored a new

technology–substrate phage display–to investigate MMP-2 and MMP-9, two proteases known to be involved in breast cancer's spread in the body. He showed that the technology is sensitive enough to detect the proteases. Dr. Smith also gained valuable information about the structure of the proteins that the proteases are able to break down as markers for the presence and activity of tumor proteases. Dr. Smith is collaborating with another CBCRP-funded investigator, ***Dr. Benjamin Cravatt*** from ***The Scripps Research Institute***. Results from this project were published in *Analytical Biochemistry* 294:176-184 (2001) and the *Journal of Biological Chemistry* 276: 20572-20578 (2001).

# Research in Progress

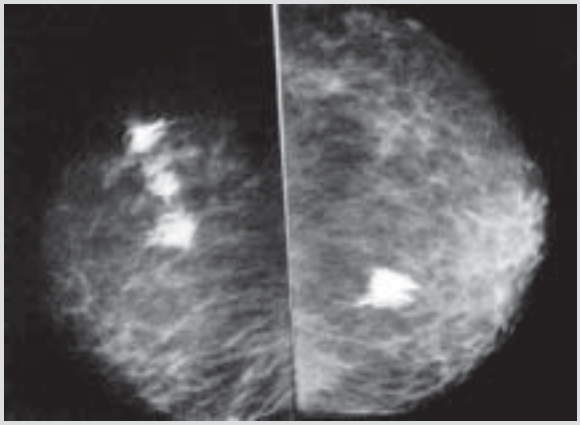
**Developing and Improving Imaging Technologies**

**Non-Invasive Optical Characterization of Breast Physiology.** ***Bruce Tromberg, Ph.D.***, from the ***University of California, Irvine***, is making excellent progress on developing a Laser Breast Scanner, which uses harmless near-infrared light to create an image of water, fat, and blood making up breast tissue. The ability to measure concentrations of blood is important, since this could indicate the presence of unusual blood vessel structures that would be expected in tumors that have acquired the ability to recruit their own blood supply. Dr. Tromberg's approach is non-invasive, and compared to mammography, appears to work well for younger women. The hand-held scanner is slightly larger than an ultrasound device; in the future it could be available at low cost in many doctors' offices. Results from this project have been published in *Proceedings National Academy of Sciences*, USA (2001) 98:4420-5 and *Academic Radiology* (2001) 8:211-8. Dr. Tromberg is collaborating with ***Randall Holcombe, M.D.*** and ***John Butler, M.D.***, also from the ***University of California, Irvine***.

**UCLA Biomedical Physics Graduate Training in Breast Cancer.** ***Virgil Cooper, Ph.D.***, of the ***University of California, Los Angeles***, is training graduate students to design and improve early detection and diagnostic imaging equipment, and to solve problems involving these technologies. The training emphasizes awareness of the needs of clinicians and patients. During the second year, five students have been in training. Among the projects on which they have worked are quality control for digital mammography, breast ultrasound, breast density prediction, and reduced compression of the breast in mammography.

## Improving Women's Access to Screening

**Increasing Breast Health Access for Women with Disabilities.** ***Mary E. Smith, M.S., C.R.C.***, of the ***Alta Bates Foundation***, Berkeley, ***Ann Cupolo Freeman, M.S., C.R.C.***, of the ***Alta Bates Medical Center***, Berkeley, and ***Carol N. D'Onofrio, Ph.D.***, of the ***Northern California Cancer Center***, Union City, are investigating problems women with disabilities face with getting breast health services. Using data from a 1994 study, the National Health Interview Survey, they have found that the odds of a woman having had a mammogram within the recommended time period for her age group go down the more physical limitations she has. African American women with disabilities are more likely to be up-to-date with mammograms than white women with disabilities. The team is analyzing data from their own local survey and completing a manual to encourage community organizations to take action to improve disabled women's access to mammograms and other breast health services.



**Does Mobile Mammography Increase Screening in Older Women?** Many older women don't get mammograms to check for breast cancer, despite expert consensus that they should. ***David B. Reuben, M.D.***, and ***Roshan Bastani, Ph.D.***, of the ***University of California, Los Angeles***, recruited women age 60–84 from community sites where older people gather. The team provided health education that included the benefits of mammograms to 247 women; 254 received the health education along with access to a mammogram van at the community site. On-site mammograms resulted in more women having a mammogram than health education alone, especially among older African American, Hispanic, Asian, and Pacific Islander women. The team is now analyzing their data to discover characteristics that predict whether or not older women will get mammograms, and calculating the number of women who would need to have one at each site to make it cost-effective.

**Novel Screening Approaches**

**Profiling of Tyrosine Phosphatases in Breast Cancer.** Many of the processes that allow cancer cells to multiply and spread are controlled through a type of reversible chemical reaction among proteins in the cell. The chemical reaction either adds or subtracts a molecule of phosphorus to the protein. These cellular processes are also involved in breast cancer acquiring resistance to drug treatments like tamoxifen. Enzymes called tyrosine kinases add a phosphorus molecule to a protein and tyrosine phosphatases remove one. The balance between these two sets of enzymes controls the fate of the cell. ***Clifford Tepper, Ph.D.***, at the ***University of California, Davis***, used a novel method that allowed his team to examine all the tyrosine phosphatases in a cell, combined with another technique that allowed them to examine at the same time 12,500 genes. The information gives a detailed fingerprint of a tumor and allowed the team to discover phosphatases that appear at unusual levels in certain types of breast cancers or in response to certain therapies. The most exciting discovery was a novel tyrosine phosphatase that was not found in two breast cancer cell lines that had higher levels of the HER2 protein. Higher levels of HER2 indicate that the cancer is more likely to be fatal, and also that its growth can be slowed with the drug Herceptin. This tyrosine phosphatase could potentially serve as an indicator of whether Herceptin therapy would be effective. The team also found five tyrosine phosphatases affected by levels of estrogen in cells. One of them, DUSP1, increases 3.5-fold when estrogen is withdrawn from cells. DUSP1 inhibits pre-programmed cell death. Tamoxifen therapy induces cell death by activating a kinase that DUSP1 inactivates. Increases in levels of DUSP1 in cells could lead to tamoxifen resistance.

**Molecular Staging of Breast Cancer Progression.** ***Cheng-Ming Chuong, M.D., Ph.D.***, of the ***University of Southern California, Los Angeles***, is looking for new ways to accurately diagnose breast cancer and predict whether it is likely to spread. Biological researchers are working to develop a set of molecular signatures that can help predict whether a tumor is likely to grow fast, spread, and also whether it can be stopped by various treatments. Microarray technology is likely to be useful to analyze the tumor's RNA. However, current technology requires a large amount of tissue, 20 mg., for RNA analysis. Dr. Chuong recently developed, and is now refining, a technology called RNA-polymerase chain reaction technology that will allow analysis of the RNA of a very small tissue sample. So far, the technology is accurate for a sample of 500 cells, and they hope to increase the sensitivity to be able to analyze single cells.

**Clinical Utility of Breast Cancer DNA Markers in Plasma.** ***David Hoon, Ph.D.***, of the ***John Wayne Cancer Institute***, Santa Monica, is trying to determine whether DNA specific to breast cancer can be detected in the blood. The team has blood and tumor tissue samples from over 270 women. They have isolated DNA from the blood and tumors and are now searching for DNA markers–parts of the DNA that are specific to the tumors–and comparing DNA markers in the blood and tumors. So far, they have developed an array of genetic markers frequently found in breast tumors and have demonstrated that these circulating genetic marker alterations correlate with those occurring in the patient's tumors, and thus may be useful as surrogate markers of breast cancer disease. The number of markers rises as the disease progresses, and the markers in the blood are similar to those in the tumors. The findings of this study will hopefully aid in earlier identification of disease recurrence and help in staging disease to allow early disease intervention which should improve survival.

# Research Initiated in 2001

**Developing and Improving Imaging Technologies**

- **Breast CT for Much Earlier Detection of Breast Cancer.** ***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. They believe this scanner will allow the detection of tumors almost a year earlier in the course of the disease, will use comparable or less radiation than conventional mammograms, and won't require breast compression.
- **Optical Spectroscopic Detection and Imaging of Breast Cancer.** ***Stavros Demos, Ph.D.***, at the ***Lawrence Livermore National Laboratory***, and ***Rajen Ramsamooj, M.D.***, at the ***University of California, Davis***, are investigating an alternative approach to breast cancer detection using polarized light and lasers. If this approach succeeds, it could detect cancers far smaller than those that can currently be detected with mammograms.
- **Breast Cancer Imaging by 2-D Magnetic Resonance Spectroscopy.** ***M. Albert Thomas, Ph.D***., at the ***University of California, Los Angeles***, is investigating whether two-dimensional correlated magnetic resonance spectroscopy is a viable and non-invasive technique to locate breast tumors, classify tumors, differentiate benign tumors from malignant disease, monitor the effectiveness of therapy, and detect recurrence of the disease. The technique, a variation of the widely used MRI test, uses magnetic resonance to detect the amounts and types of fatty acids and other chemicals in tissues. Tumors contain different amounts of these chemicals than do normal tissues, and there is also variation among tumors.

- **Two-Dimensional Magnetic Resonance Spectroscopy of Breast Tumors.** ***Nathaniel Wyckoff, Ph.D.***, at the ***University of California, Los Angeles***, is investigating the same new technology as the study described above, two-dimensional magnetic resonance spectroscopy. The technology uses magnetic resonance, as does the widely used MRI test; in this case, the purpose is to detect the type and amount of various chemicals in tissue. Dr. Wyckoff will examine the relative levels of certain chemicals that have not been well-researched in breast tumors and in benign tissue.

**Novel Screening Approaches:**

- **LPC as a Potential Tumor Marker for Recurrent Breast Cancer.** There are no reliable blood tests to detect recurrence of breast cancer. Two available tests are not accurate enough to be useful. ***Helen K. Chew, Ph.D.***, at the ***University of California, Davis***, will test whether measuring the level of a fat found in the blood, called lysophosphatidlycholine (LPC), can be used to detect a recurrence of breast cancer. Her research team will also test whether the LPC level in blood can be used to predict a recurrence of breast cancer or to determine whether treatment is working against breast cancer that has spread to other body parts.
- **Clinical Utility of Breast Cancer DNA Markers in Serum.** ***David S. Hoon, Ph.D.***, of the ***John Wayne Cancer Institute***, Santa Monica, is checking the DNA from blood and bone marrow of women in an early stage of breast cancer for genes frequently found in breast tumors. The team is investigating whether this information can predict whether the disease is likely to recur. This project continues research previously funded by the CBCRP, reported above under "Research Conclusions".
- **Targeting of Tumor Promoting Galectins in Breast Cancer**. ***Margaret Huflejt, Ph.D.***, at the ***Sidney Kimmel Cancer Center***, San Diego, is investigating galectins, proteins found in cancer cells, but not in normal cells, although cancer cells do release galectins into surrounding tissues. Galectins may keep the body's immune system from fighting the cancer, play a role in cancer cells spreading to other parts of the body, and block the normal process of cell death. The team is also investigating substances that may naturally inhibit galectins.
- **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 is most likely to prevent the tumor recurring. ***Syed Ashraf Imam, Ph.D.***, of ***Huntington Medical Research Institute***, Pasadena, is investigating whether measuring the amount of LEA.135, a protein found on the surface of some breast tumor cells, can predict whether the tumor will recur and which treatment will be most effective to prevent recurrence. A preliminary study funded by the CBCRP showed that a tumor with LEA.135 on the cell surface was less likely to recur.

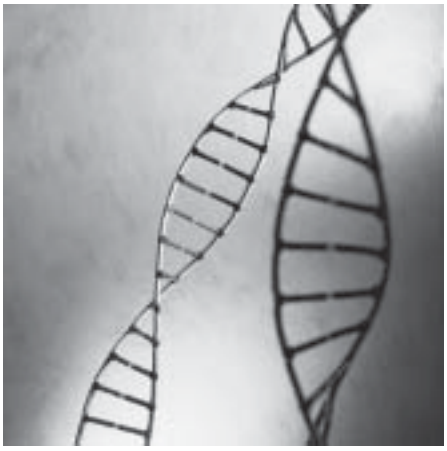
# *Etiology:*

## *Finding the Causes*

Etiology: Finding the Causes

# *Etiology:*

## *Finding the Causes*



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

# Research Conclusions

**Environment and Gene/ Environment Interactions: Nature vs. Nurture**

**Xenoestrogens and Breast Cancer in African American Women.**
Organocholorine compounds are human-made chemicals that include dioxins, furans, PCBs, and certain pesticides. They have been spread throughout our environment and can accumulate in human and animal tissues. The term "xenoestrogen" refers to these compounds' ability to take the place of the hormone estrogen in humans and animals. Xenoestrogens affect hormones and promote cancer in animals. Researchers suspect they also play a role in human breast cancer. ***Peggy Reynolds***, of the ***Public Health Institute***, Berkeley, originally planned to compare levels of xenoestrogens in the breast fat of African American women. However, when she couldn't recruit enough African American women, she included women of all races. In general, Dr. Reynolds found that women of color had higher levels of dioxins and furans in their breast fat than non-Hispanic white women, especially of the compounds PeCDD, DDE, HCB, and p-HCH. Since older women generally have higher levels of these chemicals in their breast tissue, Dr. Reynolds adjusted exposure-specific estimates of risk for age. Women of all ethnic groups who had higher levels of p-HCH also had a higher breast cancer risk. Women who had higher levels of the other compounds did not have a higher breast cancer risk. The sample size of 154 women was small, so these results are preliminary. However, the results offer pilot information on ethnic groups who have not been included in most previous studies of breast cancer risk and xenoestrogens.

**The Insulin-Like Growth Factor (IGF) System and Breast Cancer.**
The insulin-like growth factor (IGF) system consists of several proteins produced by many cells in the body and circulating in the blood. They can work together to increase or decrease cell division. The IGF system may contribute to breast cancer by causing breast cells to divide, either directly or by working along with estrogens. A recent study found a strong association between high blood levels of one protein in the IGF system, IGF-1, and increased breast cancer risk in pre-menopausal white women. ***Brian E. Henderson, M.D.***, at ***University of***

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

***Southern California***, Los Angeles, investigated whether levels of IGF in the blood vary among post-menopausal African American, Japanese, Latina and white women. After controlling for age and weight, his team found differences among some ethnic groups in blood levels of four proteins from the IGF system. Latina women had the lowest levels of two of the proteins, IGF-1 and IGFBP-3. Post-menopausal Latina women also have the lowest rate of breast cancer. In addition, Dr. Henderson found that women with a repeat of a sequence [CA] in the structure of the gene that produces the IGF-1 protein had lower levels of IGF-1 in their blood than women with other IGF-1 genetic structures. However, the difference was not statistically significant. Identifying the gene structures that determine IGF system levels may provide greater understanding of individual variations in breast cancer risk, and potentially serve as indicators for women who would benefit most from screening or specific types of therapy.

## Hormones and Nutrition: Understanding the Modern Woman's Lifestyle

### Mammography Density and Sex Steroid Genes.

Women with a larger percentage of dense areas in the mammogram image of their breasts have a higher risk of breast cancer. Hormones influence breast density. Menstruating women have more dense areas than post-menopausal women. Women who take hormone replacement therapy after menopause may also have more dense areas. ***Sue Ingles, Ph.D.***, at the ***University of Southern California***, Los Angeles, tested the hypothesis that genes involved in the production of female sex hormones are associated with breast density. Her team analyzed the genes of 453 white and African American women with breast cancer. The team looked at four genes: cytochrome p450c 17 (CYP 17), 17(hydroxy steroid dehydrogenase 1 (HSD17B1), 3b- HSD II, and the progestin receptor (PR) gene. On each gene, the team looked for variations called single nucleotide polymorphisms (SNPs). They turned up some evidence that dense breasts are associated with a variation called the A2 allele on the CYP17 gene. If these genes are associated with dense breasts, it could help researchers better understand the role natural hormones in the body play in breast cancer. It could also help predict which women are at a high risk for breast cancer if they use hormone replacement therapy.

### Gene-Diet Tobacco Interactions in Breast Cancer in Asians.

***Anna H. Wu***, at the ***University of Southern California***, Los Angeles, investigated several enzymes, smoking, and soy foods in relation to the risk for breast cancer. The enzymes she studied are all involved in the activation and detoxification of a large number of compounds commonly found in our diet and in tobacco smoke. The amount of these enzymes in cells is governed by genes, and Dr. Wu investigated whether variations in these genes can make women more susceptible to breast cancer. Analyzing the blood samples of 372 Asian women who had breast cancer and 354 who did not, Dr. Wu found no association between

rates of breast cancer and variations in the genes that produce four enzymes–CYP1A1, GSTM1, GSTT1, and GSTP1. However women who smoke and who also have genes that produce less or no GSTM1 and GSTP1 appear to have a greater risk for breast cancer. Dr. Wu also investigated the same group of Asian women's intake of soy foods. Those who ate the most soy foods during adult life had a 30% lower risk of breast cancer than those who ate the least soy foods. In addition, women who ate tofu at least 4 times a week during adolescence had a 35% lower risk than women who ate tofu once a month or not at all as teenagers.

# Research in Progress

**Environment and Gene/ Environment Interactions: Nature vs. Nurture**

**Breast Cancer Susceptibility Genes in Very High Risk Women.** A woman with relatives who have had breast cancer is at a higher risk for the disease than a woman whose relatives haven't had it. A woman whose identical twin has had breast cancer is at an even higher risk. ***Ann S. Hamilton, Ph.D.***, at the ***University of Southern California***, Los Angeles, is testing the hypothesis that a structure on the CYP17 gene may occur more often in twins where one or both of the women have had breast cancer than in women who haven't had the disease. She is completing laboratory work on tissue that was preserved when the cancer was first diagnosed in 92 twins and recruiting more study subjects.

**Marin County Breast Cancer Study of Adolescent Risk Factors.** ***Margaret Wrensch, Ph.D.,*** of the ***University of California, San Francisco***, and ***Georgiana Farren, M.D.***, of ***Marin Breast Cancer Watch***, Marin County, are studying women in Marin County, a community with high rates of breast cancer. The research team is looking at a group of women diagnosed with breast cancer between 7/1/97 and 6/30/99, and comparing them with women who have not had breast cancer. They are looking for differences in the age at which the women had their first menstrual period, the age at which the women's breasts developed, major life events before age 21, adolescent and adult socioeconomic status, age-adjusted lifetime years of residence in Marin County, and other events during adolescence which may have affected the women's lifetime risk. The team has completed in-person interviews with 235 out of a projected 300 women with breast cancer and 181 out of a projected 300 women without the disease.

**Oral Contraceptives, Hormonal Risk Factors, and BRCA1.** A large number of women who get breast cancer at an early age may have mutations on the gene BRCA1. Recent evidence suggests, however, that not all women with one of these mutations will develop breast cancer. ***Giske Ursin, M.D., Ph.D.***, at the ***University of Southern California***, Los Angeles, is investigating whether oral

contraceptive use has any effect on rates of breast cancer among women with mutations on their BRCA1 genes. Dr. Ursin will look at oral contraceptive dose, length of time the women used oral contraceptives, age at first use, and how recently the women used oral contraceptives. She will compare the risk of breast cancer associated with oral contraceptive use by women with mutated BRCA1 with data from previous studies for rates of breast cancer associated with oral contraceptive use by women in the general population. Working with tissue samples, she is using the new ABI 3700 sequencer to sequence the women's BRCA1 genes. To date, the research team has conducted 756 interviews, collected mammograms on 235 women, and completed sequencing of the genes of 92 women. They are in the process of sequencing the genes of 192 more women. Over the next year, they will analyze the data.

**Influence of Localized DDT Exposure on Breast Cancer.** The pesticide DDT can mimic or interfere with the action of hormones in humans and animals, and once it enters our bodies, it is stored in our fat. So DDT has tremendous potential to influence the development of breast cancer. In the body and in the environment, DDT is broken down into compounds that either act like the female hormone estrogen, or inhibit male sex hormones. ***Vicki L. Davis, Ph.D.***, at the ***Cedars-Sinai Medical Center,*** Los Angeles, is examining how the individual compounds into which DDT breaks down in the body influence the development of mammary tumors in mice. Mouse mammary tumors provide a good model to investigate cellular and genetic changes which lead to breast cancer in women. The research team has treated the mammary tissue of mice with one of the following: a DDT compound that mimics estrogen, a DDT compound that inhibits male hormones, an estrogen naturally produced in women, and an inhibitor of male hormones that is used to treat prostate cancer. The treatments are designed to affect only the mammary gland and not the entire body, to determine if DDT in breast fat influences cancer formation. The team will compare the number of mice that develop tumors, how early they develop them, and the tumor growth rates for the four groups.

**Hormones and Nutrition:**
**Understanding the Modern Woman's Lifestyle**

**Physical Activity and Diet in Adolescents with Disabilities.** A number of studies suggest that physical activity and diet may be associated with a risk for breast cancer, but none of these studies have targeted women with disabilities. ***Carol Koprowski, Ph.D., R.D.***, and ***K. Sarah Hall, Ph.D.***, both at ***California State University, Northridge***, are developing appropriate assessment tools to measure physical activity and diet in adolescent females with disabilities. They have recruited adolescent women with disabilities, along with their families, from three southern California school districts. The research team is conducting focus

groups where participants discuss their views on whether current recommendations about diet and exercise are appropriate for adolescents with disabilities. They are also interviewing the young women about their own diets and exercise habits.

