



California  
Breast  
Cancer  
Research  
Program

Annual Report  
1998



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## Annual Report to the State of California Legislature 1998

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

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In 1998, the Breast Cancer Research Council and Staff grieved the loss of one of our Council members, who lost her long battle with metastatic breast cancer.

In 1998, one of our Council members joined us by telephone from her hospital bed, where she was being treated for an infection in her arm (a consequence of her surgery many years ago).

As we approached 1998, another Council member underwent the mastectomy that she was able to avoid three years previously because her cancer recurred.

In 1998, all of us sat in stunned silence when we heard that yet another member of the Council had been diagnosed with metastases just weeks after passing her seven-year check-up.

And while we fight our personal battles with breast cancer, and stand by friends and loved ones in their struggle, another 19,300 California women and men are estimated to have started down the long road of breast cancer in 1998, and 4,585 people are estimated to have been lost.



# Introduction

One cannot be faced over and over again with this reality and not feel an urgency, an impatience, an anger with what we still do not know and how helpless medical science still is in preventing these tragedies. And we believe that we need this sense of urgency, this impatience, this anger to push science further and faster to find the answers that will stop the epidemic in our lifetime.





The California Breast Cancer Research Program is a constructive expression of the anger and frustration of women with breast cancer. It arose and continues to grow through the energy, wisdom, and dreams of women that have resulted from their experience with breast cancer.

One of the principles upon which BCRP was created is that activists' voices should be heard in all aspects of the Program.

We have heard over and over from scientists who have not worked with breast cancer activists before working with the California Breast Cancer Research Program that the experience they have had with the Program has changed the way they approach their own research and the way they think about science.

Breast cancer activists participate in all levels of Program activities and decision-making. Some of this inclusion was built into the Program with the enabling legislation (such as the composition of the Advisory Council). Through active collaboration between breast cancer advocates and the Program administrators, we have made this relationship and inclusion much broader.

At the broadest level are the people of California, who are the ultimate recipients of any benefits the Program produces. Efforts to reach these people with the results of research funded by the Program fall into two major activities — dissemination and discussion of research results, and translation of research results into services that reach women.

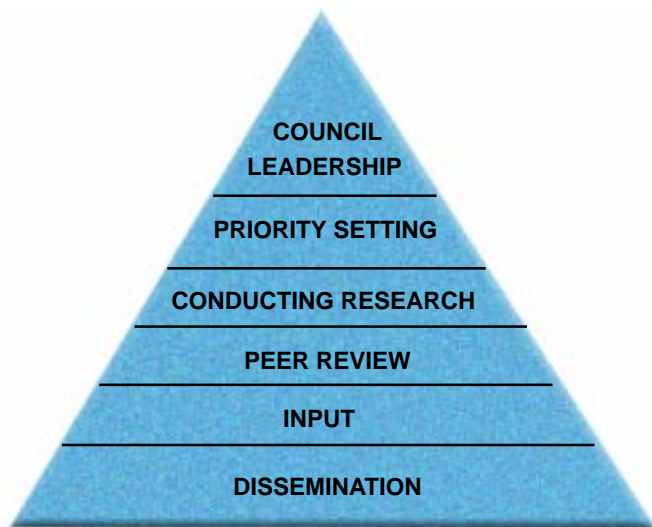
We are currently planning the 1999 California Breast Cancer Research Symposium, to be held in Los Angeles on September 17-18, 1999. We are building upon the success of the 1997 California Breast Cancer Research Symposium in Sacramento, at which over half of the 700+ participants were lay people who interacted with scientists presenting their research results. This is one way to ensure that the people of California have the opportunity to hear about the latest advances and discuss them with scientists.

To help ensure that the research funded by the Program benefits women in the State, the Program emphasizes translation — development of new treatments and services — in its awards. Research funded by the Program has led to clinical trials of new therapies; training manuals for outreach programs that utilize state-of-the-art methods; and development of new services for breast cancer patients. It also supports and encourages risk-taking, translating in a constructive way the impatience felt by many with the slow pace of research.

collaboration

Active participation of activists in generating ideas and advising the Program on its strategies to make a difference in breast cancer is a founding principle of BCRP. The current BCRP Research Priority Issues were developed from recommendations made at the 1996 Public Advisory Meeting. At that meeting, BCRP brought together activists, advocates, survivors, health care providers, health educators, biotechnology scientists and academic scientists, who worked together to develop and prioritize the issues they thought were most critical to breast cancer research.