**Postmenopausal Breast Cancer: Obesity and the Leptin Receptor.** Obese women and women who gain weight during adulthood have an increased risk for breast cancer after menopause. ***Leslie Bernstein, Ph.D.***, at the ***University of Southern California***, Los Angeles, is investigating the relationship between body composition, hormones, and a candidate gene for obesity, the leptin receptor gene. Leptin is a recently-discovered hormone produced by human fat cells. It plays a role in fat storage and metabolism, and may be involved in breast cancer. The leptin receptor gene produces a protein that allows cells to take in leptin. Dr. Bernstein is investigating the levels of leptin and variations in the leptin receptor gene in healthy obese women. The research team has recruited and collected data on 21 women. They are continuing to recruit more women. Results from this study could shed light on the causes of breast cancer after menopause.

**Genes Determining Estrogen Susceptibility in Breast Cancer.** Many breast tumors depend on the hormone estrogen for growth and survival and can be treated with anti-estrogen drugs like tamoxifen. However, some tumors eventually progress to an estrogen-independent form and become drug resistant. ***Wensheng Wei, Ph.D.***, at the ***Stanford University School of Medicine***, Palo Alto, is attempting to identify, isolate, and map the structure of estrogen susceptibility genes that are required for breast cells to respond to estrogen stimulation. Dr. Wei is using a technique called Random homozygous knock-out (RHKO), removing genes from cells and observing the cells for changes in behavior. During the first year, Dr. Wei has solved technical problems with the RHKO technique and constructed the target cell line. Eventually, Dr. Wei hopes to identify changes in estrogen susceptibility genes that lead to tumors becoming estrogen independent.

## Other Searches for the Causes

**Breast Cancer Risk Factors: Lesbians and Heterosexual Women.** Only a small amount of information is known about lesbians and breast cancer, but scientists believe lesbians' risk of getting the disease may be two to three times higher than that of heterosexual women. ***Suzanne L. Dibble, D.N.Sc.***, of the ***University of California, San Francisco***, and ***Stephanie Roberts, M.D.***, of ***Lyon-Martin Women's Health Services***, San Francisco, are investigating whether lesbians indeed have a higher risk. They distributed surveys to lesbians age 40 and older throughout the state of California, and asked each lesbian to have one heterosexual female friend who lives in California and a sister (if she has

one) to fill out an identical survey. To date, 543 lesbians, 543 heterosexual friends, and 359 sisters have completed surveys. The research team is analyzing the data. If lesbians do turn out to have a greater risk for breast cancer, it may be possible to lower some of this risk through culturally-specific interventions.

**Breast Cancer in California Teachers–Regional Variations.** Rates of breast cancer in the San Francisco Bay Area are higher than in other parts of the nation. Scientists have known for a long time 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. During the first year, she identified cases of breast cancer among the women in the survey, and coded 96% of the women who took part in the survey for geographic location. She will examine risk factors for breast cancer that include reproductive history, family history, physical activity, exposure to hormones, diet, and other lifestyle factors. She will consider both current and historic place of residence, along with environmental exposures and social patterns in the women's neighborhoods. An initial assessment of the data indicates that breast cancer in teachers tends to mirror statewide patterns, with the San Francisco Bay Area having higher rates than other areas of the state. The initial assessment also indicates that teachers living in the San Francisco Bay Area may be at higher risk for breast cancer for reasons other than geographic location.

# Research Initiated in 2001

**Environment and Gene/Environment Interactions: Nature vs. Nurture**

- **HER-2/neu Gene Variations and Breast Cancer Risk.** ***Michael Press, Ph.D.***, at the ***University of Southern California***, Los Angeles, is analyzing blood cells from African American and white women, half of whom have breast cancer and half of whom do not. The team is looking at two different variations in a gene associated with breast cancer, HER-2/neu, to see if women with either of these variations are more likely to have the disease. These gene variations are widespread in the population and currently considered to be normal. The research team will also investigate whether either variation of the gene creates a higher risk of breast cancer in women who have other factors that increase their risk, such as early menses, late menopause, fewer or no pregnancies, or lack of exercise.
- **Pesticides and Breast Cancer in Hispanic Women in California.** ***Paul Mills, Ph.D.***, at the ***Public Health Institute***, Berkeley, will attempt to determine if the risk of breast cancer in Hispanic California women is increased due to their exposure to a class of commonly-used pesticides, the organochlorines and the triazine class of herbicides. The research team will compare breast cancer rates among Hispanic women and amounts of the pesticides applied in each of 58 California counties. They will also compare the pesticide exposure of women members of the United Farm Workers of America who have breast cancer with women members who do not have the disease.

**Hormones and Nutrition: Understanding the Modern Woman's Lifestyle**

- **Dietary Fat, Fat Metabolizing Genes, and Breast Cancer Risk.** A diet high in certain types of fat may promote breast cancer. **Sue Ann Ingles, Ph.D.**, of the ***University of Southern California***, Los Angeles, is investigating whether genetic differences in fat metabolism make some women more prone to breast cancer if their diets are high in these fats.

### Other Searches for the Causes

- **Migration and Breast Cancer Risk in Hispanics.** Foreign-born Hispanic women living in the San Francisco Bay Area have a lower risk of breast cancer than second- and third-generation migrants. Women who migrated after age 40 have a lower risk than women who migrated at a young age. ***Esther John, Ph.D.***, of the ***Northern California Cancer Center*** in Union City, is investigating breast cancer risk and migration-related lifestyle changes in Hispanic women. The lifestyle changes include menstrual and reproductive events, physical activity, diet, body size, weight change, hormone use, smoking, and alcohol consumption. In addition, her team will see if exposure to heterocyclic amines (chemicals formed when meats and fish are cooked at high temperatures) and late infection with the Epstein Barr virus increase breast cancer risk.

# *Health Policy and Health Services:*


Health Policy and Health Services:
Serving Women's Needs

# *Health Policy and Health Services:*

## *Serving Women's Needs*

If research findings are going to lead to action and change, then gathering important information 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, and we encourage research on actions that will reduce inequalities in access to prevention and treatment among California's geographically and ethnically diverse population. The CBCRP encourages more research in the health policy and health services area.

# Research Conclusions

**Samoans and Breast Cancer: Evaluating a Theory-Based Program.** Samoan American women have a high incidence of breast cancer, a low awareness of the disease, and a low rate of use of early-detection services. ***Shiraz I. Mishra, Ph.D.***, at the ***University of California, Irvine,*** and ***Pat H. Luce-Aoelua, M.S.,*** at the ***National Office of Samoan Affairs,*** Carson, implemented and evaluated an innovative, theory-based, culturally sensitive, and linguistically appropriate breast cancer control educational program for Samoan American women. The goals were to enhance breast cancer awareness, increase the rate at which Samoan American women get mammograms, and over time, potentially lower breast cancer incidence and deaths in this marginalized community. The education program included specially developed English and Samoan-language educational materials, skills building exercises, and interactive group discussions. The research surveyed 776 women of Samoan heritage, age 42 or over, who had not had a mammogram within two years or longer, or who had never had one. There were 391 women who received the educational intervention and 389 who did not. Results of this study indicated that over 58% of the women participating in the study had never had a mammogram. Those more likely to never have had a mammogram were more likely to be older, less educated, uninsured, unemployed, with less than $10,000 per year in family income, and interviewed in Samoan. Women were more likely to have had a mammogram if they had positive group norms for obtaining one, health insurance, positive belief in the effectiveness of mammograms, fewer misconceptions about the cause of breast cancer, fewer culture-specific beliefs about the causes of breast cancer, and higher self-efficacy. Analyses to assess the efficacy of the intervention are in progress.

# Research in Progress

**Does a Peer Navigator Improve Quality of Life at Diagnosis?** ***David Spiegel, M.D.***, of ***Stanford University***, is collaborating with ***Caroline Bliss-Isberg, Ph.D.***, of the community organization ***WomenCARE***, in Santa Cruz, in a pilot study to gather data in order to conduct a larger study. The goal is to evaluate the effectiveness of matching women who have just learned they have breast cancer with trained volunteer beast cancer survivors (peer navigators). Each navigator and woman with cancer make at least one contact a week for three months. The relationships can be renewed by mutual agreement every three months. This study addresses the needs of women newly diagnosed with breast cancer at the time when they say they have the greatest need for counseling. Many women don't seek formal counseling services because they feel overwhelmed, are unfamiliar with available resources, or are concerned about stigma in seeking counseling. The Peer Navigator Program provides emotional support, peer modeling, survival modeling, and information on resources for women who have just been diagnosed with breast cancer. In this preliminary study, the research team has matched 37 newly-diagnosed women with peer navigators. The team has extensively promoted the program within the local medical community, so that women are sometimes referred by medical professionals within 1-2 days of diagnosis.

**Race/Ethnicity, Socioeconomic Status and Breast Cancer.** ***William Wright, Ph.D.***, at the ***Public Health Institute***, Berkeley, is investigating the relationship between race/ethnicity and socioeconomic status in the risk of developing breast cancer. Women in California from different ethnic groups or socioeconomic levels are not equally affected by breast cancer. Dr. Wright is using innovative statistical methods to analyze data from California's statewide cancer registry and the Women's Health Survey, a 1998 survey of 4,000 California women from various ethnic groups. He is trying to determine whether the relationship between socioeconomic status and stage of diagnosis for breast cancer varies among ethnic groups. So far, he has found that Asian/other women with higher socioeconomic status are more likely to have their disease diagnosed at the earliest in situ stage, when the changes in the breast are still

pre-cancerous. Hispanic women with higher socioeconomic status are more likely to have their breast cancer diagnosed at an early stage. Women in both ethnic groups with lower socioeconomic status are more likely to be diagnosed with cancer at later stages. Socioeconomic status itself is not a risk factor for breast cancer stage at diagnosis. Women with high socioeconomic status were more likely to have had a mammogram or clinical breast exam. Dr. Wright has also shown that due to the way race data were collected on the 2000 US Census, the California Cancer Registry won't be able to calculate breast cancer rates by ethnic group in 2000 and beyond, or monitor trends in breast cancer by ethnicity.

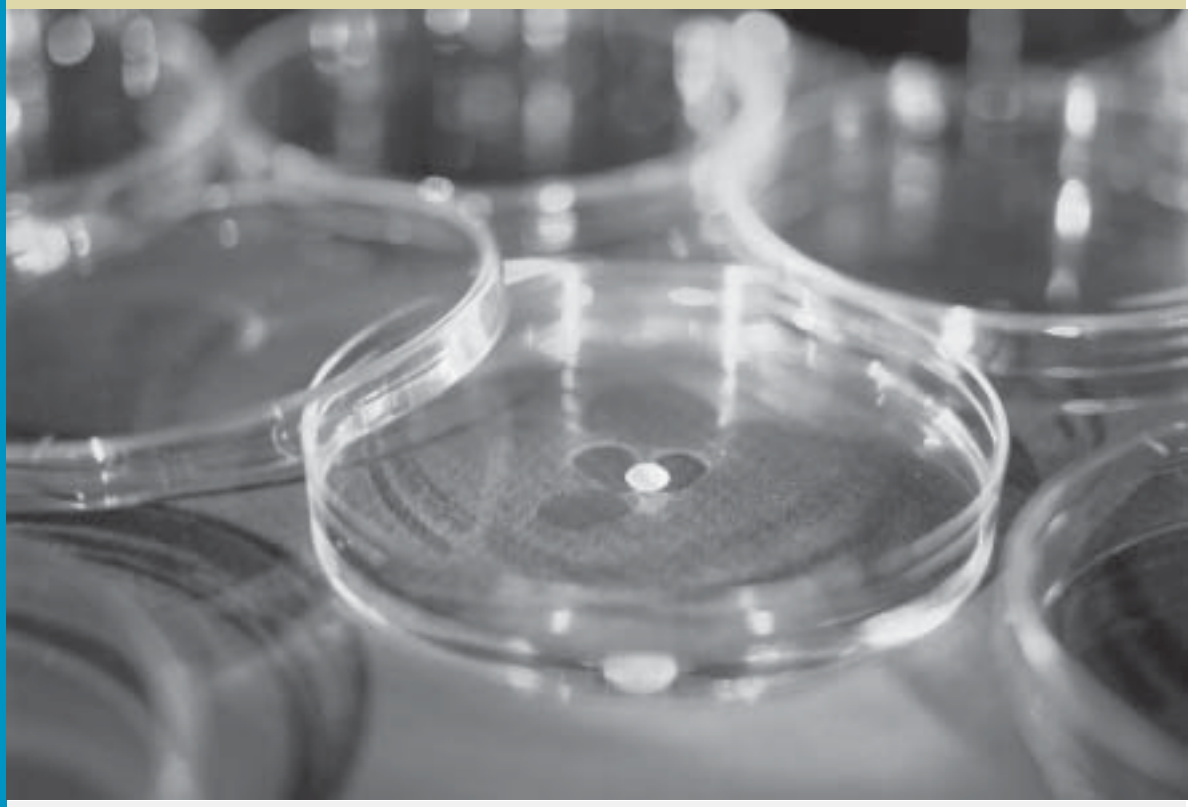
# Research Initiated in 2001

- **Geographic Variation in Breast Cancer Stage at Diagnosis.** Women whose breast cancer is diagnosed at the earliest stage, before it has spread to surrounding tissue or distant sites in the body, have a better chance of surviving. Among California counties, the percentage of breast cancer patients who are diagnosed at this early stage ranges from 40% to 71%. ***Pamela Davidson, Ph.D.***, at the ***University of California, Los Angeles***, is investigating how community-level factors, such as the health care delivery system, influence the stage at which a woman's breast cancer is diagnosed. 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.
- **Does a Peer Navigator Improve Quality of Life at Diagnosis?** ***David Spiegel, M.D.***, of ***Stanford University***, is collaborating with ***Caroline Bliss-Isberg, Ph.D.***, of the community organization ***WomenCARE***, in Santa Cruz, to evaluate the effectiveness of matching women who have just learned they have breast cancer with trained volunteer beast cancer survivors (peer navigators). The research team will investigate whether peer navigators improve the women's quality of life, coping skills and communications with doctors, and also whether women with peer navigators have less depression and trauma. This study is built on a pilot study funded previously by the CBCRP.

- **Return to Work Following Breast Cancer Surgery.** ***Diane R. Estrin***, of the ***Women's Cancer Resource Center***, a Berkeley community organization, and ***Rani B. Eversley, Ph.D.***, of the ***University of California, San Francisco***, are looking at what helps–and what hinders–women returning to work after breast cancer surgery. Building on a pilot study funded by the CBCRP, they will interview 588 Caucasian, African American and Latina women 6 and 12 months after surgery. The goal is to determine how returning to work at pre-surgery levels is affected by race, ethnicity, income, household support, presence of dependent children or elderly relatives in the home, stage of the disease, breast cancer treatment, fatigue, disability benefits, work flexibility, and social support for returning to work.

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

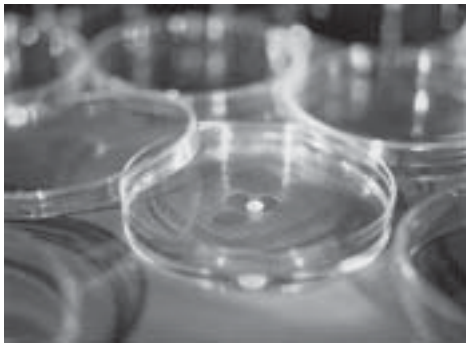
# *Innovative Treatments:*
## *Search for a Cure*



Innovative Treatments:
Search for a Cure

# *Innovative Treatments:*

## *Search for a Cure*



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

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

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

# Research Conclusions

**Immune Therapy: Mobilizing the Body's Defenses**

**HER2/Neu DNA Vaccines for Breast Cancer.**
The Her-2/neu gene is found in invasive breast tumors and also in about 50% of cases of DCIS, a pre-cancerous condition of the breast that may turn in to cancer. ***Michael Campbell, Ph.D.***, from ***University of California, San Francisco***, explored new ways to develop a vaccine against breast cancer. Dr. Campbell's approach was to inject into mice portions of the cancer gene Her-2, in the form of DNA linked to a virus. The thinking was that the virus would infect cells in the mice and they would synthesize portions of Her-2 to generate antibodies. This approach differs from the normal method of injecting a protein produced by a gene, rather than parts of the gene itself, to stimulate the immune system. In addition, Dr. Campbell "boosted" his DNA vaccine method by incorporating proteins known to enhance the immune response. Unfortunately, the preliminary experiments showed that much more work was needed to optimize the route of administration (i.e., oral vs. injected), and there are technical problems in combining the Her-2 and the DNA into the virus. Nevertheless, the research pursued an important avenue of investigation, using Her-2 in a vaccine approach.

**New Drug Design: Creative Science**

**Heregulin-specific Diphtheria Toxin as a Cancer Therapy.**
***Gordon Louie, Ph.D.***, at the ***Salk Institute for Biological Studies***, La Jolla, attempted to modify the diphtheria toxin into a molecule that would attack cancer cells, but not normal cells. The engineered toxin would, in theory, bind only to a protein–heregulin–found preferentially at the surface of breast cancer cells. Prior to this research, Dr. Louie and his colleagues found that diphtheria toxin would bind to a protein very similar to heregulin. The research team was able to advance the theoretical basis for engineering diphtheria toxin, but wasn't able to develop a way to test whether the modified toxin binds only to heregulin.

**HER-2**
HER-2, also known as HER-2-neu and ErbB2, is a protein found on the surface of breast tumor cells. It is a receptor, which means that another protein from outside the cell can combine with it like a key in a lock, and turn on other changes in the cell. If HER-2 is present in high amounts, the tumor is more likely to be fatal. About 20% of breast tumors have high levels of HER-2.

Herceptin, an immune-based drug that binds with HER-2, slows the progression of tumors. Although it doesn't stop breast cancer, Herceptin can be used to treat tumors that formerly could not even be slowed down.

Researchers are investigating HER-2 as a target for new ways to treat tumors that are resistant to other therapies.

**Novel Breast Cancer Anti-Angiogenic Compounds.**
Breast tumors can't grow without hijacking the body's blood supply and creating a new network of blood vessels. ***Mai Nguyen, M.D.***, at the ***University of California, Los Angeles***, investigated a variety of plant extracts for potential to be developed into a potent drug with low toxicity that could stop the growth of new blood vessels. Dr. Nguyen identified and purified compounds from a palm plant, Livistonia, that block new blood vessel growth. Water-based extracts from the seed shell and skin appear to contain the active agent(s). This extract material blocked the growth of cancer cells and also of endothelial cells (cells that line organs in the body, including the heart and blood vessels). The extract did not appear to cause any toxicities in mice. The results were published in *Oncology Reports* 8:1355-7 (2001).

**Novel Anti-vascular Agents for Breast Cancer Therapy.**
Breast cancer can't grow without a network of blood vessels from normal tissue to supply oxygen and nutrients and to remove waste products. When a tumor outgrows its blood supply, it can stimulate the formation of new blood vessels to support its growth, and this process is necessary for the tumor to become malignant. However, the blood vessels the tumor creates are impaired, compared to normal blood vessels. This makes these tumor-created blood vessels attractive targets for chemotherapy. ***Keith Laderoute, Ph.D.***, from ***SRI International***, Menlo Park, investigated a new drug compound, BTO956. It keeps tumor cells from dividing. BTO956 also suppresses the growth of human breast cancers implanted in mice, with very little toxicity to normal tissues. Dr. Laderoute and his collaborators at Duke University found, in addition, that BTO-956 stops the growth of blood vessels that nourish tumors. This study was published in *Clinical Cancer Research* 7:2590 (2001).

**SXR: A Novel Target for Breast Cancer Therapeutics.**
***Michelle M. Tabb, Ph.D***., at the ***University of California, Irvine***, is investigating the SXR gene's role in the anti-cancer effects of diverse compounds such as the drug tamoxifen, plant-derived estrogens called phytoestrogens found in soy foods, anandamide, and Vitamin A. Dr. Tabb's team has found the protein produced by the SXR gene in several breast cancer cell lines. They have also found a variant form of SXR in some cell lines that is turned on by different compounds than the normal form. When they treated the cell lines that contain the SXR protein with compounds that turn on the SXR gene, these compounds demonstrated the ability to stop the growth of breast cancer cells. The compounds that turn on the gene the most are also the best at stopping the growth of breast cancer cells. Dr. Tabb plans future research to investigate the mechanism behind the effectiveness of compounds that turn on SXR and to discover whether SXR is responsible for stopping the growth of breast cancer cells. This could provide information leading to a new anti-cancer drug, and lead to understanding of the way substances found in the diet, such as phytoestrogens, are effective in breast cancer prevention.

**In Vitro Testing of Chinese Herbs for Breast Cancer.**
***Debasish Tripathy, M.D.***, at the ***University of California, San Francisco***, tested 71 herbs used in traditional Chinese medicine for the treatment of cancer. The team boiled each herb in water and tested whether the extract inhibited growth of four human breast cancer cell lines (SK-BR-3, MCF7, MDA-MB-23 1, and BT-474) and one mouse breast cancer cell line (MCNeuA). Nineteen of the extracts inhibited growth on three or more of the cell lines. Sixteen strongly inhibited growth on at least one cell line. Seven of the active extracts caused cancer cell death. The team began identifying the substances in the extracts that are active against breast cancer, and purified one of them. Further studies with these extracts will improve understanding of how these herbs may be acting in cancer patients and may also lead to the isolation of anti-tumor compounds.

## Hormone and Chemotherapy Targets: Improving Today's Arsenal

**Identifying the Breast Cancer Target for Indole-3-Carbinol.**
Indole-3-Carbinole (I3C), a compound found in cruciferous vegetables such as broccoli and Brussels sprouts, appears to inhibit growth of breast tumors. I3C works both on tumors that respond to estrogen (which can be treated with the drug tamoxifen) and tumors that don't respond to estrogen (which can't be treated with tamoxifen). ***Urmi Chatterji, Ph.D.***, of the ***University of California, Berkeley***, attempted to find the protein within breast cancer cells that initially binds with I3C. She completed the first step in this process, determining that the cell nucleus contains the I3C binding protein. The study described below, from the same laboratory, also deals with I3C.

**Indole Derivatives as Novel Breast Cancer Therapeutics.**
***Gary Firestone, Ph.D.***, at the ***University of California, Berkeley***, continued his investigation of potential anti-cancer compounds found in cruciferous vegetables, such as broccoli and Brussels sprouts. Previous CBCRP-funded work in Dr. Firestone's lab has shown that a compound called indole-3-carbinol (I3C) appears to inhibit the production of certain proteins cells need to produce in order to divide and form new cells. I3C, which is also the subject of the study discussed above, appears to be effective against breast cancer cells that depend on the hormone estrogen for their growth, as well as those that do not. In this project Dr. Firestone worked with a colleague, ***Leonard Bjeldanes, Ph.D.***, at the ***University of California, Berkeley***, to develop synthetic compounds derived from I3C that might be the basis for more potent anti-breast cancer treatments. They have been able to modify the constituent indole ring in I3C to produce a molecule that can inhibit growth in human breast cancer cells at greater than 100 times the potency of the natural compound. This research was published in *Biochemistry* (2000) 39(5):910-8. Dr. Firestone's research may lead to cancer-inhibiting drugs that work against a wide-spectrum of breast

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

**Pharmacogenomics**
Current breast cancer drugs treat the disease, but often ignore variations in the genetics and biology of each patient.

Pharmacogenomics is a new discipline that has evolved to address this clinical uncertainty. According to the Human Genome Project: "Pharmacogenomics is the study of how an individual's genetic inheritance affects the body's response to drugs. The term comes from the words pharmacology and genomics and is thus the intersection of pharmaceuticals and genetics.

Pharmacogenomics holds the promise that drugs might one day be tailor-made for individuals and adapted to each person's own genetic makeup. Environment, diet, age, lifestyle, and state of health all can influence a person's response to medicines, but understanding an individual's genetic makeup is thought to be the key to creating personalized drugs with greater efficacy and safety." In practical terms, this may prove difficult, since unrelated humans may differ in up to 100,000 single parts of their DNA. The parts of DNA where these variations occur are called SNPs (single nucleotide polymorphisms). In *Impact*, the

cancers, especially estrogen receptor-negative types resistant to the chemotherapy medication Tamoxifen, and that might be used in combination with other drugs.

## Gene Therapy and Other Treatments: New Frontiers

### Tibetan Medicine for Advanced Breast Cancer.

***Debasish Tripathy, M.D.***, of the ***University of California, San Francisco***, treated eleven women who had breast cancer with Tibetan herbal medicine. The women's cancer had spread to other body parts, they had already received conventional treatment, and at the beginning of the study, they had few or no symptoms due to cancer. Dr. Yeshi Dhonden prescribed an herbal regiment for each of the eleven women enrolled in the study, examining them every four months and changing the herbal formula as needed. The women's tumors were measured every three months; the women also received monthly examinations and safety assessments. Of 9 women whose data were evaluated for this study, one completed the study with no disease progression. Three were stable for 6-12 months. Four were stable for less than 6 months. One patient had a partial response. The patients didn't experience any significant toxic side effects. The therapy in this trial proved to be both safe and feasible. Further studies are needed to evaluate a broader range of Tibetan herbal treatments.

### Breast Cancer Gene Expression Using Amplified Core Biopsies.

***Stefanie Jeffrey, M.D.***, from ***Stanford University***, Palo Alto explored a cutting-edge technology to measure genetic variation in breast tumors. Dr. Jeffrey and collaborators are using gene chips, a technique also known as cDNA array technology that allows the research team to simultaneously measure the level of 23,000 different genes from breast tumor samples. Dr. Jeffrey's team is trying to solve a problem with current technology, which can only be used to get a gene profile from large core biopsy tissue samples. However, most women have smaller needle biopsies, which yield too little tissue. Dr. Jeffrey found that she could amplify samples from needle biopsies and get a gene profile previously possible only with larger core biopsies. In addition, her team gained information on tumor heterogeneity (different types of cells within a single tumor) and found genetic similarities between primary tumors and cells obtained from lymph nodes. This information puts them in a better position to use needle biopsies for gene chip analysis. Ultimately, they hope this new procedure will help predict whether a tumor would respond to chemotherapy.

**Bispecific Antibodies for Radiotherapy of Breast Cancer.**
Once breast cancer has spread to other organs such as the lung and bone, current therapy options offer less than two years of survival, in most cases. However, radioimmunotherapy shows promise against cancer that has spread to other body parts. Radioimmunotherapy uses antibodies cloned in a lab (monoclonal antibodies), which attach to cancer cells. When radiation is administered later, the antibody "captures" the radioactive molecule and delivers the radiation to the cancer cell. The large size of a monoclonal antibody limits its effectiveness. To create a more effective therapy, ***Michelle Winthrop, Ph.D.***, at the ***University of California, Davis***, developed a single-chain antibody fragment that binds to the MUC-1 antigen, a protein found on the surface of many breast tumor cells. The team created a model of the antibody's molecular structure to construct antibody fragments specific to MUC-1. This research was published in *Quarterly Journal of Nuclear Medicine* 2000 44:284-95. Using animal models, the team is currently testing the most promising antibody fragments for their ability to target breast tumor cells and capture a radioisotope injected later.

UCSF Foundation's online magazine, Kathleen Giacomini, Ph.D., professor and chair of Biopharmaceutical Sciences at UCSF, has predicted, "Pharmacogenomics will take three or four forms. One will be looking at genes and their protein offspring, which are potential drug targets. That will facilitate the development of new drugs.

"Then we'll need to find out the variations that people have of that gene. There could be three forms, for example, of one gene. The next step would be to create drugs for each of those targets, or gene variations.

"Pharmacogenomics will also affect clinical trials. For example, if 3 people out of 1,000 die during a clinical trial due to a drug reaction, that drug will not make it to the market.

"The reality is that even though that drug could have worked for a majority of people, it's too dangerous to prescribe because we don't know who falls in the minority that can't tolerate it. But, by understanding the genetic qualities of the people who have these adverse reactions, we can avoid adverse reactions and a greater number of people could benefit from the drug."

# Research in Progress

## Immune Therapy: Mobilizing the Body's Defenses

**Cell-Based Immunotherapy for Breast Cancer.** The human immune system protects us from illness by recognizing and attacking cells that are infected with viruses and bacteria. The immune system does not normally attack the body's own tissues. Because cancer cells are derived from the body's own tissues and don't display any foreign characteristics, the immune system does not attack them. In cancer immunotherapy the challenge is modify tumor cells in a way that the body's immune system will recognize them as dangerous and destroy them. ***Nabila Jabrane-Ferrat, Ph.D.***, at the **University of California, San Francisco**, is developing a method of incorporating genes involved in normal immune response into tumor cells. The strategy is to create a "danger signal" in the tumor that will activate the immune system. During the first year, the research team created tumor cells that produce one of three proteins, CIITA, IFN-gamma, or B7.1. These proteins signal the immune system to attack the tumor cells. They injected these tumor cells into mice that were genetically engineered to produce tumors. The hypothesis is that these tumor cell vaccines will stimulate the mouse immune system not only to attack the injected tumor cells, but also to attack other tumors developing in the mice.

**Antibody-IL-2 Fusion Proteins for Breast Cancer.** T cells are part of the body's immune system. They circulate in the blood and kill infected or malignant cells. However, the body can disable T cells that have the potential to recognize cancer cells, because cancer cells are similar to other cells in the body. ***Joseph Lustgarten, Ph.D.***, at the ***Sidney Kimmel Cancer Center***, La Jolla, is working on a way to overcome the body's disabling of T cells that have the potential to destroy breast cancer cells. His team generated two fusion proteins, anti-Her-2/neu-IL-2 and Heregulin-IL-2. Fusion proteins are two separate proteins that have been combined to make a single new protein. In laboratory and mouse models, these two fusion proteins redirect non-specific T cells to tumors that have the Her-family receptors Her-2/neu, Her-3 and Her-4. Receptors are proteins on or in cells that combine with another substance from outside the cell,

causing further changes within the cell. The Her-family receptors are found in tumors that are likely to spread or be fatal. Once at the tumor, the T cells destroy it. This immunotherapeutic approach is an alternative strategy to eliminate tumors with Her receptors (Her-positive tumors).

**New Drug Design: Creative Science**

**Targeted Delivery of an Anti-breast Tumor Agent.** ***Francis Markland, Jr.***, Ph.D., from the ***University of Southern California***, Los Angeles is continuing work supported by the CBCRP since 1995 to develop a snake venom protein into a breast cancer treatment. The Southern copperhead snake has a venom protein, contortrostatin, (CN). CN blocks breast cancer cells from forming blood vessels, starving the tumor and preventing its growth. Dr. Markland is working with co-investigators, **Nori Kasahara, M.D., Ph.D.**, at the ***University of Southern California***, Los Angeles, and ***Gary Fuji, Ph.D.***, at ***Molecular Express, Inc.***, Los Angeles. The group is testing methods of drug delivery, with the aim of testing the drug in animals. The team is well on its way toward the goal of developing a method of injecting CN into the blood of patients with breast cancer, targeting the primary cancer site and any sites to which the tumor has spread. Dr. Markland has used previous funding from the CBCRP to demonstrate the biological basis for the action of the drug.

**Hormone and Chemotherapy Targets: Improving Today's Arsenal**

**Targeted Chemotherapy to Treat Breast Cancer.** Liposomes are laboratory-synthesized microscopic particles with a fatty outer layer and a water-soluble center. Liposomes can circulate in the blood for long periods and carry chemotherapy drugs, genes, or other therapeutics to selected locations. ***Francis Szoka, Ph.D.***, at the ***University of California, San Francisco***, is working to increase the ability of drug-carrying liposomes to locate and bind to breast cancer cells, but not to normal cells. This would isolate the drug from the body until it is absorbed by breast cancer, minimizing side effects. The key to making this work for breast cancer is to target the liposomes to the cancer cells, and get them to bypass normal cells. Dr. Szoka is targeting liposomes by incorporating into them special sugar molecules that bind to a protein, CD44, found on breast cancer cells. The initial phase of this project was published in *Cancer Research* 61:2592-2601 (2001).

**Gene Therapy and Other Treatments: New Frontiers**

**Can Molecular Markers Predict Response to Adjuvant Therapy.** Tumor-related markers are genes or proteins found in tumors that may provide information on the nature and severity of the disease. ***Shelley M. Enger, Ph.D.***, of ***Southern California Kaiser Permanente***, and ***Michael F. Press, M.D., Ph.D.***, at the ***University of Southern California***, Los Angeles, are investigating whether some of these markers–including Her-2/neu, p53 and Bcl-2–can be used to predict whether the patient is likely to respond to various treatments. To date, they have collected data from medical records of 1,310 breast cancer patients, about 75% of the total they wish to study. It is critical that physicians treating breast cancer have information to better match treatment with individual characteristics of tumors.

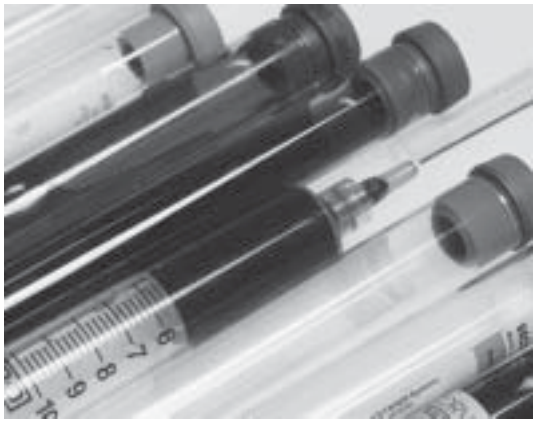
# Research Initiated in 2001

**Immune Therapy: Mobilizing the Body's Defenses**

- **A New Genetic Vaccine Therapy for Breast Cancer.** ***Edward Nelson, M.D.***, at the ***University of California, Irvine***, is testing an anti-tumor vaccine. The vaccine could eventually be used after treatment for breast cancer to stimulate the immune system to kill any remaining cancer cells and prevent a recurrence. Dr. Nelson's vaccine combines a gene found in many breast tumors with a substance that delivers the vaccine, VEE Replicon Vector. The VEE Replicon Vector stimulates the immune system's most potent cells, the dendritic cells.
- **Engineering Antibodies Specific for Breast Cancer Proteases.** ***Jeonqhoon Sun, Ph.D.***, at the ***University of California, San Francisco***, is engineering human antibodies that can inhibit the action of invasion proteases, which are proteins cancer cells produce that allow them to spread to other body parts.

**New Drug Design: Creative Science**

- **Targeting the EphB4 Receptor to Inhibit Breast Tumor Growth.** EphB4 is a protein 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, is investigating whether the portion of EphB4 that is exposed on the cell surface stimulates the formation of blood vessels that allow a tumor to grow. Results could form the basis for a treatment to inhibit tumor growth.



- **Blood Vessel Markers in Breast Cancer.** ***Erkki Ruoslahti, M.D., Ph.D.***, at ***The Burnham Institute***, La Jolla, is engineering small pieces of protein called peptides that are present on viruses. These proteins allow the viruses to bind to other specific proteins found on tumor blood vessels, but not on normal blood vessels. Eventually, these "homing peptides" can be designed to carry chemotherapy drugs. This could lead to a new way to target chemotherapy to tumors, with fewer toxic effects on normal tissues.
- **Novel Inhibitors of Rad51-DNA Repair in Breast Cancer.** Both radiation and chemotherapy kill cancer cells (and also normal cells) by damaging the cell's DNA. Breast tumors contain elevated levels of DNA repair enzymes that repair the damage caused by radiation and chemo-

therapy, creating resistance to these treatments. Breast tumors contain high levels of the DNA repair enzyme Rad51. ***Gurucharan Reddy, Ph.D.***, at ***Pangene Corporation***, Fremont, is developing Rad51 inhibitors that may improve conventional breast cancer therapy and possibly result in novel therapies.

- **A New System for Breast Cancer Drug Delivery.** ***Daryl Drummond, Ph.D.***, from the ***California Pacific Medical Center***, San Francisco, is building on research previously funded by the CBCRP, where he succeeded in formulating liposomes (microscopic fat particles) that contained a chemotherapy drug, and injected them into the blood of mice with human breast tumors. These liposomes did not release the chemotherapy drug until after the breast cancer cells took up them up. This should reduce the toxic side effects of chemotherapy in other parts of the body. In this study, Dr. Drummond will attempt to improve this potential treatment so that it allows more of the drug to reach the cancer, which would reduce the total amount of the drug that needs to be administered. He will also try reduce toxic side effects of liposomes that circulate in the blood for long periods.
- **Interaction of PPARg and Retinoid Ligands in Breast Cancer.** Compounds derived from Vitamin A (retinoids) show promise for prevention and treatment of breast cancers that depend on hormones to survive and grow, but not for hormone-independent breast cancers. ***Sharon James, Ph.D.***, of ***The Burnham Institute***, La Jolla, is testing compounds that may make one class of retinoids more effective against hormone-independent breast cancers.
- **PPARδ Ligands for Inhibition of Breast Cancer Progression.** ***Brian Murphy, Ph.D.***, at ***SRI International***, Menlo Park, is testing new drugs in mice that have been implanted with human breast cancer that spreads to other body parts. The drugs inhibit a protein, PPARd, that is produced in much higher levels in this type of breast cancer cells than in closely-related cells that don't spread to other body parts. Toxic side effects from this novel class of drugs should be minimal because the PPARd+protein has no known critical role in normal tissue.

**Hormone and Chemotherapy Targets: Improving Today's Arsenal**

- **Dietary Indole Effect on Estrogen Urinary Metabolites.** ***Gary Firestone, Ph.D.***, ***Leonard Bjeldanes, Ph.D.***, and ***Kathie Dalessandri, M.D.***, at the ***University of California, Berkeley***, are collaborating to test a possible breast cancer preventive agent. Indole 3 Carbinol (I3C) is a substance found in vegetables such as cabbage and broccoli. In the lab, it inhibits the growth of human breast cancer cells. The human body converts I3C to Diindolymethane (DIM). The research team will give DIM capsules, which have been shown to be safe and stable when taken orally, to 30 Marin County women with a history of early stage breast cancer. Another 30 similar women will receive placebos. The research team will test the women's urine for lower levels of certain chemical forms of estrogen, which would provide evidence that DIM is working to prevent breast cancer.

**Liposomes**

Researchers are looking for ways to deliver chemotherapy directly to tumors, instead of exposing a woman's entire body to toxic drugs. One promising way is by using liposomes. Liposomes are tiny fat particles like balloons; they can be filled with a variety of substances. Research progress with liposomes is being made on several fronts.

- **Novel Technologies to Identify Tissue-Selective Estrogens.** Estrogen-dependent breast tumors contain a specific protein (the estrogen receptor) that binds to the hormone estrogen. This binding causes tumors to grow. ***Fred Schaufele, Ph.D.***, at the ***University of California, San Francisco***, is using novel technology to test many proteins in living cells in order to identify a drug that will block estrogen in the breast, but preserve the beneficial effects of estrogen in other organs.
- **Patient-Individualized Chemotherapy in Breast Cancer.** ***Daniel H. Silverman, M.D., Ph.D.***, at the ***University of California, Los Angeles***, is working on a novel strategy to develop a test that would show, in advance, if a particular chemotherapy will eliminate an individual breast cancer patient's tumor. The research team is using a form of positron emission tomography (PET) scanning, called microPET imaging. With the scans, they hope to detect very small, non-toxic amounts of various chemotherapy drugs as they enter and pass 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.

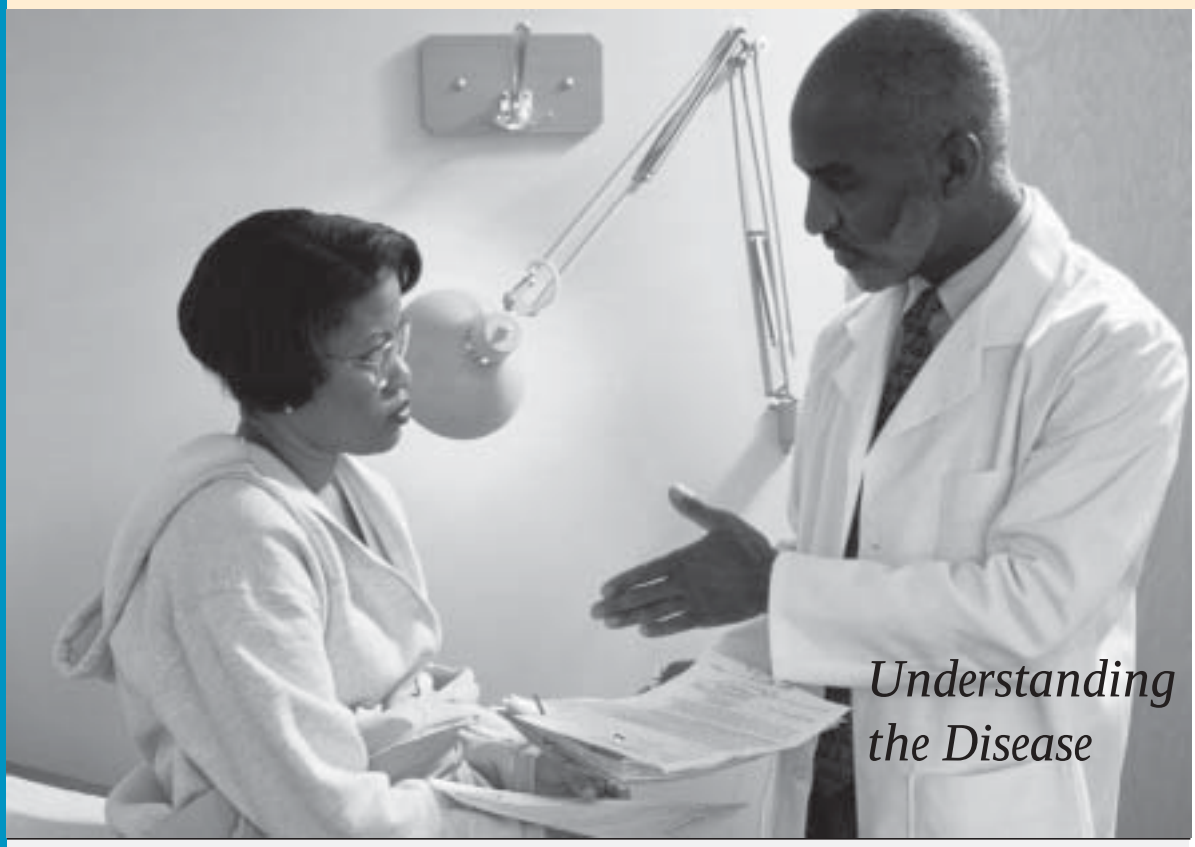
**Gene Therapy and Other Treatments: New Frontiers**

- **In Vivo Effects of Chinese Herbal Extracts on Breast Cancer.** ***Michael J. Campbell, Ph.D.***, at the ***University of California, San Francisco***, is testing extracts of Chinese herbs that have traditionally been used to treat cancer. Over 70 of these extracts have been tested on breast cancer cells in lab culture. Dr. Campbell's team will orally administer to mice with breast cancer the extracts that have been shown to be most effective against breast cancer cells.
- **Herba Scutellaria Barbatae for Metastatic Breast Cancer.** ***Debasish Tripathy, M.D.***, at the ***University of California, San Francisco***, is conducting a scientifically rigorous clinical trial of a Chinese herb traditionally used to treat breast cancer that has spread to other parts of the body. Twenty-five women whose breast cancer has spread will receive a tea containing herba scutellaria barbatae as their only cancer therapy, for one year or until the disease gets worse.