At yet another level, activists have always brought their unique perspective to assessing the innovativeness, potential impact, significance, and feasibility of individual research proposals submitted to the Program. Breast cancer advocates review every proposal submitted for funding, and breast cancer advocates serve as full voting members of the peer review panels.



## activists

Another area in which we have advanced the inclusion of activists is in the actual performance of research. The Community Research Collaboration Award requires a partnership between community members (such as a breast cancer advocacy organization) and research scientists. The partnership works together to identify the research question, develop the research plan, carry out the research, interpret the results and disseminate information to the community. The result is mutual learning and research that is important to both scientists and communities.

The voices of breast cancer survivors are carried into all major Program decisions by involvement of advocates on the Advisory Council — the body that determines the Program's strategies and funding priorities. With a full one-third of the members being breast cancer activists, a diverse range of activist opinions are heard and brought to bear on all decisions.

Finally, the Advisory Council has chosen to ensure that breast cancer survivors are not only seated at the table, but share the leadership of the Council. In all of its five years, the Chair or Vice Chair of the Council has been a breast cancer advocate.

This model of activist inclusion and partnership gives me hope that BCRP will find answers that will help women, and will find them more quickly. And this hope is bolstered by the tremendous portfolio of research progress and research findings described in this Annual Report.





# California Breast Cancer Research Program Background



**I**n 1993, the California legislature recognized the need to respond to the tragic toll that breast cancer was taking on the people of California. At that time, the state had no comprehensive public health plan to address breast cancer. With the passage of AB2055 and AB478, an ongoing source of funds from tobacco taxes was secured to support three arms of a state effort to decrease the human and economic cost of breast cancer in California. Forty-five percent of the funds was allocated to the Breast Cancer Research Program (BCRP), 50% to the Breast Cancer Early Detection Program and 5% to the California Cancer Registry. The California Breast Cancer Research Program was established at the University of California.

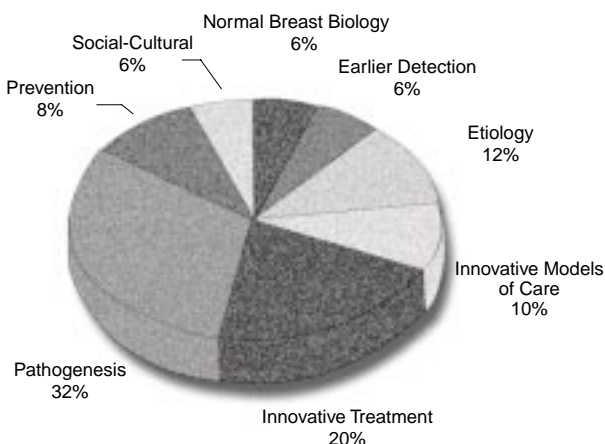
The mission of the California Breast Cancer Research Program is to reduce the impact of breast cancer in California by supporting research on breast cancer and facilitating the dissemination of research findings and their translation into public health practice.

The Breast Cancer Research Council, which is an advisory committee to the University, determines the goals and priorities of the research program, establishes program policies, oversees peer review of submitted applications and makes funding recommendations. Review committees composed of expert scientists and breast cancer advocates from outside California are brought together each year to evaluate the scientific merit of applications.

## funding

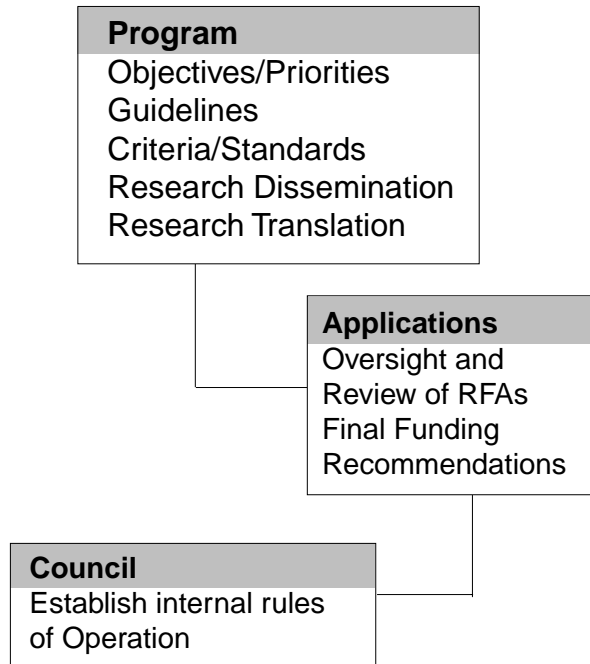
The BCRP funds support research projects and training of both beginning and experienced scientists in breast cancer research. The funds that the Program directs to research on the causes, prevention, detection and cure of breast cancer are not just monies spent, but are investments in the future of Californians. By encouraging and identifying innovative research on breast cancer, and attracting and training some of the most talented and gifted scientists into this area of research, California is making an investment that can pay vital dividends for all Californians in years to come. The specific areas of research supported, as determined by the Breast Cancer Research Council with input from stakeholders across the state, include basic and clinical science, social and behavioral science, technology development, and public health research. New program areas in translational and collaborative research, as well as community partnerships, have been developed. BCRP's funding provides critical leverage in developing new scientific infrastructure and networks crucial for a comprehensive approach to the problem of breast cancer. One BCRP's goal is to allocate funds rapidly and flexibly to assure that new and promising ideas are brought quickly to bear on the understanding and prevention, detection and cure of breast cancer.