First, putting chemotherapy drugs inside liposomes keeps the drugs circulating in the blood longer, so the tumor gets exposed to the drug more. A drug that doesn't work on its own may work if delivered inside liposomes. Second, putting antibodies on the liposome surface targets the drug specifically to cancer cells. Third, liposomes are being investigated as a way to deliver gene therapy.

- **Selective Targeting of Breast Cancer with Radioiodide.** Some thyroid cancers take up and concentrate iodide, which is a substance necessary to human health that is added to table salt. These thyroid cancers can be successfully treated with radioiodide, and there are few toxic side effects. ***Irene Wapnir, M.D.***, at ***Stanford University***, Palo Alto, recently discovered that breast tissue also contains a protein that takes up and concentrates iodide. Her research team will attempt to treat human breast tumors in mice with radioiodide, in a manner that doesn't damage the mouse thyroid gland.

# *Pathogenesis:*



## *Understanding the Disease*

Pathogenesis: Understanding the Disease

# *Pathogenesis:*

## *Understanding the Disease*

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

We divide the pathogenesis priority area into five broad sub-topics:

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

# Research Conclusions

**Angiogenesis**
A number of studies in this section deal with angiogenesis. When tumors grow larger than 1-2 millimeters, they can no longer survive with the blood vessels that feed surrounding tissue. To grow, the tumors need to hijack the body's blood supply and generate their own blood vessels, a process known as angiogenesis. Angiogenesis is also a key event in tumors developing the ability to spread to other parts of the body (metastasis). Researchers are investigating the cell-level biochemical processes involved in cancer forming new blood vessels, many of which are not yet understood. The eventual goal is to develop treatments that shrink tumors and prevent their spread by blocking angiogenesis.

**Outbreak–How Cancer Spreads: Angiogenesis, Invasion, and Metastasis**

**Understanding Breast Cancer Cell Metastasis to Bone.**
Breast cancer often spreads to the bone, but there is currently no understanding of the molecular mechanism underlying this process. Researchers have discovered specific interactions between some types of cancer cells released from an original tumor and the cells at the new location in the body to which they spread, but not for cancer that spreads from breast to bone. ***Sonoko Narisawa, Ph.D.***, at ***The Burnham Institute***, La Jolla, investigated protein molecules in tissues adjacent to the bone that might allow breast cancer cells that break off from the original tumor and circulate in the blood to attach to the bone. After overcoming many technical hurdles, Dr. Narisawa identified a possible homing protein, called CD59, attached to the surface of cells adjacent to bone. Identifying a protein that allows breast cancer cells to attach to the bone via the blood could lead to treatments to prevent the spread of breast cancer or tests to predict whether a particular tumor would spread to the bone.

**Intracellular Signaling by PI3K in Breast Cancer Metastasis.**
***Earl Sawai, Ph.D.,*** from the ***University of California, Davis***, studied critical proteins than might regulate the spread of breast cancer to other body parts. His group used a unique mouse model system to compare human breast tumors that have high and low rates of spreading. The key difference is that the tumors that spread activate a protein that triggers other changes in the cell. This protein is called phosphoinisitol-3-kinase (PI3K). Dr. Sawai found that a number of other proteins associated with the spread of breast tumors appeared to increase in amount in the PI3K-activated tumors. This data provides the groundwork for future studies to establish the proteins involved in the spread of breast tumors.

**Leukocyte Recruitment, Angiogenesis, and Breast Cancer.**
***Pragada Sriramarao, Ph.D.***, from the ***La Jolla Institute for Molecular Medicine***, investigated how immune cells attach to blood vessels within tumors, which may be part of the process the immune system uses to shrink tumors. Dr. Sriramarao's team grew tumors just below the skin of mice and used a direct

visualization procedure called intravital microscopy to observe immune cells (white blood cells) attaching to the cells that line tumor blood vessels. When breast tumors are growing, they secrete a variety of proteins to stimulate the process of blood vessel formation (angiogenesis). Dr. Sriramarao found, first, that tumors produced high levels of proteins that encourage the formation of new blood vessels and interfere with immune cells attaching to tumor blood vessels. Second, injecting two soluble cytokines (kinds of proteins that cells secrete) into blood vessels near tumors increased immune cells' ability to attach to the blood vessels. Finally, when cells lining the blood vessels had proteins on their surface, called selectins, that were exposed to the blood, more immune cells attached to the blood vessels. This study illustrates the fine-tuned molecular regulation in tumor blood vessels, and suggests that both blocking a tumor's ability to form blood vessels and increasing proteins that help immune cells attach to tumor blood vessels would potentially allow a better immune response to breast cancer.

**Breast Cancer Cell Binding to the Endothelium.**
***Brunhilde Felding-Habermann, Ph.D.***, at ***The Scripps Research Institute***, La Jolla, investigated how breast cancer spreads to organs such as the bone, lungs, liver, and brain. Once cells break away from the original tumor, they spread through the lymph system and bloodstream. Dr. Felding-Habermann studied an integrin adhesion receptor, a substance found in both normal breast cells and cancer cells. Integrin adhesion receptors help keep normal cells in place, but they play a role in the spread of breast cancer cells. The research team found that an integrin adhesion receptor found on breast cancer cells, called $\alpha v\beta 3$, exists in both an activated and a de-activated state. Activated $\alpha v\beta 3$ allows the cells to leave the bloodstream and attach themselves to the endothelial cells that line the target organs. Activated $\alpha v\beta 3$ allows the cell to invade the new organ more effectively by cooperating with an enzyme, MMP-9, which breast cancer cells produce in order to digest the extracellular matrix, the structure that would restrict movement in their immediate environment. This research identifies activated $\alpha v\beta 3$ as a marker for breast cancer cells that can spread and invade other organs. This information may lead to ways to test whether a tumor is likely to spread. Results from this research were published in the *Proceedings of the National Academy of Sciences*, USA 98:1853-8 (2001).

**Role of Chemokine Receptors in Breast Cancer Metastasis.**
***Brett Premack, Ph.D.***, at the ***University of California, Los Angeles***, surveyed existing breast cancer cell lines for the presence of chemokine receptors. Chemokines are a family of fairly small proteins that are often secreted from injured tissue, inflamed tissue, or some white blood cells. White blood cells have proteins on their surface that combine with chemokines; these proteins are chemokine receptors. When the chemokines combine with the receptors, they play a role in white blood cells moving and attaching themselves to other cells, for example, in the processes of inflammation and autoimmune diseases.

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

Dr. Premack's premise was that chemokines might play a similar role in breast cancer cells being able to spread to other parts of the body. He surveyed 13 different chemokines and receptors in eight breast cancer cell lines, and found that a specific chemokine receptor, CxCR4, was present, but only in a small percentage of the cells in a given population. He used a technique called calcium signaling assays to confirm that CxCR4 does work with a chemokine. Unfortunately, Dr. Premack was unable to clearly associate the presence of CxCR4 with differences in the breast cancer cells' ability to invade other body parts. Continued work in this topic is useful, because drugs being developed to address immune disorders might someday find an application for treating breast cancer.

**Spatial Control of Matrix Proteolysis in Breast Cancer.**
***Alex Strongin, Ph.D.***, from ***The Burnham Institute***, La Jolla, studied molecular interactions that occur when breast cancer cells are migrating to other parts of the body. The goal is to find ways to keep the cells from migrating by interrupting these molecular interactions. The team studied interactions between two types of proteins, metalloproteinases, and adhesion receptors. Since the interactions between these proteins occur on the surface of cells, it may be easier to interrupt them than to block molecular processes that occur within cells. Dr. Strongin's team identified molecular processes involved in activating metalloproteinases, such as MT1-MMP and metalloproteinase-2 (MMP-2), on breast cancer cells. The team characterized the chemical interaction that MT1-MMP uses to make an adhesion receptor, the integrin aV chain, work more efficiently to allow cells to move and attach to new places in the body. The team also found a protein, gC1qR/p33, that acts like a "chaperone" for MT1-MMP. Several publications were supported by this funding, including one in *The Journal of Biological Chemistry* (2001) 276(28):25705-14 and another in *Experimental Cell Research (*2001) 263(2):209-23.

**A Novel Inhibitor of Breast Tumor Angiogenesis.**
***YingQing Sun, Ph.D.***, from ***The Burnham Institute***, La Jolla, studied molecular-level interactions of a protein–plasminogen kringle 5 (K5)–that inhibits breast cancer cells' ability to form new blood vessels. Cancer cells need to develop this ability to form their own blood vessels (angiogenesis) in order to spread in the body. Dr. Sun discovered two receptors (proteins that bind with K5) on the surface of cells that line blood vessels. Further research on this topic could lead to a novel way to block blood vessel formation in tumors.

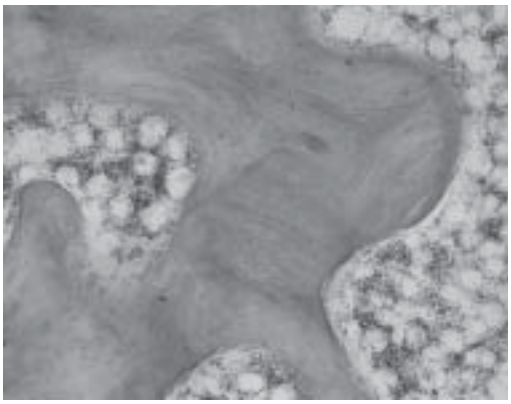
Biotechnology) and BMS-275291 (Bristol-Myers Squibb), are being tested in humans to see if they block cancer progression and angiogenesis. This therapeutic approach does not directly kill cancer cells, but can shrink tumors and is attractive in combination therapy with other drugs. In other clinical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

**The Shp-2 Tyrosine Phosphatase in Breast Tumor Migration.**
***YingQing Sun, Ph.D.***, from ***The Burnham Institute***, La Jolla, investigated Shp2, a type of enzyme called a kinase. Kinases are found in human cells; they transmit signals that come from the cell surface to control cell functions, including gene activity. Shp-2 plays a pivotal role in triggering the production of metalloproteinase enzymes (MMPs). Breast cancer cells secrete MMPs to facilitate moving to other parts of the body. Using biochemical methods, Dr. Sun identified several proteins in cancer cells that Shp-2 may act on to trigger the molecule-level changes that lead to production of MMPs.

**Identifying Breast Cancer Targets for Protease Inhibitors.**
***Yongsheng Liu, Ph.D.***, from the ***Scripps Research Institute***, La Jolla, used a novel method for detecting proteases, which are proteins breast cancer cells secrete that break down other proteins and allow the cells to move. Up to 2% of the human genes revealed through the Human Genome Project are predicted to be proteases, and only a fraction of them have known functions. Dr. Liu was looking for proteases that can be blocked by serpins. Serpins are types of protease inhibitors, which are proteins produced in the human body that block the action of proteases. Serpins are the principle types of protease inhibitors found in the plasma portion of human blood. Other research shows that serpins inhibit breast cancer cells' ability to invade other body parts. Discovering which proteases serpins act against could lead to new targets for drug therapy. Before resigning from this CBCRP-funded research to take another position, Dr. Liu was able to confirm that the novel method for detecting proteases works.

**The Role of IL-8 and its Receptors in Angiogenesis.**
Interleukin-8 (IL-8) is a substance produced in the human body known for its role in inflammatory diseases, where it attracts white blood cells into an area of tissue injury. IL-8 is also found at high levels in breast cancer cells, especially in more deadly cases of breast cancer. ***Ingrid Schraufstatter, M.D.***, from the ***La Jolla Institute for Molecular Medicine***, studied IL-8 in relation to the primary type of normal blood vessel cell that responds to the chemicals tumors secrete to grow their own blood supply. Her research team found that when they inhibited IL-8 receptors (proteins that combine with IL-8) on the surface of normal blood vessels cells, it stopped processes cancer cells need to form new blood vessels. Dr. Schraufstatter also partially traced the biochemical processes IL-8 triggers inside normal blood vessel cells. These experiments predict that blocking the biochemical process IL-8 initiates in normal blood vessel cells has potential as a treatment for breast cancer. Dr. Schraufstatter presented her findings at the 2002 Federation of American Societies for Experimental Biology (FASEB) meeting.

**How Does Endostatin Inhibit Breast Cancer Angiogenesis?**
Endostatin is an anti-angiogenic protein (a protein that inhibits the formation of blood vessels). A large amount of research is being done on endostatin, because it eliminates cancer in mice without side effects or creating tumor resistance. However, researchers don't understand very clearly how it works. ***Kristiina Vuori, M.D., Ph.D.***, from ***The Burnham Institute***, La Jolla, investigated how endostatin affects the ability of the cells that line blood vessels to adhere to other cells. Dr. Vuori and collaborators reported (*Proceedings National Academy Sciences*, USA 2001 98(3):1024-9) that endostatin binds to two classes of endothelial integrin adhesion receptors. These receptors are proteins found on the surface of cells that line blood vessels. Their main function is to attach the cells to surrounding cells that provide structure. This research supports the concept of targeting blood vessels as a promising strategy for eliminating breast cancer.



**Cell Adhesion and Drug Resistance in Breast Cancer.**
Breast cancer cells can sometimes avoid being killed by chemotherapy, and researchers are studying the many biological ways that this resistance develops. ***Kristiina Vuori, M.D., Ph.D.***, from ***The Burnham Institute***, La Jolla, confirmed her hypothesis that one key element of drug resistance has to do with the way breast cancer cells are attached to the scaffold of supportive cells that surrounds them. Chemotherapy works by starting a natural process of cell death called apoptosis. Dr. Vuori found that when breast cancer cells are attached to surrounding cells via proteins called β1 integrin adhesion receptors, it reduces the effectiveness of the chemotherapy drugs vincristine and paclitaxel. The biochemical reactions leading to cell death that these drugs start are greatly reduced. How can this be corrected? Dr. Vuori has identified a series of biochemical reactions–called signaling pathways–that link attachment to surrounding cells via β1 integrins to inhibition of the biochemical processes involved in cell death. If the biochemical process that leads to cell death can be restored by drugs, chemotherapy could successfully treat these breast cancers. Results from this research were published in *Oncogene* (2001) 20:4995-5004. The CBCRP funded Dr. Vuori during 2001 to pursue this work in greater detail.

**Proteins**
Many researchers on these pages are investigating proteins. Proteins are complex, highly varied molecules that interact chemically within the cells of the body. In every process a cell goes through, proteins are involved. One protein within a cell can break or create a chemical bond in the molecular structure of a second protein, changing the second protein in a way that causes it to change other proteins. Eventually, these changes set off a cascade of chemical reactions that causes the cell itself to change. Genes cause cells to have the characteristics they have by making proteins. Some proteins can turn genes on and off. By studying proteins and their actions in breast cancer cells, researchers are hoping to find new ways to stop or prevent the disease.

**Targeting Breast Cancer Blood Vessels.**
***Jan Schnitzer, M.D.***, from the ***Sidney Kimmel Cancer Center***, San Diego, discovered proteins on the surface of blood vessels cells in breast tumors that are not found on the surface of normal blood vessel cells. The research team made antibodies to these proteins. When injected into the bloodstream, these antibodies had the ability to specifically target tumor tissue. The long-term plan is to use these proteins as targets for drug therapy. Current attempts to use antibodies to deliver anti-cancer drugs directly to breast tumors have met with limited success. When these antibody-delivered drugs are injected into the bloodstream, they don't get across the blood vessel wall to attack the tumor. Cells lining tumor blood vessels are more accessible. Drugs targeted to these cells with antibodies could be used to treat breast cancer by choking off the tumor blood supply. Interestingly, the preliminary results of this research indicate that a naturally occurring cell nutrient and receptor recycling structure in cells called the caveolae that line the blood vessels might prove the most promising avenue for targeting the tumor blood vessels.

## Too Much Cell Growth: Defective Messages and Internal Signaling

**Novel Binding Functions of Mutant p53 in Breast Cancer Cells.**
***Koji Itahana, Ph.D.***, from the ***Lawrence Berkeley National Laboratory***, studied p53 tumor suppressor pathway dysfunctions in breast cancer. The p53 pathway is a series of interactions among proteins in cells that leads to cell death after chemotherapy or radiation treatments. Only about 25% of breast cancers appear to have either mutations in or loss of the protein that starts the p53 pathway. Researchers are interested in finding other defects in the proteins involved in the p53 pathway that might also prevent cell death. Dr. Itahana failed to find what he was originally searching for–mutations that made p53 more effective. However, his work led him to study a protein that appears to control the abundance of other proteins in the p53 pathway, but not p53 itself. This protein is a transcription factor, a protein that binds to DNA and controls gene activity. Dr. Itahana found a subtle variation in this protein in some breast cancer cells, but not in normal cells. When this slightly different protein binds to a gene that generates one of the proteins involved in the p53 pathway, the gene generates a slightly aberrant protein. Dr. Itahana plans future research to sort out the role of this process in breast cancer.

**COX-2 and Apoptosis Regulation in Breast Cancer.**
Normal cells have a lifespan; they die naturally and are replaced by new cells. The pre-programmed death process is carried out through a series of molecule-level interactions in the cell, and is known as apoptosis. Defects in apoptosis interactions allow cancer cells to survive beyond their normal lifespan, to spread to other body parts, and make them hard to kill with chemotherapy or radiation.

So it's important to understand on the molecular level how tumors evade pre-programmed cell death. ***Youngsoo Kim, Ph.D.***, from ***The Burnham Institute***, La Jolla, began his research by investigating a prostaglandin. Prostaglandins are chemical compounds produced in the body; they are involved in smooth muscle contraction, blood clotting, inflammation, and many other functions. Dr. Kim tested whether the prostaglandin produced by the COX-2 gene inhibits apoptosis. It didn't, but another prostaglandin, $PGJ_2$, appeared to make breast cancer cells more likely to undergo apoptosis. $PGJ_2$ influenced a protein in or on the nucleus of cells called PPARγ. PPARγ combines with other substances produced in the body and also certain drugs, which causes the breakdown of another protein in the cell called FLIP. Loss of FLIP, in turn, allows breast cancer cells to respond to the apoptosis process. These findings solve part of the puzzle of why TRAIL (a protein found in many cells in the body, Tumor Necrosis Factor-related apoptosis-inducing ligand) causes apoptosis in cancer cells. Excess FLIP protects cancer cells from TRAIL-caused death. Knowing the key pathways within cancer cells responsible for cell death provides an opportunity to explore ways of enhancing the ability of chemotherapy drugs and other agents in treating the disease.

## Searching the Unknown: Novel Breast Cancer Genes

### Role of DNA Damage Response Gene in Breast Cancer.

Damage to DNA is widely considered to be a dominant force in the generation of cancer. Understanding how cells prevent DNA damage can lead to methods to prevent cancer. ***Eric J. Brown, Ph.D.***, of the ***California Institute of Technology***, Pasadena, investigated the ATR gene, which may play a role in either DNA repair or in preventing cells that have cancer-like properties from multiplying. His team created genetically-altered mouse cells and a recombinant virus that could eliminate the ATR from the cells. Their experiments showed that cells need ATR to grow and multiply, but not to function in a stable manner. This study suggests that a chemotherapy that inhibits ATR may prevent tumors from growing. In future studies, Dr. Brown plans to investigate whether ATR has any effect on genes known to be involved in the development of breast cancer, including BRCA1, Chk1, Chk2, and p53. A publication based on this study appeared in *Genes and Development* 14(4):397-402.

### Chromatin Regulation of Breast Cancer Cell Senescence.

Every cell's chromosomes contain DNA bundled with proteins to form a complex known as chromatin. Some chromatin proteins protect chromosomes from damage that accumulates as cells age. ***Paul Kaufman, Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, is exploring how damage occurs to DNA in human cells during cellular aging, and how chromatin proteins might delay this process. His team studied a protein called Chromatin Assembly Factor, or CAF-1. CAF-1 is responsible for assembling chromatin, and Dr. Kaufman at-

**DNA and Cancer**
All cells in the human body contain an "operations manual" made up of DNA molecules. The information in the manual is divided into "chapters" called genes. Genes cause the cells to make proteins that tell the cell how to function. Changes in DNA, called mutations, can be subtractions from, additions to, or rearrangements of the structure of the original DNA molecule. Mutations can happen in the course of cell division, or in the process of normal cell function. Cells can repair most mutations. Cells divide to replace worn-out cells, and the DNA replicates itself to pass on the same traits to the two new cells. If a cell divides before a mutation is repaired, both new cells will have the mutation. Most mutations can't make a cell cancerous. Proteins produced by a very small proportion of cell's genes regulate cell growth and division. A series of mutations in these genes can eventually lead to cancer. Buildup of these mutations may take years. Cells that divide frequently, such as breast cells, are at higher risk for mutations.

tempted to examine its role in living cells by blocking its function. It was difficult to do at first, but the team succeeded by using a fragment of CAF-1 to inhibit it. Continuous blocking of CAF-1 arrests cell growth. With more research, this information might lead to a treatment that inhibits breast cancer cell division, or reveal how chromatin changes as normal breast cells age, making them more susceptible to cancer.

**Molecular Structure of BAG-1: A New Protein in Breast Cancer.**
***Kathryn Ely, Ph.D.***, at ***The Burnham Institute***, La Jolla, studied the three-dimensional structure of BAG-1, a key protein that regulates apoptosis, the process of programmed cell death. The level of BAG-1 is elevated in breast cancers. It promotes tumor growth and the spread of breast cancer to other parts of the body, which makes breast tumors resistant to anti-cancer drugs such as tamoxifen. Dr. Ely generated a molecular image of BAG-1 using nuclear magnetic resonance (NMR). She found the key structural elements that allow BAG-1 to interact with another protein, called Hsp70. How BAG-1 and Hsp70 function to stabilize each other will take much more research. However, this type of work is critical to explain the mechanism of breast cancer resistance to anti-estrogen drugs such as tamoxifen. This research also points the way toward strategies to overcome treatments that fail women with breast cancer. Dr. Ely's research was published in *Nature Structural Biology* 4:349-352 (2001). The CBCRP funded continued research on this topic in 2001.

**Characterization of hAG-2 and Its Role in Breast Cancer.**
When surgeons remove breast tumors or perform biopsies to get samples of tumors, the tissue gets evaluated for several characteristics that help determine the prognosis and best treatment. One of the most useful of the characteristics is the presence of proteins called estrogen receptors (ER), because tumors that contain this protein often respond well to anti-estrogen drug treatment. ER-positive breast cancer is also the most common form. ***Devon Thompson, Ph.D.***, from ***Stanford University***, Palo Alto, studied a protein, hAG-2, which was found together with ER in 79% of the tumors she examined. She was not able to determine whether hAG-2 plays any role in breast development or whether it responds to hormones. Dr. Thompson and colleagues published related work on estrogen-responsive genes in *Cancer Research* 60:6367-75 (2000). Even though ER-positive tumors respond to therapy, there is the need for new drug targets to enhance treatment options and deal with the problem of resistance to the drug tamoxifen.

**Suppressor Genes of Breast Cancer.**
Research over the past two decades has shown that cancer is caused by changes in genes within cells, thus leading to the theory that cancer is a genetic disorder. Many genes present in normal cells are absent in cancer cells. This suggests that there are a large number of genes that suppress the growth of tumors, and that their absence allows genes that promote tumor growth to be

active. Unfortunately, to date only a handful of tumor suppressors have been identified. ***Shi Huang, Ph.D.***, of ***The Burnham Institute***, La Jolla, studied a group of genes which are members of a family of genes, the PR family. Other known members of this gene family suppress cancer formation and growth of new cells. Dr. Huang investigated three genes from this family, PFM4, 7, and 11. These genes produce proteins that inactivate other genes. When the genes are absent from a cell's DNA, other genes that are normally inactive would be expected to be active. Dr. Huang's team examined the DNA in tissue samples from 40 primary breast cancers for changes in the three PMF genes. PMF4 was either absent or altered in only about 20% of the samples. Dr. Huang plans to continue investigating these genes to see whether other reasons might account for the genetic "silencing" of PFM4.

**Unraveling the Path to Breast Cancer:**
**Tumor Progression**

**Id-1 Expression During Breast Cancer Progression.**
***Pierre-Yves Desprez, Ph.D.***, at the ***California Pacific Medical Center Research Institute***, San Francisco, investigated Id-1, a type of protein called a transcription factor, in various stages of breast cancer. Using tissue samples from tumor biopsies, he found that the Id-1 protein was mostly absent in samples taken from women diagnosed with DCIS (non-cancerous lesions that may later develop into cancer) and Grade 1 tumors (which do not spread). In contrast, the Id-1 protein was present in substantial amounts in more than half of the Grade 2 and 3 tumors, which are more likely to spread. Other work from Dr. Desprez's laboratory shows that Id-1 plays a key role in allowing breast cells to activate genes for invasive metalloproteinase enzymes. Cells release these enzymes to pave the way to migrate in the body. Thus, blocking Id-1 would be useful in preventing the spread of breast cancer, and knowing whether Id-1 was present could provide information about whether a breast tumor is likely to spread. The CBCRP has funded Dr. Desprez in 2001 to continue this work and examine an additional protein, Id-2, for its role in breast cancer.

# Research in Progress

**Outbreak–How Cancer Spreads: Angiogenesis, Invasion, and Metastasis**

**Profiling Serine Protease Activities in Breast Cancer.** ***Benjamin Cravatt, Ph.D.***, at ***The Scripps Research Institute***, La Jolla, is using proteomics, the simultaneous analysis of the complete protein content of given cell or tissue, to study breast cancer. He has developed a special technique to measure active protease enzymes. This approach is an improvement over methods that only measure the presence of genes and proteins and do not actually determine the associated enzyme activity. Breast cancer cells use these proteases to break down proteins in their environment and move to other parts of the body. Dr. Cravatt is developing key information on forms of breast cancer that do not depend on the hormone estrogen for growth (ER-negative breast cancer). ER-negative breast cancer cells frequently utilize a protease called urokinase to invade other cells. It is important to develop more information on ER-negative breast cancer, since this form is not well controlled by chemotherapy medications such as tamoxifen. Dr. Cravatt's methods were published in *Biochemistry* (2001) 40:4005-15.

**Role of MMPs in Breast Tumor Initiation and Aggressiveness.** Metalloproteinases (MMPs) are enzymes that normal cells secrete to perform a variety of normal processes. Breast cancer cells produce more MMPs than normal; this increases the tumor blood supply and allows tumors to grow and spread. ***Jimmie Fata, Ph.D.***, of the ***Lawrence Berkeley National Laboratory***, is investigating how MMPs can cause normal breast epithelial cells (the type of cells where most cancer arises) to develop an unusual characteristic called epithelial to mesenchymal transition (EMT). EMT is associated with aggressive breast cancers. Dr. Fata is studying the process by which MMPs cause EMT on the cell and molecule level, as well as looking at what happens on the cell and molecule level as a result of this process.

## Too Much Cell Growth: Defective Messages and Internal Signaling

**A Novel Signal Transduction Pathway in Breast Cancer.** ***Yixue Cao, Ph.D.***, from the ***University of California, San Diego***, showed that a protein called IKK-alpha is critical for mammary gland development. Dr. Cao developed mice with a specific mutation in the gene that produces the IKK-alpha protein. These mice are normal, except that they fail to produce milk. The next step is to find out whether this mutation in the IKK-alpha gene suppresses tumor growth in mice. This preliminary work suggests that a drug that works by blocking IKK-alpha will not cause side effects in other organs. For 2001, the CBCRP funded a much larger grant to Dr. Cao's mentor, Dr. Michael Karin, to expand these studies. (See the "Biology of the Normal Breast" section of this annual report, "Research Initiated in 2001.")

**Anti-E-Cadherin Apoptosis of Inflammatory Breast Carcinoma.** Inflammatory breast carcinoma is one of the most deadly forms of breast cancer. ***Mary Alpaugh, Ph.D.***, at the ***University of California, Los Angeles***, and colleagues investigated a protein, E-cadherin, that normal breast cells produce and which allows the cells to attach in layers to other cells. The research team confirmed that E-cadherin promotes the ability of inflammatory breast cancer cells to spread locally in the breast. This finding challenges the current thinking about the role of E-cadherin, which has maintained that if normal breast cells lose the ability to produce E-cadherin, they become cancer cells. Results from this project were published in *Cancer Research* 61:5231-5241 (2001).

**Studies on the Role of the ER-beta in Breast Cancer.** Estrogen receptors are proteins on or in cells that chemically bond with the hormone estrogen, which circulates in the blood. Once this bonding takes place, it triggers other chemical reactions in the cell. Breast cancer cells that have the most widely-studied estrogen receptor, ER-alpha, depend on estrogen for their growth. This type of breast cancer is the most commonly occurring subset of the disease; it grows more slowly than many other types and can be treated with anti-estrogen drugs like tamoxifen. ***Eli Gilad, Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, is studying a recently-discovered estrogen receptor, ER-beta. ER-beta may be involved in molecular interactions inside breast cancer cells with both ER-alpha and a gene that promotes more deadly forms of cancer, Her-2. Dr. Gilad has found that ER-beta will promote tumor growth even in the absence of estrogen. Surprisingly, ER-beta inhibits tumor growth when it interacts chemically with Her-2. This line of research will contribute to treatment decisions, especially for women with breast cancer that is resistant to treatment with anti-estrogen drugs. Dr. Gilad works in the laboratory of ***Ruth Lupu, Ph.D.***, who was funded by the CBCRP from 1997-1999 to develop key background on this topic.

**Cell Growth Control of Breast Epithelial Cells.** ***Ulla Knaus, Ph.D.***, at ***The Scripps Research Institute***, La Jolla, is investigating two proteins that appear to be involved in the growth of normal breast cells. The two proteins are called Rac3 and Rac1. They are turned on by hormones and by proteins called growth factors that come from outside the cell. Rac3 is also consistently turned on in tumors, while Rac1 is not; Rac3 may be tricking cells into growing at inappropriate times. Rac3 does not have mutations, so Dr. Knaus is investigating where inside breast cells this protein is attached. Her team introduced fluorescent copies of both proteins into normal human breast cells. Rac1 distributed itself throughout the cell, but Rac3 attached to membranes inside the cell. In future experiments, they will try to find the particular cell structure that attaches Rac3. They also found that several growth-stimulating substances that activate Rac1 don't activate Rac3.

## Mistakes on the Master Blueprint: Molecular Genetics and Gene Regulation

**A Role for RAD51B in Breast Cancer.** Every cell in the human body contains DNA, a "blueprint" for the cell. When cells divide in two to replace worn-out cells, the DNA also replicates itself. Errors can occur in replication, and DNA can get damaged during normal cell function. So special DNA repair proteins found naturally within cells are continually removing small sections of DNA and correcting the damage. ***Joanna Albala, Ph.D.***, from the ***Lawrence Livermore National Laboratory***, is studying a DNA repair protein, called RAD51, that works with the hereditary breast cancer genes BRCA1 and 2. Normal BRCA genes prevent tumors. When mutations in the BRCA genes are present, then RAD51 cannot repair DNA and mutations are passed on to the next generation of cells. Dr. Albala is investigating which of the five RAD51 proteins form the active complexes in breast cancer cells. Part of this research was published in Molecular and *Cellular Biology* 17:6476-82 (2000).

**DNA Packaging Defects in Breast Cancer.** ***Terumi Kohwi-Shigematsu, Ph.D.***, from the ***Lawrence Berkeley National Laboratory***, is continuing to study ways that the DNA of breast cancer cells differs from that of normal cells. She has identified a protein called poly (ADP-ribose) polymerase (PARP) that binds to a specific stretch of DNA, the matrix attachment regions (MARs). PARP plays a role in DNA repair. Dr. Kohwi-Shigematsu's hypothesis is that breast cancer cells produce PARPs at higher levels than normal cells, and that the PARPs organize the cell's DNA to allow it to maintain its growth rate and invade other cells. Dr. Kohwi-Shigematsu is comparing cells with high and low levels of PARPs to see how PARPs affect the action of other genes in these cells. She is using microarray technology, a technique that allows her to simultaneously check 20,000 genes, so as to find the 'needle in the haystack' of possible genes affected by the PARP variation. She will also use mice that have been genetically

engineered to spontaneously form breast cancer that spreads to the lung, and find out if the cancer will still grow if these mice are further engineered so that they cannot produce PARP. A publication based on this research appeared in the *Journal of Cellular Biochemistry* 35:36-45 (2001).

**Searching the Unknown:**
**Novel Breast Cancer Genes**

**Metastasis Suppressor Genes for Breast Cancer.** ***Stanley Cohen, M.D.***, at ***Stanford University***, Palo Alto, is attempting to discover novel tumor suppressor genes, which might be a means to inhibit breast cancer growth and prevent its spread to other body parts. The underlying theory is that cancer cells acquire a single mutation in their DNA that de-activates a tumor suppressor gene and then allows the cancer cells to spread. Dr. Cohen is using a technique called Random Homologous Knock Out (RHKO) that allows him to screen a tissue sample for thousands of genes at a time and to quickly identify a target gene. When he finds a possible suppressor gene, he will check to see if it is missing in breast cancer cells, then test to see if inserting it in breast cancer cells makes them behave more like normal cells. As part of this research, Dr. Cohen is working with biotech collaborators to develop a way to externally detect very small tumors that have spread to the lung in living animals, using the fluorescent protein produced by fireflies and a type of video camera. This will allow testing to see if a particular gene causes tumors to spread, without having to sacrifice the animals the animals and interrupt the remainder of the experiment.

**Unraveling the Path to Breast Cancer:**
**Tumor Progression**

**A Study of the Molecular Heterogeneity of LCIS.** Women who have the breast disease lobular carcinoma in situ (LCIS) have an increased breast cancer risk. However, LCIS may actually be several diseases, and only a subset of them may lead to a high risk for breast cancer. ***Sanford Barsky, M.D.***, at the ***University of California, Los Angeles***, is comparing the genetic profiles of 200 tissue samples of LCIS. After analyzing 100 samples, Dr. Barsky has tentatively divided LCIS into three types. The first type share characteristics in their genes that suggest that they have progressed to invasive cancer. The second type has genetic profiles that suggest that the disease could develop into cancer. The third type shows no obvious differences in genes with normal breast tissue, suggesting that this type may be harmless. Over the coming year, the team will analyze the rest of the 200 tissue samples to see whether the three-tier classification system holds.

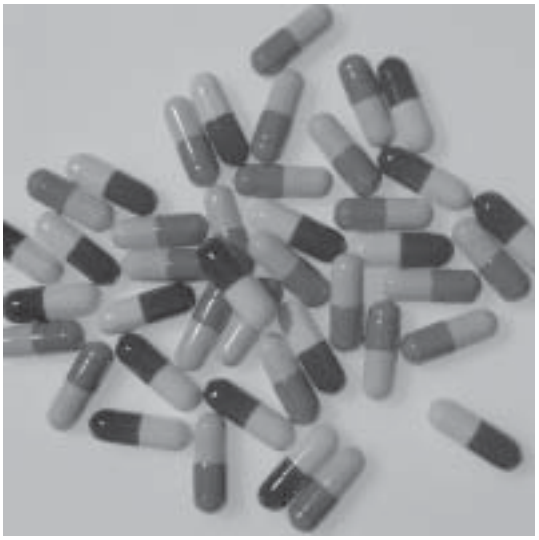
**TGF-beta Receptor Signaling and Breast Cancer.** TGF-beta is a protein inside breast cells. It inhibits the growth of normal cells, but not the growth of breast cancer cells that have the ability to spread to other body parts. ***Kunxin Luo, Ph.D.***, of the ***Lawrence Berkeley National Laboratory***, is investigating TGF-beta's role in the normal process of breast cells becoming specialized and in the process that changes normal cells to cancer. Dr. Luo discovered two proteins located in the breast cell nucleus, Ski and SnoN, that block TGF-beta. Over-production of the two proteins kept TGF-beta from inhibiting cell growth. The research team tested normal and cancerous cells for levels of SnoN. They found little or no SnoN in normal cells, very high levels in early tumor cells that didn't have the ability to spread, and moderate levels in tumor cells with the ability to spread. Thus, a high level of SnoN is a sign that cells are becoming cancerous, and SnoN may play a role early in this process. Next, the team will examine levels of Smad proteins in normal and cancerous breast cells.

**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, the site of most breast tumors. ***Mary Helen Barcellos-Hoff, Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, is pursuing 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. Her team is using mouse mammary epithelial cells that lack a gene, p53, that normally suppresses tumors. They predict that when these cells are transplanted into a stromal cell framework that has been exposed to radiation, they will become cancerous more rapidly. They are running the same experiments using epithelial cells with normal p53 genes. Understanding how radiation alters normal mechanisms that stromal cells use to keep epithelial cells from turning cancerous may provide new strategies for augmenting these mechanisms to prevent or reverse cancer.

# Research Initiated in 2001

**Outbreak–How Cancer Spreads: Angiogenesis, Invasion, and Metastasis**

- **Trypsin-Like Proteases as Metastatic Agents in Breast Cancer.** ***Kathryn DeFea, Ph.D.***, at the ***University of California, Riverside***, is investigating PAR2, a protein on the membrane of tumor cells that appears to play a key role in the spread of breast cancer to other parts of the body. The eventual goal is the development of drugs that block the spread of breast cancer by inhibiting PAR2 or chemical changes in cells that PAR2 triggers.
- **Lasp-1 Signaling in Breast Carcinoma Cell Invasion/Migration.** ***Yi Hsing Lin, Ph.D.***, at the ***Scripps Research Institute***, La Jolla, is investigating the Lasp1 gene. Dr. Lin's research team has already shown that overproduction of the protein produced by Lasp1 is linked to breast cancer cells moving to other body parts. They will now attempt to determine what part of the protein's structure is involved in cell movement. The information may lead to drugs that block the spread of cancer by blocking the action of the Lasp-1 protein.
- **Smoking Effect on Pulmonary Metastasis from Breast Cancer.** Smokers are more likely to die of breast cancer than non-smokers, but smokers don't get breast cancer any more often. ***Susan Murin, M.D.***, of the ***University of California, Davis***, will compare the number and size of breast cancer deposits in the lungs



of mice exposed to a level of cigarette smoke comparable to that experienced by actively smoking adults and in the lungs of mice not exposed to smoke. To approximate the situation of a woman who stops smoking after she learns she has breast cancer, they will also compare a third groups of mice who stop being exposed to smoke after their breast cancer has grown awhile.

- **Novel Enzymes Associated with Breast Cancer Angiogensis.** ***Steven Rosen, Ph.D.***, at the ***University of California, San Francisco***, and his team are investigating enzymes and genes they have discovered that may play a role in tumors developing the ability to hijack the body's blood supply by forming their own blood vessels.

**Too Much Cell Growth: Defective Messages and Internal Signaling**

- **Molecular Study of BAG Domains: A New Motif in Breast Cancer.** ***Klara Briknarova, Ph.D.***, at ***The Burnham Institute***, is investigating proteins from the BAG family. The founding 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 anti-cancer drugs such as tamoxifen. The team has identified a part of the BAG protein that is the likely source of its cancer-promoting action. They plan to map this part's molecular structure and study its action in more detail.
- **The Role of SGK in Breast Cancer Cell Proliferation.** ***Masaaki Hayashi, M.D., Ph.D.***, at ***The Scripps Research Institute***, La Jolla, is investigating two proteins, glucocorticoid-inducible kinase (SGK) and BMK1. Together, they may play a key role in the uncontrolled growth of cells that is the hallmark of breast cancer.
- **Genetic Analysis of ErbB Signaling in C. Elegans.** ***Nadeem Moghal, Ph.D.***, at the ***California Institute of Technology***, Pasadena, is using nematode worms, C. elegans, to rapidly identify and analyze genes that may interact with the ErbB genes and the proteins these genes produce. In many cases of breast cancer, mutations in ErbB or other genes cause proteins produced by ErbB genes to become too active or increase in amount. Drugs such as Herceptin inhibit ErbB2 (also called Her-2/neu), but this is only effective about half the time. Understanding the role of other genes could translate into better treatments for breast cancer. Nematode worms and humans share common genes for growth processes, and studies on these worms have led to the discovery of other proteins that block the activity of ErbB genes.
- **Molecular Characterization of ErbB2 Positive Breast Cancers.** The ErbB2 protein is present at high levels in 20-30% of all breast cancers, and these tumors are more deadly. The role is this protein is complex; fewer than 20% of these tumors respond well to Herceptin, a drug targeted at ErbB2. ***Richard Neve, Ph.D.***, of the ***Buck Institute for Age Research***, Novato, is hunting for the genes that are turned on or off by ErbB2 and by ESX, a protein that may be associated with ErbB2's effect on cells. The goal is to develop better treatments for this type of tumor.
- **SBP-1: A Novel Survivin Binding Protein in Breast Cancer.** Survivin is a molecule that is present in normal breast cells and consistently over-produced in breast cancer cells. Survivin is necessary for tumor cell division and survival; inhibiting survivin's action would stop cancer cells from dividing and trigger them to die. ***Kazuya Okada, M.D., Ph.D.***, of ***The Burnham Institute***, La Jolla, has discovered a protein that binds to survivin, SBP-1. His research team is attempting to unravel the molecular mechanism by which SBP-1 influences the activity of survivin, and explore SBP-1's effect on cell division and cell survival.

**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

- **P130Cas and Anti-Estrogen Resistance of Breast Cancer.** Breast tumors, especially in the early stages, depend on the hormone estrogen for growth. A common therapy uses anti-estrogen molecules to block the chemical changes estrogen initiates in tumor cells. The problem is that tumors eventually become resistant to anti-estrogens and continue to grow. One molecule found in cells that may cause anti-estrogen resistance is p130Cas. ***Marko Rehn, Ph.D.***, of ***The Burnham Institute***, La Jolla, will study the molecule-level mechanisms through which p130Cas causes anti-estrogen resistance, with the goal of finding drugs that can overcome anti-estrogen resistance.

**Mistakes on the Master Blueprint: Molecular Genetics and Gene Regulation**

- **The Role of BRCA1 in Nucleotide Excision DNA Repair.** Mutations in two genes, BRCA1 and BRCA2, are responsible for 5-10% of all breast cancers. ***Anne-Renee Hartman, M.D.***, at ***Stanford University***, Palo Alto, is investigating the role of the normal BRCA1 gene in the normal process of repairing damage to DNA from environmental toxins, including cigarette smoke and ultraviolet radiation. Failure to correctly repair DNA leads to an accumulation of mutated genes, a characteristic of cancer.
- **The Functions of BRCA2 in Repairing DNA Damage.** Women with an abnormal version of the BRCA2 gene are more likely to get breast cancer. But scientists do not understand how loss of the function of the normal BRCA2 gene causes this predisposition to the disease. ***Yi-Ching Lio, Ph.D.***, at the ***Lawrence Berkeley National Laboratory***, is investigating whether the protein produced by the normal BRCA2 gene plays a role in the normal process of repairing damage to cell DNA, and how it plays this role. The theory is that this loss of repair function allows damaged DNA to accumulate in a cell's genes, eventually leading to uncontrolled growth.
- **Regulation of the ATR Checkpoint Response in Breast Cancer.** By the time a cell has turned into cancer, many changes have accumulated in its genes. Genetic mutations occur constantly in normal cells, but special genes–known as DNA damage checkpoints–usually detect and correct them. ***Dawn Yean, Ph.D.***, at ***Stanford University***, Palo Alto, is investigating the ATR gene, which produces one of the first proteins that recognizes damaged DNA. The research team is studying the interaction of the ATR protein with DNA, and searching for other proteins involved in the process.

**Searching the Unknown: Novel Breast Cancer Genes**

- **Pathway-Specific Gene Expression in Breast Cancer Cells.** Approximately 90% of cases of breast cancer are not due to hereditary defects in genes; however, the cancer cells' genes develop defects that occur only in tumors. ***Colleen Sweeney, Ph.D.***, at the ***University of California, Davis***, is using innovative technology to identify a large number of

from the breast that eventually compromises the function of the organ, leads to a critical tumor load (1-2 kg), and overwhelms any therapeutic intervention. Research in metastasis is focusing in the cell surface adhesion receptors and proteases of cancer cells that allow them to migrate, enter the blood/lymph, and exit into other organs. Any breakthroughs that might reduce metastasis and growth in secondary organs is likely to represent a huge advance in reducing deaths from breast cancer.

genes that are involved in the growth and spread of breast cancer cells. The research team is focussing on genes associated with two processes that are part of the growth and development of normal breast cells; abnormalities in these processes have also been implicated in tumor cell growth, survival and movement. The two cell processes are called the ras-Erk pathway and the P13-kinase/Akt pathway.

**Unraveling the Path to Breast Cancer: Tumor Progression**

- **The PTEN/Akt Pathway in Ductal Carcinoma in Situ.** Ductal carcinoma in situ (DCIS) is a pre-cancerous condition of the breast; about 25-30% of DCIS cases progress to become invasive cancer. Right now, there's no way to predict whether DCIS will become cancer or not. ***Shikha Bose, M.D.***, at the ***Cedars-Sinai Medical Center***, Los Angeles, is comparing hundreds of DCIS and invasive breast cancer tissue samples, searching for altered genes. The research team is focussing on genes associated with a recently-identified gene, PTEN, which is frequently lost in invasive breast cancer. PTEN serves as a brake on certain key cell growth processes; losing PTEN opens the way for cancer.
- **Role of Id-2 in Breast Cancer and its Relationship to Id-1.** ***Pierre-Yves Despres, Ph.D.***, at the ***California Pacific Medical Center Research Institute***, San Francisco, is studying a protein called Id-2 that is produced in normal and cancerous breast cells. Breast cancer cells that are able to spread to other body parts normally have low levels of Id-2. The research team will engineer these cells to produce high levels of Id-2, and determine if this keeps them from being able to spread. They will also lower the levels of Id-2 in breast cancer cells that don't have the ability to spread, and see if this makes them develop the ability to spread.
- **Genes That Modulate Dioxin-Induced Breast Cancer.** While inherited susceptibility to breast cancer accounts for 10-15% of all cases, the rest are thought to relate to lifestyle and environmental pollutants. Dioxins are widespread environmental toxins known to cause cancer. They are accumulating in foods, including breast milk. Several studies suggest dioxin may be responsible for some breast cancer cases. ***Quan Lu, Ph.D.***, of ***Stanford University***, will search for genes that either promote or suppress breast cancer initiated by dioxin. The research team will use two techniques. One, RHKO, has been used to discover genes that inhibit tumor growth. The second is microarrays, a technology that allows a researcher to study thousands of genes at the same time.
- **Rodent Model for Human Ductal Carcinoma in Situ.** Improved mammograms detect a large number of very small cancers called ductal carcinomas in situ (DCIS) and lobular carcinomas in situ (LCIS). Some of these will progress to invade the surrounding tissue and become breast cancer; others pose little threat, and there's no way to tell the difference. ***Satyabrata Nandi, Ph.D.***, of the ***University of California, Berkeley***, will induce a large variety of DCIS and LCIS in rats to investigate the structure and need for hormones of DCIS and LCIS that are likely to become breast cancer.

- **Tumor Suppression by Dystroglycan in Breast Epithelial Cells.** ***John L. Muschler, Ph.D.***, of the ***Lawrence Berkeley National Laboratory***, has recently discovered a that molecule called dystroglycan is important to the process that keeps breast epithelial cells (the cells where most cancer arises) attached to the structure that supports them (the basement membrane). Dystroglycan also plays a role in arresting breast cell growth. The molecule is non-functional in most breast cancer. Restoring dystroglycan function in breast cancer cells makes them more like normal breast cells. Dr. Muschler is investigating how dystroglycan functions in normal breast cells and how it suppresses tumors.
- **Are EGF-Receptors Activated by IL-8 in Breast Cancer?** ***Ingrid Schraufstatter, M.D.***, at the ***La Jolla Institute for Molecular Medicine***, is investigating three proteins found in or on cells that may interact to stimulate tumor cells to migrate to other body parts. The three proteins are called IL-8, CXCR2 and the epidermal growth factor receptor (EGFR).
- **Overcoming Drug Resistance in Breast Cancer.** ***Kristiina Vuori, M.D., Ph.D.***, at ***The Burnham Institute***, La Jolla, is investigating the molecule-level interactions caused by a group of proteins called integrins found on the surface of cells. The research team has previously identified specific integrin molecules that trigger processes in breast cancer cells that allow the cells to escape death from chemotherapy drugs. Dr. Vuori's team is also performing preliminary testing of anti-integrin compounds for their ability to make chemotherapy drugs more effective against breast tumors in mice.

# *Prevention and Risk Reduction:*

## *Ending the Danger of Breast Cancer*

Prevention and Risk Reduction:
Ending the Danger of Breast Cancer

# *Prevention and Risk Reduction:*

## *Ending the Danger of Breast Cancer*

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

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

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

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

# Research Conclusions

**Safer Preventive Drugs: Investigating Naturally Occurring Compounds**

**Dietary Indole Analogs for Breast Cancer Prevention.** Indole-3-carbinol–found in cruciferous vegetables, such as cabbage, broccoli, and Brussels sprouts–is a promising breast cancer preventive. However, when it appears naturally in food, indole-3-carbinol isn't potent enough for use as a preventive therapeutic. ***Ling Jong, Ph.D.***, at ***SRI International***, Menlo Park, modified the structure of indole-3-carbinol to create more potent anti-cancer agents. These indole analogs work against various human breast cancer cell lines. In animals, they shrink tumors and can be given orally. These are two highly desirable properties that make indole analogs good candidates for testing as a breast cancer prevention drug. Dr. Jong's team found that their most promising indole analog compounds inhibit the growth of human breast cancer cell lines that require estrogen for growth, as well as those that don't. The indole analogs are highly potent against breast cancer cells that do not respond to tamoxifen, a drug currently used to prevent breast cancer. Against one type of human breast cancer cell, an indole analog was more potent than tamoxifen. The researchers fed low doses of indole analogs to mice; this prevented the growth of mammary tumors (the mouse equivalent of breast tumors) that depend on estrogen. At high doses, the indole analogs stopped the growth of mouse mammary tumors. None of the mice showed any adverse effects. This research shows that indole analogs are strong candidates to be developed into drugs that women–especially those at high risk–could safely take for long periods of time to prevent breast cancer.

**Diet and Other Active Lifestyle Modification: What Women can do Now**

**Diet and Breast Cancer in the California Teachers Study Cohort.** ***Pamela Horn-Ross, Ph.D.***, of the ***Northern California Cancer Center***, Union City, investigated diet as a possible breast cancer prevention strategy. In 1995-96, as part of the California Teachers Study, over 133,000 female teachers and adminis-

trators answered a 16-page questionnaire about their intake of over 100 foods and beverages, and also of vitamins. Dr. Horn-Ross analyzed data from over 111,000 of these women. By the end of 1997, 711 had been diagnosed with invasive breast cancer. No food or beverage appeared to prevent or stimulate breast cancer, except one. Women who drank 20 grams or more of alcohol per day (the amount in two glasses of wine) were more likely to develop breast cancer than women who didn't drink alcohol. The only dietary change this study's findings suggest will help prevent breast cancer is reducing alcohol intake to a drink per day or less.

**Exercise, Hormones, and Cancer Prevention.**
***Donna Williams-Hill, Ph.D.***, of the ***University of Southern California Keck School of Medicine***, Los Angeles, investigated the roles of exercise, hormones, pregnancy, and Vitamin E in the development of breast cancer using the Wistar Furth rat as a model. This rat carries at least three genes that make it susceptible to mammary cancer (the equivalent of breast cancer in humans) and no genes that make it resistant. It is highly susceptible to tumors when given a single dose of a chemical compound called DMBA. The research team found that rats that were exercised had fewer tumors, and the tumors developed later, compared to rats that weren't exercised. The more intense the exercise, the stronger the effect. Pregnancy decreased the number of tumors, but did not increase the amount of time before the first tumor appeared. However, pregnancy was not as effective as exercise alone. Vitamin E had no impact; in fact, rats that exercised and were fed Vitamin E had more tumors than rats that simply exercised. These results indicate that exercise–an amount equivalent to jogging 15 minutes per day, five days per week–is a simple, non-invasive, inexpensive means of cancer prevention. The research team also removed the ovaries of some of the rats and gave them replacement estrogen. These rats did not get tumors at all. This indicates that in order to grow, tumors need some substance the ovaries produce in addition to estrogen, possibly progesterone. This result is interesting in light of the controversy surrounding hormone replacement therapy in post-menopausal women.

# Research in Progress

**Safer Preventive Drugs: Investigating Naturally Occurring Compounds**

**Breast Cancer Prevention with Phytoestrogens in Grape Juice.** Grape juice suppresses breast cancer cell growth by preventing the synthesis of the female hormone estrogen. About 60% of breast tumors in pre-menopausal women and 75% of those in post-menopausal women depend on estrogen for growth. This suggests that drinking grape juice may prevent breast cancer. ***Shiuan Chen, Ph.D.***, at the ***Beckman Research Institute, City of Hope***, Duarte, is isolating compounds from red grape juice and red wine and testing them for their ability to prevent tumor formation in animal cell lines. Dr. Chen's team has found that red wine extract completely stops the action of aromatase, an enzyme that generates estrogen in cells. They have started to study the action of purified extracts from grape juice and red wine in animals. The goal is an affordable preventive medication.

**Breast Cancer Prevention by Inhibition of Estrogen Action.** Many types of breast cancer need the female hormone estrogen to develop and grow. However, estrogen has enormous benefits to most other tissues in the body. So researchers are looking for ways to reduce estrogen action in the breast, without reducing estrogen in the rest of the body. ***Vicki L. Davis, Ph.D.***, at ***Cedars-Sinai Medical Center***, Los Angeles, is studying mice that have been genetically engineered to develop tumors in the mammary gland (analogous to the breast in humans). The test group of mice also have a gene, ERdelta3, that appears to block estrogen action in the breast, inhibit the growth of tumors, and work in the presence of normal estrogen levels. If this turns out to be true, it might be possible eventually to devise a therapy that turns on the ERdelta3 gene to inhibit estrogen action in the breast, while maintaining normal estrogen levels in the rest of the body. So far, the mice with the ERdelta3 gene have fewer tumors than control group mice, and the tumors appeared at later ages.

**Breast Cancer Prevention by Analogs of EGCG from Green Tea.** ***Nurulain Zaveri, Ph.D.***, at ***SRI International***, Menlo Park, is building on previous successful CBCRP-funded research to improve the breast cancer preventive action of a compound found in green tea, epigallocatechin-3-gallate

(EGCG). Because of the way EGCG is absorbed and digested in the body, a woman has to drink 8-10 cups of green tea per day to get a preventive effect. Since each cup contains 70 mg. of caffeine, drinking large amounts of green tea leads to caffeine-related side effects, a problem in current studies where women are drinking green tea. This year, Dr. Zaveri has synthesized a chemically-modified version of EGCG. In the lab, this EGCG analog inhibits the growth of breast cancer cells, both those that need estrogen for survival and those that do not. Dr. Zaveri has also set up a method for testing whether this EGCG analog might be better absorbed in the human body. During the coming year, her team will synthesize more chemically-modified versions of EGCG and test them for action against breast cancer cells and potential ease of absorption in the human digestive tract.

**Mechanisms of Reduced Metastasis by Conjugated Linoleic Acid.** Conjugated linoleic acid is a naturally-occurring compound found in some sources of dietary fat, including beef and dairy products. In small amounts, it has been shown to reduce the spread of mammary cancer in mice. ***Kent L. Erickson, Ph.D.***, of the ***University of California, Davis***, is investigating how conjugated linoleic acid can reduce the growth and spread of tumors. Dr. Erickson has found that mice fed various amounts of conjugated linoleic acid produced lower levels of proteins that are known to enhance the formation of tumors. It took longer for tumors to form in mice fed conjugated linoleic acid than in mice with a diet free of the substance. Fewer tumors spread to the lung in mice fed conjugated linoleic acid, even at a level of 0.1% of the diet. Conjugated linoleic acid also appears to keep breast cancer cells from lodging in the lung and growing, even after they have spread. At the levels it was fed to mice, conjugated linoleic acid does not appear to be harmful to humans; this study is providing additional evidence to support testing it in humans.

**Diet and Other Active Lifestyle Modification: What Women can do Now**

**Bovine Leukemia Virus Infection and Human Breast Cancer Risk.** ***Gertrude Buehring, Ph.D.***, at the ***University of California, Berkeley***, is testing the speculative hypothesis that bovine leukemia virus is associated with an increased risk of breast cancer. She has previously shown that a majority of women have antibodies to bovine leukemia virus. This virus is found in beef and milk and can be transmitted to humans. It causes mammary tumors in animals (the equivalent of human breast tumors). The antibodies in women may be a response to a live virus, or to a harmless, de-activated part of the virus, and it isn't possible to determine which through laboratory testing. Dr. Buehring is using a case-control study of 338

women to see if women with breast cancer are more likely to have the virus in their breast tissue than women with no history of breast cancer. So far, she has collected 40 tissue samples and solved some of the technical problems of detecting the virus in the samples. If the rate of infection with the bovine leukemia virus is significantly higher in breast tumors than in normal breast tissue, this would justify launching a larger study to determine if the virus can cause some breast cancer.

**Estrogen Metabolizing Genes, Soy, and Breast Cancer in Asians.** ***Anna H. Wu, Ph.D.***, at the ***University of Southern California***, Los Angeles, is studying genes that may interact with soy foods in the diet of Asian women to affect the development of breast cancer. Building on two studies previously funded by the CBCRP, Dr. Wu is collecting and analyzing blood specimens from 1,300 Asian women with breast cancer and an equal number from women who don't have the disease. She is investigating whether the risk of breast cancer is higher in women with particular types of CYP17 and COMT genes, two genes that metabolize the female hormone estrogen, and whether these genes interact with soy in the diet to cause breast cancer. Preliminary results suggest that women with one type of CYP17 gene have a small increased risk for breast cancer.

**How Hormones or Environmental Contaminants Interact with Other Known Risk Factors**

**Upregulation of BRCA1 as a Cancer Preventive Strategy.** ***Colin K. Hill, Ph.D.***, and ***Donna Williams-Hill, Ph.D.***, at the ***University of Southern California,*** Los Angeles, are investigating how tumor suppressor genes interact with hormones in the breast, and how these interactions might translate into breast cancer risk. Normal BRCA1/BRCA2 genes help to prevent cancer. The hypothesis of this study is that cells need a minimum level of the proteins produced by these genes to keep from forming tumors, and hormone levels may be associated with how much BRCA1 protein cells produce at various stages of development. The team is analyzing the amount of BRCA1 protein in cells from the mammary glands of rats (the mammary gland in rats is the equivalent of the breast humans) at various stages of development. They eventually propose to study the level of BRCA1 protein in breast tumor tissue and normal breast tissue. The ultimate aim is to understand the critical points in breast development where risk is greatest so that strategies can be designed to offset that risk. It may be possible, for example, to increase the amount of BRCA1 protein in cells during susceptible years of development, or later in life.

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

**Genetic and Environmental Modifiers of Breast Cancer Risk.** ***Argyrios Ziogas, Ph.D.***, of the ***University of California, Irvine***, is investigating how three types of genes interact to raise or lower breast cancer risk. The first type of genes are BRCA1 and BRCA2, on which abnormalities are already known to increase a woman's risk of breast cancer. The second type of gene interacts with cancer-causing chemicals in the environment and may elevate breast cancer risk. The third type of gene is involved in the metabolism of the hormone estrogen. Dr. Ziogas is using data from the unique resource of a breast and ovarian cancer registry of 1,176 families, a questionnaire providing environmental exposure and lifestyle information, and analysis of the families' genes. Results should add to our understanding of the BRCA genes' role in breast cancer, and of interactions between BRCA genes and genes that interact with environmental contaminants and estrogen. This could lead to improved individualized risk prediction, and targeted preventive strategies.

# *Research Initiated in 2001*

**Safer Preventive Drugs: Investigating Naturally Occurring Compounds**

**Evaluation of Essiac Tea to Prevent Mammary Tumors.** Essiac tea, an herbal mixture introduced in the 1920s to treat cancer, is commonly used today by breast cancer survivors to try to prevent recurrence. The individual herbs used in one Essiac tea mixture have biological activities associated with decreasing cancer risk. Many herbs used in Essiac tea have long histories of use in Asian diets and medicine. Yet there are no published scientific studies evaluating Essiac tea's effectiveness in preventing breast cancer. ***Michelle Bennett, Ph.D.***, of the ***Lawrence Livermore National Laboratory***, will investigate whether Essiac tea inhibits mammary tumor growth in mice and rats.

# *Sociocultural, Behavioral, and Psychological Issues:*

## *The Human Side*

# *Sociocultural, Behavioral, and Psychological Issues:*

## *The Human Side*

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

# Research Conclusions

**Perceived Support in the Work Place and Return to Work.** ***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***, in a pilot study investigated problems women with breast cancer face after returning to work. The team surveyed 116 women who had undergone breast cancer surgery. Forty percent had changed jobs after surgery; 17% were terminated or laid off. Twenty-nine percent felt they were harassed on the job due to breast cancer. Average monthly income dropped from $1,812 before surgery to $1,167 after. Caucasian women were off work an average of 23 weeks, African American women an average of 37 weeks, and Latinas, 11 weeks. African American women were twice as likely as Caucasian women not to be working after one year. Women who had children at home, were enrolled in disability insurance or who received a mastectomy were more likely to take off more time from work. Latinas returned to work more quickly, even when their disease was advanced. Very few had disability benefits. These findings may be related to their immigration status. The results of this study provide the basis for a larger research study funded in 2001 by the CBCRP.

**Effectiveness of Electronic Support Groups for Breast Cancer.** ***Morton A. Lieberman, Ph.D.***, of the ***University of California, San Francisco***, tested the feasibility of conducting professionally-led support groups for women with breast cancer over the Internet. Since rural women may be unable to take part in face-to-face groups, the research team recruited two-thirds of their study participants from rural areas. After taking part in online support groups during the 16-week experiment, women with breast cancer had significant decreases in depression, expressed more zest for life, saw new possibilities, deepened their spiritual lives, and had fewer negative reactions to pain they were experiencing. Women who dropped out of the groups had, at the onset, a low ability to contain their anxiety and

suppress negative thoughts about cancer. Pain was also interfering more with their lives. Online support groups are less likely to help women with these characteristics. The researchers found that online support group leaders need to intervene in ways different from those face-to-face leaders use. Online support groups don't provide any cues from tone of voice, body language or facial expression, so leaders must more often ask for clarification, express their own reactions, help the group focus on one issue at a time, direct members to interact with each other, and use metaphor and anecdotes to draw out members' feelings and reactions.

**Quality of Life**
When new breast cancer treatments are tested on humans, the U.S. and Canadian governments now require researchers to find out not just how the treatment works against the disease, but how it affects the patient's quality of life. Researchers and practicing physicians are also paying more attention to quality of life. Both developments have come since the upsurge in breast cancer activism over the past decade. Quality of life includes psychological well-being (such as anxiety, depression, mental functioning); physical functioning (such as the ability to work, play and be self-sufficient); bodily symptoms (such as pain, premature menopause, hair loss, nausea); social relationships, and a general sense of well-being that includes spirituality. For some patients, especially the elderly, quality of life is as important as added years of survival. QOL is measured by having the patient fill out a questionnaire.

# Research in Progress

**Breast Cancer Prevention: The Views of Women and Physicians.** ***Celia Kaplan, Ph.D.***, of the ***University of California, San Francisco***, is investigating how doctors advise their patients about breast cancer risk, and the knowledge, attitudes and practices of women and physicians with regard to breast cancer prevention. She is conducting a telephone survey of 1,200 women ages 40-75, from four ethnic groups, who have recently had mammograms. Women at high and low risk of breast cancer from each ethnic group will be included in the survey. Dr. Kaplan is also surveying 1,000 randomly selected Bay Area physicians about their views on obstacles to breast cancer prevention. The research team has drafted questionnaires for both women and physicians, and begun designing a database to analyze future data. Next, they will hold focus groups to improve the questionnaires, recruit participants, and begin the telephone surveys.

**Mechanisms of Radiation-Induced Fatigue in Breast Cancer.** Fatigue is one of the most common side effects of radiation treatment, significantly disrupting the lives of women who receive this therapy. Little research has been done on radiation-induced fatigue, and women have few resources to help them manage this symptom. ***Juliene Bower, Ph.D.***, at the ***University of California, Los Angeles***, is investigating factors that contribute to fatigue during radiation treatment. The team is looking into changes in the immune system, as well as psychological and behavioral responses women have to breast cancer. They are collecting blood samples and questionnaires from women diagnosed with early-stage breast cancer–before, during, and after radiation treatment. The research team has recruited ten women so far, and plan to recruit more over the coming year. 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.

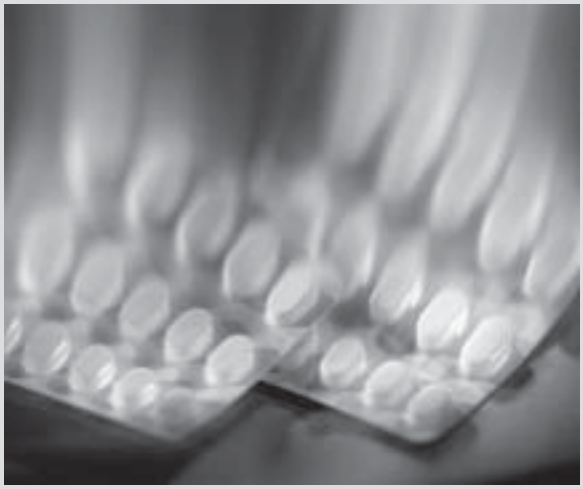
**Communicating Breast Cancer Risk in Ethnically Diverse Women.** Women can now take the chemotherapy drug tamoxifen to reduce their risk of breast cancer. Other preventive medications are likely to become available. ***Linda Lillington, R.N., D.N.Sc.***, at ***Harbor-UCLA Research & Education Institute***, is investigating how best to communicate complex issues about breast cancer risk reduction. Patients need education to make informed decisions about risk-reduction therapy with their health care providers. Careful consideration must be given to individual risk factors and the potential risks and benefits of prescribed treatments. There are currently no educational materials

that health care providers can use to effectively present quantitative information about recent breast cancer prevention results to ethnic minority women. Dr. Lillington is developing, and beginning to evaluate, educational materials written at a 6th-grade level and designed to give English-speaking and Spanish-speaking women at a public hospital a clear understanding of the risks and benefits of taking tamoxifen to reduce their risk of breast cancer. To date, the research team has held focus groups for health care providers, as well as separate groups for African American, Hispanic and Caucasian women. Preliminary results show that women over 50 feel less vulnerable to breast cancer and that women in their 40s often seek care because they know someone recently diagnosed with breast cancer.

**Cognitive Changes After Adjuvant Therapy for Breast Cancer.** Many breast cancer patients who receive chemotherapy say that they suffer memory and concentration problems, even years after therapy. Some recent publications also suggest that cognitive deficits may occur in women treated with high-dose or standard post-operative chemotherapy. ***Rebecca Rausch, Ph.D.***, at the ***University of California, Los Angeles***, is investigating possible cognitive changes in four groups: (1) breast cancer patients receiving standard-dose adjuvant chemotherapy after surgery; (2) breast cancer patients treated with anti-estrogen (tamoxifen) therapy after surgery; (3) breast cancer patients not treated with chemotherapy or hormonal therapy; and (4) healthy women with no history of cancer. Dr. Rausch is also investigating the relationship of any cognitive impairments to hormone changes induced by therapy, and assessing the role of factors such as menstrual history, age, educational level and tumor stage. Preliminary data suggests that women scheduled to undergo chemotherapy do not rate their memory differently from other individuals.

**Communication, Content, and Impact of Genetics in Breast Cancer.** ***Deborah MacDonald, R.N., M.S., C.S.***, at the ***City of Hope National Medical Center***, Duarte, is investigating how to improve genetic counseling and testing services for women who may have inherited a higher-than-average risk for breast cancer. Using questionnaires and focus groups, the research team is aiming to discover the motivations, concerns and characteristics of women who seek genetic counseling and testing. The team will also measure the impact of counseling and testing on the women's perceptions of their risk of cancer, their concerns, the actions they take to reduce their risk, and their moods. Finally, the research team in investigating why some women for whom genetic testing is appropriate decide to get tested and others do not. To date, 275 women have taken part in the study, and 103 have agreed to participate in focus groups. Study results will allow health care professionals to provide more appropriate and responsive care to women who seek genetic counseling, and also educate health care professionals about the complex ethical, social, medical, psychological, and

legal issues involved. Results may also lead to more appropriate referrals of women for genetic counseling and testing, ultimately contributing to the prevention and earlier detection of breast cancer.



**Tamoxifen Prevention: Is it Acceptable to Women at Risk?** The chemotherapy drug tamoxifen has been shown to reduce the incidence of breast cancer in women at high risk for the disease who have been enrolled in clinical trials. However, numerous concerns remain about tamoxifen's potential adverse effects and the drug's benefits for high-risk women in the general population. ***Joy Melnikow, M.D., M.P.H.***, of the ***University of California, Davis***, is developing a deeper understanding of how women at high risk of breast cancer weigh the risks and benefits of tamoxifen. She has developed an educational script, which includes a flip chart and color-coded beads to represent probability of risk, to be used to educate women at high risk for breast cancer about the potential benefits and risks of tamoxifen. After interviewing 183 white, Asian, Latina, African American and other women, Dr. Melnikow has found that women who are eligible to take tamoxifen greatly over-estimate their risk of getting breast cancer. After receiving the education developed for this study, the number of women who were inclined not to take tamoxifen increased from 28% to 49%.

**Breast Cancer Survivorship: Partner's Role in Recovery.** The transition from being a breast cancer patient on active treatment to being a survivor on long-term follow-up can be upsetting and disruptive. This is especially true for women who don't get support from their intimate partners. ***Beth E. Meyerowitz, Ph.D.***, of the ***University of Southern California***, Los Angeles, is investigating how partners' reactions during this transition relate to patients' quality of life, relationship adjustment, personal growth, and coping. She has developed, designed, and printed questionnaires. Ninety-five partners of women with breast cancer have completed the first questionnaire, two months after the women complete treatment. Partners will also complete a second questionnaire at a later date. Understanding the role that partners play in patient adjustment will enable medical teams to provide couples with information to enhance quality of life and communication.

**Improving Quality of Life in Older Women after Breast Cancer.** ***Rose Maly, M.D., M.S.P.H.***, at the ***University of California, Los Angeles***, has found that newly-diagnosed older and ethnic minority breast cancer patients are less likely to receive a wide range of breast cancer-specific information, compared to younger and white patients. The types of information covered in this study included books, videos, pathology reports, and information provided in conversations with physicians about tumor aggressiveness and chance of recurrence. Although they received less of this information, older and minority patients rate the informational sources and topics as more helpful than do white patients. In the general population, women who receive more information are more likely to have a lumpectomy rather than a mastectomy. Differences in the amount of information older and minority women receive may account for differences in the treatments they receive.

**Alternative Support for Rural and Isolated Women in an HMO.** ***Cheryl Koopman, Ph.D.***, ***Stanford University***, and ***Mary Anne Kreshka, M.A.***, ***Sierra Nevada Memorial Hospital Cancer Center***, are investigating a support alternative for women with breast cancer who are psychologically, socially or geographically isolated. The team has adapted a workbook-journal developed in a pilot CBCRP study. They have enrolled 71 women in the study and are continuing to enroll more. The research team is assessing the women three and six months after diagnosis, to determine whether receiving the workbook-journal reduces the women's distress and increases their coping skills, compared to women who do not receive the workbook-journal. The team will also examine characteristics of women who benefit most from the workbook-journal.

**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 mammograms. The research team has surveyed 552 Hmong women in three communities to assess current community practices, breast cancer screening rates,

and breast health resources. They are in the process of holding culturally-tailored breast health workshops with 451 of the women. The team is also including 300 Hmong men in the workshops. Workshop materials developed for this study include a flip chart, a brochure, a video, and a key chain made of beads that represent various sizes of lumps that can be detected by different forms of screening. After the workshops are completed, the team will assess the women for changes in breast health knowledge and attitudes.

**Beliefs and Risks of Breast Cancer Among African Immigrants.** Cultural beliefs affect women's health care behavior. Understanding cultural beliefs can help shed light on why some groups of women don't get early detection services and tend to consult a doctor when their disease has progressed to later stages. Women diagnosed with breast cancer in Africa are, on average, a decade younger than their counterparts in this country, and the disease is most often advanced at the time of diagnosis. ***Yewoubdar Beyene, Ph.D.***, of the ***University of California, San Francisco***, is conducting a qualitative anthropological study. He has held in-depth interviews with 20 African immigrant women and held focus groups with 100. The goal is to identify culturally-specific factors that influence how African immigrant women in California understand breast cancer symptoms and perceive their risks, as well as how these beliefs create barriers to early detection. Data from this study suggests that immigrant African women do not generally feel comfortable with breast self-examination, even in private, because touching the breast is considered sexual. They often associate breast cancer with death. African immigrant women generally have little knowledge about treatments available when a diagnosis is made early. The most common consequence of breast cancer they mention and fear is mastectomy. Many Africans believe in reincarnation, and that a person who has body parts removed will return with those body parts missing. Disability and disfiguring carry strong stigma that affects the whole family; therefore women with breast cancer never disclose their illness to others and have no social support outside of their families. The media and current guidelines are not reaching African immigrant women. Small group discussions seem to be the best way to educate this population.

**Breast Cancer Screening in Women Surviving Hodgkin's Disease.** Women who had radiation treatment for Hodgkin's disease have a risk of breast cancer 5.35 times higher than the general population. Survivors of Hodgkin's disease also get breast cancer at younger ages. ***Steven L. Hancock, M.D.***, of ***Stanford University***, Palo Alto, is examining how being notified of this increased risk emotionally impacts survivors of Hodgkin's disease. He is also evaluating whether the women are getting breast cancer screening, and investigating whether telephone counseling helps decrease the emotional impact of learning about being at high risk and increases the women's rates of screening for breast cancer. So far, 65 women are taking part in the study, and Dr. Hancock is recruiting more participants. A complicating factor is that many of the Hodgkin's disease survivors are under age 27, the minimum appropriate age for screening mammograms.

# Research Initiated in 2001

- **Women with Breast Cancer: Quality of Life and Diet Adherence.** A diet that includes high amounts of vegetables, fruit and fiber may protect women from recurrence of breast cancer. ***Wayne A. Bardwell, Ph.D.***, at the ***University of California, San Diego,*** is looking for personal characteristics that might determine who will stick with this type of strict diet and investigating whether the diet improves women's mood, daily functioning and relationships. The team will also look at the women's use of dietary supplements and the role that hot flashes–a common problem after breast cancer treatment–have on how women feel and function.
- **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. They will also investigate the psychological characteristics of women who benefit from Internet support groups and determine which processes make Internet support groups function best.
- **A Network-Based Intervention For Chamorros in Southern California.** ***Sora Park Tanjasiri, Ph.D.***, of the ***University of California, Irvine***, is collaborating with Lola Sablan-Santos, of the community organization Guam Communications Network, Inc., in Long Beach. The research team is testing the effectiveness of using lay health leaders to provide information about breast health and breast cancer to Chamorro women (Chamorros are people indigenous to the Mariana Islands, including Guam).
- **Breast Cancer Prevention and Control Among Deaf Women.** Breast cancer and breast health programs are often inaccessible and inadequate for women who are deaf or hard of hearing. Little research has been done on deaf women and breast cancer. ***Barbara Berman, Ph.D.***, of the ***University of California, Los Angeles***, and ***Heidi B. Kleiger***, of the ***Greater Los Angeles Council on Deafness, Inc.***, will conduct the first-ever exploratory research to obtain information necessary to craft excellent, tailored breast health and breast cancer programs for deaf and hard-of-hearing women.
- **Influence of Child's Stress on Women with Breast Cancer.** ***Elen Levine, Ph.D.***, of the ***California Pacific Medical Center Research Institute***, San Francisco, and ***Dalia Drucker, Ph.D.***, of the ***California School of Professional Psychology***, Alameda, are investigating how teenagers from various ethnic groups react emotionally and cope with their mothers being treated for breast cancer. The team will investigate factors that might influence the teenager's reactions, including the severity of their mother's illness, the intensity of side effects from her treatment, increased household responsibilities the teenager might have to take on, and the teenager's social support. The team is also looking at how the teenager's reaction affects the mother's quality of life.

- **Efficacy of a Community Program in Increasing Access to STAR.** Although African American women have a lower rate of breast cancer than other ethnic groups, their death rate from the disease is higher. African American women are under-enrolled in clinical trials that test whether chemotherapy can prevent breast cancer. ***Patricia Ganz, M.D.*** of the ***University of California, Los Angeles***, and ***Kathleen Brown, M.D.***, of the ***Association of Black Women Physicians***, Los Angeles, are collaborating on methods to increase awareness of chemotherapy prevention trials among African American physicians and women. The goal is a tested method to increase African American participation in these trials.

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Walter Price, Dr. P.H.

# *California 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 non-profit 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.

**MARY ANN JORDAN**
(7/1/98 - 6/30/01)

# chair

Mary Ann Jordan, Ph.D., earned her BA in mathematics, magna cum laude from the University of Minnesota, and her Ph.D. in cell biology from the University of Rochester, Rochester NY. At the University of Rochester she was an NSF and NIH graduate fellow. She has taught and conducted research at Washington University, University of Michigan, and Utah State University. For the last 20 years, as a researcher and professor at the University of California, Santa Barbara, Dr. Jordan has focused on the mechanisms of anti-mitotic, anti-cancer drugs including vinblastine, taxol, and novel drugs such as the cryptophycins and dolastatins in binding to microtubules, suppressing microtubule dynamics, and the completion of mitosis and cell proliferation. She is interested in control of growth and proliferation of cancer cells and overcoming the development of resistance to anti-tumor drugs.

**BARBARA BRENNER**
(7/1/98 - 6/30/01)

Ms. Brenner was 41 years old when she was diagnosed with breast cancer. She quickly learned how little was known about breast cancer and how much misinformation was being given to the public about the disease. She joined the board of Breast Cancer Action in September 1994 and became the organization's Executive Director a year later. Breast Cancer Action is a San Francisco-based national grassroots organization that carries the voices of people affected by breast cancer to compel and inspire the changes necessary to end the breast cancer epidemic. As Executive Director, Ms. Brenner is responsible for implementation of the organization's programs designed to dispel the myths about breast cancer, to inform the public about the realities of the disease, and to encourage more people to do something–besides worry–about the breast cancer epidemic. She represents Breast Cancer Action on committees addressing a wide-range of breast cancer issues, writes for Breast Cancer Action's widely-acclaimed bi-monthly newsletter, and is a frequent public spokesperson on issues ranging from detection to treatment to prevention.

# vice chair

**SANDRA WALSH**
(7/1/00 - 6/30/03)

# chair

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.

**TERESA BURGESS**
(7/1/99 - 6/30/02)

Teresa L. Burgess, Ph.D., earned her BA in Biochemistry with highest honors from the University of California, Berkeley, after receiving a solid educational foundation from California public schools, including Diablo Valley Community College. Following a move across the San Francisco bay, she received her Ph.D. for original research on peptide hormone secretion from UC San Francisco. As a Helen Hay Whitney Fellow, Dr. Burgess continued to investigate the basic cellular mechanisms of membrane trafficking at UC Santa Barbara. In 1992 she accepted a position as Research Scientist at the successful biotechnology company, Amgen Inc., where she has continued both basic and applied cell biological research. Her investigations have led to numerous peer reviewed research publications relevant to diabetes, cancer, cardiovascular disease, Alzheimer's, and most recently osteoporosis and other metabolic bone diseases. Dr. Burgess brings to the Council not only her scientific expertise, but also an enthusiastic desire to contribute to a healthier future for all women.

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**BARBARA BRENNER**
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**AKUA JITAHADI**
(7/1/99 - 6/30/02)

Akua Jitahadi is a longtime community activist who has organized around such issues as homelessness, human rights, and women imprisonment. She is a co-founder of Black Women for Wellness, a community-based organization that focuses on health issues impacting black women. Ms. Jitahadi coordinates the organization's 'Keep in Touch...Do BSEs,' an outreach and education program. She is also a member of the Los Angeles County Partnered for Progress African American Breast Cancer Taskforce.

**MICHELE RAKOFF**
(7/1/98 - 6/30/01)

Michele Rakoff is a breast cancer survivor and advocate. She is a Board Member of the Los Angeles Breast Cancer Alliance (LABCA) and the California Breast Cancer Organizations (CABCO). Ms. Rakoff has participated in the Department of Defense (DOD) Breast Cancer Research Program and the California Breast Cancer Research Program (CBCRP) grant review process as a consumer advocate. She continues to work for the passage of legislation to increase research funding and to ensure access of care for all women dedicated to patient care and psychosocial programs. She is the Director of Breast Friends, a peer support mentoring program, at Long Beach Memorial Breast Center.

**SANDRA WALSH**
(7/1/00 - 6/30/03)

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.

**DIANA CHINGOS**
(7/1/00 - 6/30/03)

Diana Chingos serves on the Board of Directors of the Los Angeles Breast Cancer Alliance, a grassroots education and advocacy organization that seeks to empower women to make informed choices about their treatment and health based on medical evidence. She also 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 "first-hand 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 2000 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.

## LAUREN JOHN
(7/1/00 - 6/30/03)

Lauren John, 43, was diagnosed with breast cancer six years ago, while in the last semester of a graduate journalism program at Boston University. Six months after completing chemotheraphy and getting her diploma, she moved west to Silicon Valley when her husband George was recruited to join an Internet startup company.

Lauren is now a freelance science and technology writer based in a home office in Menlo Park, California. She also works part time as a reference librarian at the Menlo Park Public Library. Prior to launching her freelance writing career, Lauren worked for many years in New York City as a corporate librarian for employers, including the accounting/ consulting firm of Price Waterhouse and the FIND/SVP market research firm.

In February 2001, Lauren was named to the board of Breast Cancer Action in San Francisco. She continues her membership in three other outstanding breast cancer organizations: the Massachusetts Breast Cancer Coalition, which provided her a great deal of information and support when she underwent cancer treatment in Boston; the Community Breast Health Project in Palo Alto, which assists her with research for her articles on breast cancer; and the National Breast Cancer Coalition which provided her with science and advocacy training through Project LEAD. In July 2001, she was appointed as a consumer reviewer to the federal Department of Defense Breast Cancer Research Program.

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

## FLORITA MAIKI
(7/1/00 - 6/30/03)

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

Prior to BHAWD, she has worked over ten years in community and hospital based agencies and organizations in program planning/development and evaluation capacity, serving people with disabilities. Throughout her tenure she has had extensive experience and responsibility in developing and monitoring grant proposals and other developement efforts.

**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 California 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.

# ex-officio

## TERESA BURGESS
(7/1/99 - 6/30/02)

Teresa L. Burgess, Ph.D., earned her BA in Biochemistry with highest honors from the University of California, Berkeley, after receiving a solid educational foundation from California public schools, including Diablo Valley Community College. Following a move across the San Francisco bay, she received her Ph.D. for original research on peptide hormone secretion from UC San Francisco. As a Helen Hay Whitney Fellow, Dr. Burgess continued to investigate the basic cellular mechanisms of membrane trafficking at UC Santa Barbara. In 1992 she accepted a position as Research Scientist at the successful biotechnology company, Amgen Inc., where she has continued both basic and applied cell biological research. Her investigations have led to numerous peer reviewed research publications relevant to diabetes, cancer, cardiovascular disease, Alzheimer's, and most recently osteoporosis and other metabolic bone diseases. Dr. Burgess brings to the Council not only her scientific expertise, but also an enthusiastic desire to contribute to a healthier future for all women.

## I. CRAIG HENDERSON
(7/1/00 - 6/30/03)

I. Craig Henderson, M.D., is Adjunct Professor of Medicine at the University of California, San Francisco (UCSF); a member of the staff at the UCSF/Mount Zion Cancer Center; President, Access Oncology, Inc.; and a member of the board of ALZA Corporation in Mountain View, California.

He was a member of the Harvard faculty for 18 years before moving to UCSF where he was Professor of Medicine, Chief of Hematology/Oncology, and Associate Director of the Cancer Center. In 1995 he became Chief Executive Officer and Chairman of SEQUUS Pharmaceuticals, Inc., Menlo Park, California, and continued there until the merger with ALZA Corporation in 1999.

Dr. Henderson founded the multidisciplinary Breast Evaluation Center at the Dana-Farber Cancer Institute. At UCSF he developed the Bay Area Research Program funded by a Specialized Program of Research Excellence (SPORE) grant from the National Cancer Institute. He has served as chairman of the FDA's Oncological Drug Advisory Board and is a member of the National Blue Cross/Blue Shield Association technology assessment panel.

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.

industry

**ROBERT CARLSON**
(7/1/00 - 6/30/03)

Robert W. Carlson received his M.D. degree from Stanford University School of Medicine and did his internship and junior residency in internal medicine at Barnes Hospital in St. Louis, Missouri. He returned to Stanford for his senior residency and postdoctoral fellowship in medical oncology. He joined the faculty at Stanford after his fellowship and is Professor of Medicine at Stanford University. His primary areas of investigation include breast cancer clinical trials and the use of computer-based systems to assist health care providers in the delivery of patient care. Dr. Carlson serves as Chair of the Breast Cancer Guidelines Committee and the Breast Cancer Risk Reduction Guidelines Committee for the National Comprehensive Cancer Network (NCCN).

## medical specialist

**IRENE LINAYAO-PUTMAN**
(7/1/00 - 6/30/03)

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.

**M. ELLEN MAHONEY**
(7/1/00 - 6/30/03)

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."

## non-profit organization

**HODA ANTON-CULVER**
(7/1/00 - 6/30/03)

Hoda Anton-Culver, Ph.D., is Professor and Chief of the Epidemiology Division in the Department of Medicine at the University of California, Irvine. She received her baccalaureate degree in pharmaceutical chemistry from the University of Alexandria in Egypt in 1964 followed by a Ph.D. in Epidemiology and Biochemistry at St. Andrews University, Scotland in 1968. Following her doctoral degree, she began her academic career as a Lecturer at McGill University Medical School, Canada. From 1971 to 1978, she joined Dr. Henry Lynch as an Assistant and then as Associate Professor in the Department of Preventive Medicine and Public Health at Creighton University School of Medicine, Nebraska. Since 1978, she has been at the University of California, Irvine, as an Associate Professor and then as Professor and Chief of the Epidemiology Division in the Department of Medicine. She also holds a joint appointment with the School of Social Ecology at UC Irvine, and an adjunct appointment with the San Diego State University Graduate School of Public Health.

**SUSAN BLALOCK**
(7/1/99 - 6/30/02)

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

**MARY ANN JORDAN**
(7/1/98 - 6/30/01)

Mary Ann Jordan, Ph.D., earned her BA in mathematics, magna cum laude from the University of Minnesota, and her Ph.D. in cell biology from the University of Rochester, Rochester NY. At the University of Rochester she was an NSF and NIH graduate fellow. She has taught and conducted research at Washington University, University of Michigan, and Utah State University. For the last 20 years, as a researcher and professor at the University of California, Santa Barbara, Dr. Jordan has focused on the mechanisms of anti-mitotic, anti-cancer drugs including vinblastine, taxol, and novel drugs such as the cryptophycins and dolastatins in binding to microtubules, suppressing microtubule dynamics, and the completion of mitosis and cell proliferation. She is interested in control of growth and proliferation of cancer cells and overcoming the development of resistance to anti-tumor drugs.

scientist

**TAMMY TENGS**
(7/1/99 - 6/30/02)

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

**ANNA WU**
(7/1/00 - 6/30/03)

Anna M. Wu, Ph.D., is an Associate Professor of Molecular Biology at the Beckman Research Institute of the City of Hope, in Duarte, CA, and an adjunct Associate Professor in the Dept. of Molecular and Medical Pharmacology, UCLA School of Medicine. She graduated from Radcliffe College, Harvard University, with an A.B. in Biochemistry, and obtained her Ph.D. in the Dept. of Molecular Biophysics and Biochemistry, Yale University. Postdoctoral studies were conducted at Yale University and at the University of California, San Francisco. In 1984 Dr. Wu joined the research staff at the City of Hope, where her work has focused on applications of molecular biology to the diagnosis and treatment of cancer. Current research interests include development of genetically engineered antibodies for imaging, radio-immunotherapy, and biological approaches to cancer therapy. 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.

**ELAINE ASHBY**
(7/1/00 - 6/30/03)

Elaine Ashby received her Masters degree in Mechanical Engineering from Stanford University. She practiced engineering for two years before entering medical school at the University of California, San Francisco. She received her MD degree and residency training from University of California, San Francisco. 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 ultra-sonography for breast imaging, and new technologies for prostate cancer detection.

| INSTITUTION/PI/TITLE | DUR | DIRECT | INDIRECT | TOTAL |
|---|---|---|---|---|
| Association of Black Women Physicians | | | | |
| *Kathleen Brown, M.D..* | | | | |
| Efficacy of a Community Program in Increasing Access to STAR | 1.5 | $47,445 | $11,861 | $59,306 |
| Buck Institute for Age Research | | | | |
| *Richard Neve, Ph.D.* | | | | |
| Molecular Characterization of ErbB2 Positive Breast Cancers | 2 | $80,000 | $6,400 | $86,400 |
| California Institute of Technology | | | | |
| *Nadeem Moghal, Ph.D.* | | | | |
| Genetic Analysis of ErbB Signaling in C. Elegans | 2 | $80,000 | $6,400 | $86,400 |
| California Pacific Medical Center Research Institute | | | | |
| *Pierre-Yves Desprez, Ph.D.* | | | | |
| Role of Id-2 in Breast Cancer and its Relationship to Id-1 | 2 | $190,457 | $106,084 | $296,541 |
| *Daryl Drummond, Ph.D.* | | | | |
| Enhanced HER-2 Directed Liposomal Therapeutics | 3 | $299,913 | $165,269 | $465,182 |
| *Ellen Levine, Ph.D., M.P.H.* | | | | |
| Child's Stress During Mother's Treatment for Breast Cancer | 1.5 | $100,000 | $29,000 | $129,000 |
| SUBTOTAL , CPMCRI | | $590,370 | $300,353 | $890,723 |
| California School of Professional Psychology | | | | |
| *Dalia Ducker, Ph.D.* | | | | |
| Child's Stress During Mother's Treatment for Breast Cancer | 1.5 | *Collaborative Award* | | |
| Cedars-Sinai Medical Center | | | | |
| *Shikha Bose, M.D.* | | | | |
| The PTEN/Akt Pathway in Ductal Carcinoma In Situ | 1 | $100,000 | $0 | $100,000 |
| Greater Los Angeles Council on Deafness | | | | |
| *Heidi Kleiger* | | | | |
| Breast Cancer Prevention and Control Among Deaf Women | 1.5 | *Collaborative Award* | | |

| INSTITUTION/PI/TITLE | DUR | DIRECT | INDIRECT | TOTAL |
|---|---|---|---|---|
| Guam Communications Network, Inc. | | | | |
| *Lola Sablan-Santos* | | | | |
| A Network-Based Intervention for Chamorros in Southern California | 3 | $293,437 | $73,359 | $366,796 |
| Huntington Medical Research Institute | | | | |
| *Syed Ashraf Imam, Ph.D.* | | | | |
| Early Detection of Breast Cancer and it Recurrence | 2 | $249,212 | $116,234 | $365,446 |
| John Wayne Cancer Institute | | | | |
| *Dave Hoon, M.Sc., Ph.D.* | | | | |
| Clinical Utility of Breast Cancer DNA Markers in Serum | 2 | $250,000 | $222,000 | $472,000 |
| La Jolla Institute for Molecular Medicine | | | | |
| *Ingrid Schraufstatter, M.D.* | | | | |
| Are EGF-Receptors Activated by IL-8 In Breast Cancer? | 1 | $75,000 | $80,475 | $155,475 |
| Lawrence Berkeley National Laboratory | | | | |
| *Patrick Kaminker, Ph.D.* | | | | |
| Telomere Clustering is Lost in Mammary Epithelial Tumors | 2 | $80,000 | $0 | $80,000 |
| *Sahn-Ho Kim, Ph.D.* | | | | |
| Telomere Dynamics during Breast Development | 1 | $100,000 | $57,715 | $157,715 |
| *Yi-Ching Lio, Ph.D.* | | | | |
| The Functions of BRCA2 in Repairing DNA Damage | 3 | $300,000 | $195,388 | $495,388 |
| *John Muschler, Ph.D.* | | | | |
| Tumor Suppression by Dystroglycan in Breast Epithelial Cells | 1.5 | $200,000 | $128,214 | $328,214 |
| *Rana Zahedi, Ph.D.* | | | | |
| Analysis of a Protease Involved in Mammary Development | 2 | $80,000 | $0 | $80,000 |
| SUBTOTAL, Lawrence Berkeley National Labratory | | $760,000 | $381,317 | $1,141,317 |

| INSTITUTION/PI/TITLE | DUR | DIRECT | INDIRECT | TOTAL |
|---|---|---|---|---|
| Lawrence Livermore National Laboratory | | | | |
| *Stavros Demos, Ph.D.* | | | | |
| Optical Spectroscopic Detection and Imaging of Breast Cancer | 1.5 | $99,937 | $49,730 | $149,667 |
| *Michelle Bennett, Ph.D.* | | | | |
| Evaluation of Essiac Tea to Prevent Mammary Tumors | 1.5 | $99,810 | $85,832 | $185,642 |
| SUBTOTAL, Lawrence Livermore National Laboratory | | $199,747 | $135,562 | $335,305 |
| Northern California Cancer Center | | | | |
| *Esther John, Ph.D.* | | | | |
| Migration and Breast Cancer Risk in Hispanics | 3 | $745,320 | $252,606 | $997,926 |
| Pangene Corporation | | | | |
| *Gurucharan Reddy, Ph.D.* | | | | |
| Novel Inhibitors of Rad51-DNA Repair in Breast Cancer | 1 | $73,220 | $57,112 | $130,332 |
| Public Health Institute | | | | |
| *Paul Mills, Ph.D.* | | | | |
| Pesticides and Breast Cancer in Hispanic Women | 3 | $263,488 | $46,900 | $310,388 |
| Salk Institute for Biological Studies | | | | |
| *Zhiyong Wang, Ph.D.* | | | | |
| Coactivators in Mammary Gland Development and Tumorigenesis | 2 | $80,000 | $6,400 | $86,400 |
| Scripps Research Institute | | | | |
| *Masaaki Hayashi, M.D., Ph.D.* | | | | |
| The Role of SGK in Breast Cancer Proliferation | 2 | $80,000 | $6,400 | $86,400 |
| *Yi Hsing Lin, Ph.D.* | | | | |
| Lasp-1 Signaling in Breast Carcinoma Cell Invasion/Migration | 2 | $80,000 | $6,400 | $86,400 |
| SUBTOTAL, Scripps Research Institute | | $160,000 | $12,800 | $172,800 |

| INSTITUTION/PI/TITLE | DUR | DIRECT | INDIRECT | TOTAL |
|---|---|---|---|---|
| Sidney Kimmel Cancer Center | | | | |
| *Margaret Huflejt, Ph.D.*<br>Targeting of Tumor-Promoting Galectins in Breast Cancer | 1 | $100,000 | $82,500 | $182,500 |
| SRI International | | | | |
| *Brian Murphy, Ph.D.*<br>PPARd Ligands for Inhibition of Breast Cancer Progression | 1 | $200,000 | $173,535 | $373,535 |
| Stanford University | | | | |
| *Kathie Dalessandri, M.D.*<br>Dietary Indole Effect on Estrogen Urinary Metabolites | 1 | *Collaborative Award* | | |
| *Anne-Renee Hartman, M.D.*<br>The Role of BRCA1 in Nucleotide Excision Repair | 2 | $80,000 | $6,400 | $86,400 |
| *Quan Lu, Ph.D.*<br>Genes that Modulate Dioxin-Induced Breast Cancer | 2 | $80,000 | $6,400 | $86,400 |
| *David Spiegel, M.D.*<br>Does a Peer Navigator Improve Quality of Life at Diagnosis? | 3 | $556,172 | $197,483 | $753,655 |
| *Irene Wapnir, M.D.*<br>Selective Targeting of Breast Cancer with Radioiodide | 2 | $200,000 | $115,200 | $315,200 |
| *Dawn Yean, Ph.D.*<br>Regulation of the ATR Checkpoint Response in Breast Cancer | 2 | $80,000 | $6,400 | $86,400 |
| SUBTOTAL, Stanford University | | $996,172 | $331,883 | $1,328,055 |
| The Burnham Institute | | | | |
| *Klara Briknarova, Ph.D.*<br>Molecular Study of BAG Domains: A New Motif in Breast Cancer | 2 | $80,000 | $6,400 | $86,400 |
| *Sharon James, Ph.D.*<br>Protein Factor PPARγ and Vitamin A Compounds in Breast Cancer | 2 | $80,000 | $6,400 | $86,400 |

| INSTITUTION/PI/TITLE | DUR | DIRECT | INDIRECT | TOTAL |
|---|---|---|---|---|
| *Kazuya Okada, M.D., Ph.D.*<br>SBP-1: A Novel Surviving Binding Protein in Breast Cancer | 2 | $80,000 | $6,400 | $86,400 |
| *Elena Pasquale, Ph.D.*<br>Targeting the EphB4 Receptor to Inhibit Breast Tumor Growth | 1 | $96,637 | $94,704 | $191,341 |
| *Marko Rehn, Ph.D.*<br>P132Cas and Antiestrogen Resistance of Breast Cancer | 2 | $80,000 | $6,400 | $86,400 |
| *Erkki Ruoslahti, M.D., Ph.D.*<br>Blood Vessel Markers in Breast Cancer | 2 | $199,549 | $195,558 | $395,107 |
| *Kristiina Vuori, M.D. Ph.D.*<br>Overcoming Drug Resistance in Breast Cancer | 2 | $198,183 | $194,220 | $392,403 |
| SUBTOTAL, Burnham Institute | | $814,369 | $510,082 | $1,324,451 |
| The Wellness Community-National<br>*Mitch Golant, Ph.D.*<br>Effectiveness of Internet vs. Face to Face Support Groups | 3 | $224,445 | $93,594 | $318,039 |
| University of California, Berkeley<br>*Leonard Bjeldanes, Ph.D.*<br>Dietary Indole Effect on Estrogen Urinary Metabolites | 1 | *Collaborative Award* | | |
| *Gary Firestone, Ph.D.*<br>Dietary Indole Effect on Estrogen Urinary Metabolites | 1 | $89,925 | $0 | $89,925 |
| *Satyabrata Nandi, Ph.D.*<br>Rodent Model for Human Ductal Carcinoma in Situ | 1 | $100,000 | $0 | $100,000 |
| SUBTOTAL, University of California, Berkeley | | $189,925 | $0 | $189,925 |
| University of California, Davis<br>*John Boone, Ph.D.*<br>Breast CT for Much Earlier Detection of Breast Cancer | 3 | $500,000 | $0 | $500,000 |
| *Hongwu Chen, Ph.D.*<br>Role of Chromatin Regulator in Breast Cell Growth | 3 | $286,151 | $0 | $286,151 |

| INSTITUTION/PI/TITLE | DUR | DIRECT | INDIRECT | TOTAL |
|---|---|---|---|---|
| *Helen Chew, M.D.*<br>LPC as a Potential Tumor Marker for Recurrent Breast Cancer | 1.5 | $100,000 | $0 | $100,000 |
| *Karen Lindfors, M.D.*<br>Breast CT for Much Earlier Detection of Breast Cancer | 3 | $0 | $0 | $0 |
| *Susan Murin, M.D.*<br>Smoking Effect on Pulmonary Metastasis from Breast Cancer | 1 | $75,000 | $0 | $75,000 |
| *Rajen Ramsamooj, M.D.*<br>Optical Spectroscopic Detection and Imaging of Breast Cancer | 1 | $33,866 | $0 | $33,866 |
| *Colleen Sweeney, Ph.D.*<br>Pathway-Specific Gene Expression in Breast Cancer Cells | 3 | $299,287 | $0 | $299,287 |
| SUBTOTAL, *University of California, Davis* | | $1,294,304 | $0 | $1,294,304 |
| University of California, Irvine<br>*Edward Nelson, M.D.*<br>A New Genetic Vaccine Therapy for Breast Cancer | 1 | $100,000 | $0 | $100,000 |
| *Sora Tanjasiri, Dr.PH.*<br>A Network-Based Intervention for Chamorros in Southern California | 3 | $206,214 | $0 | $206,214 |
| SUBTOTAL, University of California, Irvine | | $306,214 | $0 | $306,214 |
| University of California, Los Angeles<br>*Barbara Berman, Ph.D*<br>Breast Cancer Prevention and Control Among Deaf Women | 1.5 | $109,707 | $0 | $109,707 |
| *Pamela Davidson, Ph.D.*<br>Geographic Variation in Breast Cancer Stage at Diagnosis | 3 | $425,497 | $0 | $425,497 |
| *Patricia Ganz, M.D.*<br>Efficacy of a Community Program in Increasing Access to STAR | 1.5 | $68,350 | $0 | $68,350 |

| INSTITUTION/PI/TITLE | DUR | DIRECT | INDIRECT | TOTAL |
|---|---|---|---|---|
| *Katherine Kahn, M.D.*<br>The Impact of Structure on Quality of Breast Cancer Care | 3 | $851,916 | $0 | $851,916 |
| *Rose Maly, M.D., M.S.P.H.*<br>Determinants of Breast Cancer Treatment in the Underserved | 3 | $870,038 | $0 | $870,038 |
| *Daniel Silverman, M.D., Ph.D.*<br>Patient-Individualized Chemotherapy in Breast Cancer | 3 | $296,994 | $0 | $296,994 |
| *Michael Albert Thomas, Ph.D.*<br>Breast Cancer Imaging by 2-D Magnetic Resonance Spectroscopy | 2 | $249,137 | $0 | $249,137 |
| *Nathaniel Wyckoff, Ph.D.*<br>2-D Magnetic Resonance Spectroscopy of Breast Tumors | 2 | $80,000 | $0 | $80,000 |
| SUBTOTAL, University of California, Los Angeles | | $2,951,639 | $0 | $2,951,639 |
| University of California, Riverside | | | | |
| *Kathryn DeFea, Ph.D.*<br>Trypsin-like Proteases as Metastatic Agents in Breast Cancer | 3 | $295,980 | $0 | $295,980 |
| University of California, San Diego | | | | |
| *Wayne Bardwell, Ph.D.*<br>Women with Breast Cancer: Quality of Life and Diet Adherence | 3 | $164,427 | $0 | $164,427 |
| *Randall Johnson, Ph.D.*<br>Genetic Aspects of Physiological Response During Lactation | 3 | $593,997 | $0 | $593,997 |
| *Michael Karin, Ph.D.*<br>Role of IKKa in Mammary Gland Development | 3 | $563,696 | $0 | $563,696 |
| SUBTOTAL, University of California, San Diego | | $1,322,120 | $0 | $1,322,120 |

# Summary of Awards

| INSTITUTION / PI / TITLE | DUR | DIRECT | INDIRECT | TOTAL |
|---|---|---|---|---|
| University of California, San Francisco | | | | |
| *Michael Campbell, Ph.D.*<br>In Vivo Effects of Chinese Herbal Extracts on Breast Cancer | 2 | $200,000 | $0 | $200,000 |
| *Rani Eversley, Ph.D.*<br>Return to Work after Breast Cancer Surgery | 3 | *Collaborative Awards* | | |
| *Morton Lieberman, Ph.D.*<br>Effectiveness of Internet vs. Face to Face Support Groups | 3 | $268,554 | $0 | $268,554 |
| *Steven Rosen, Ph.D.*<br>Novel Enzymes Associated with Breast Cancer Angiogensis | 1.5 | $100,000 | $0 | $100,000 |
| *Fred Schaufele, Ph.D.*<br>Novel Technologies to Identify Tissue-Selective Estrogens | 1 | $75,000 | $0 | $75,000 |
| *Jeonghoon Sun, Ph.D.*<br>Engineering Antibodies Specific for Breast Cancer Proteases | 1 | $80,000 | $0 | $80,000 |
| *Debasish Tripathy, M.D.*<br>Herba Scutellaria Barbatae for Metastatic Breast Cancer | 2 | $232,364 | $0 | $232,364 |
| SUBTOTAL, University of California, San Francisco | | $955,918 | $0 | $955,918 |
| University of Southern California | | | | |
| *Sue Ann Ingles, Dr.P.H.*<br>Dietary Fat, Fat Metabolizing Genes and Breast Cancer Risk | 2 | $247,399 | $139,279 | $386,618 |
| *Michael Press, M.D., Ph.D.*<br>HER-2/neu Gene Variations and Breast Cancer Risk | 3 | $706,175 | $441,360 | $1,147,535 |
| SUBTOTAL, University of Southern California | | $953,514 | $580,639 | $1,534,153 |

| INSTITUTION/PI/TITLE | DUR | DIRECT | INDIRECT | TOTAL |
|---|---|---|---|---|
| WomenCARE<br>*Caroline Bliss-Isberg, Ph.D.*<br>Does a Peer Navigator Improve Quality of Life at Diagnosis? | 3 | *Collaborative Award* | | |
| Women's Cancer Resource Center<br>*Diane Estrin*<br>Return to Work after Breast Cancer Surgery | 3 | $500,000 | $125,000 | $625,000 |


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