**1998 Funding by Priority Issue**



1998 marked a year of important achievements for the BCRP. The Program moved to fund new areas of research, disseminate research results, and translate research findings into practical application, all of which results in a portfolio of exciting new projects . The BCRP budget for 1998 awards was \$16.7 million. These funds now support 52 multi-year projects to investigate the pathogenesis, etiology, prevention, early detection and treatment of breast cancer. The projects include large-scale research efforts, pilot studies of exciting and important new areas, collaborations among scientists from different fields and between scientists and community groups, and training projects for researchers early in their careers or new to breast cancer research. These studies are being carried out at universities (public and private), community agencies, medical centers, independent research institutes, federal laboratories, and biotechnology companies. Projects funded by the Program in 1995-1997 are generating exciting results, reported here.

## Breast Cancer Research Council



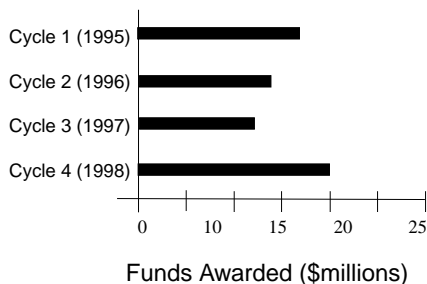
As requested by the legislature, this Annual Report includes the following elements:

1. The number and dollar amounts of research grants, including the amount allocated to indirect costs.
2. The subject of research grants.
3. The relationship between federal and state funding for breast cancer research.
4. The relationship between each project and the overall strategy of the research program.
5. A summary of research findings including discussion of promising new areas.
6. The institutions and campuses receiving grant awards.

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

# projects

### Research Expenditures





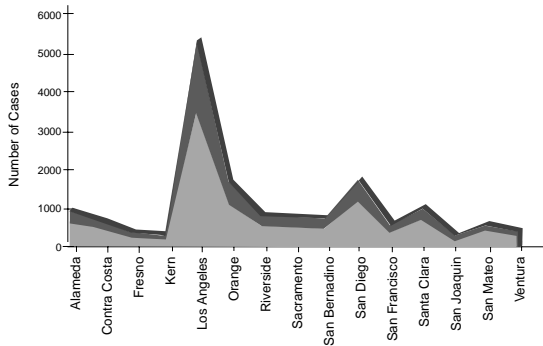
Breast cancer remains the most common cancer among women of any race or ethnic group in California. It is the most common cause of death for women ages 15-54 and is second only to lung cancer for women over 55 years of age. In 1998, it is estimated that 19,300 women and men in California were diagnosed with breast cancer and 4,585 died of the disease. The incidence of breast cancer in the state climbed steadily until 1988 during the time data were being collected (since 1973 for the San Francisco Bay and Los Angeles areas). Since 1988, rates have decreased slightly and now appear to have leveled off. Age-adjusted rates dropped from 112.7 per 100,000 in 1988 to 104.9 per 100,000 in 1995.

# Status of Breast Cancer in California

These rates, however, varied markedly by race/ethnicity in the same time period, with non-Hispanic white women having the highest rate, followed by African American women, Hispanic women, and Asian American women, respectively. Among women younger than 50, however, African American women have a higher rate than white women. African American women also have the highest rates of more advanced disease, despite the fact that they have the highest incidence of mammograms in the previous 2 years. Roughly fifty per cent of breast cancers are diagnosed among women who are less than 65 years old (20 per cent are among women less than 50).



Breast Cancer Detection in Most Populous California Counties

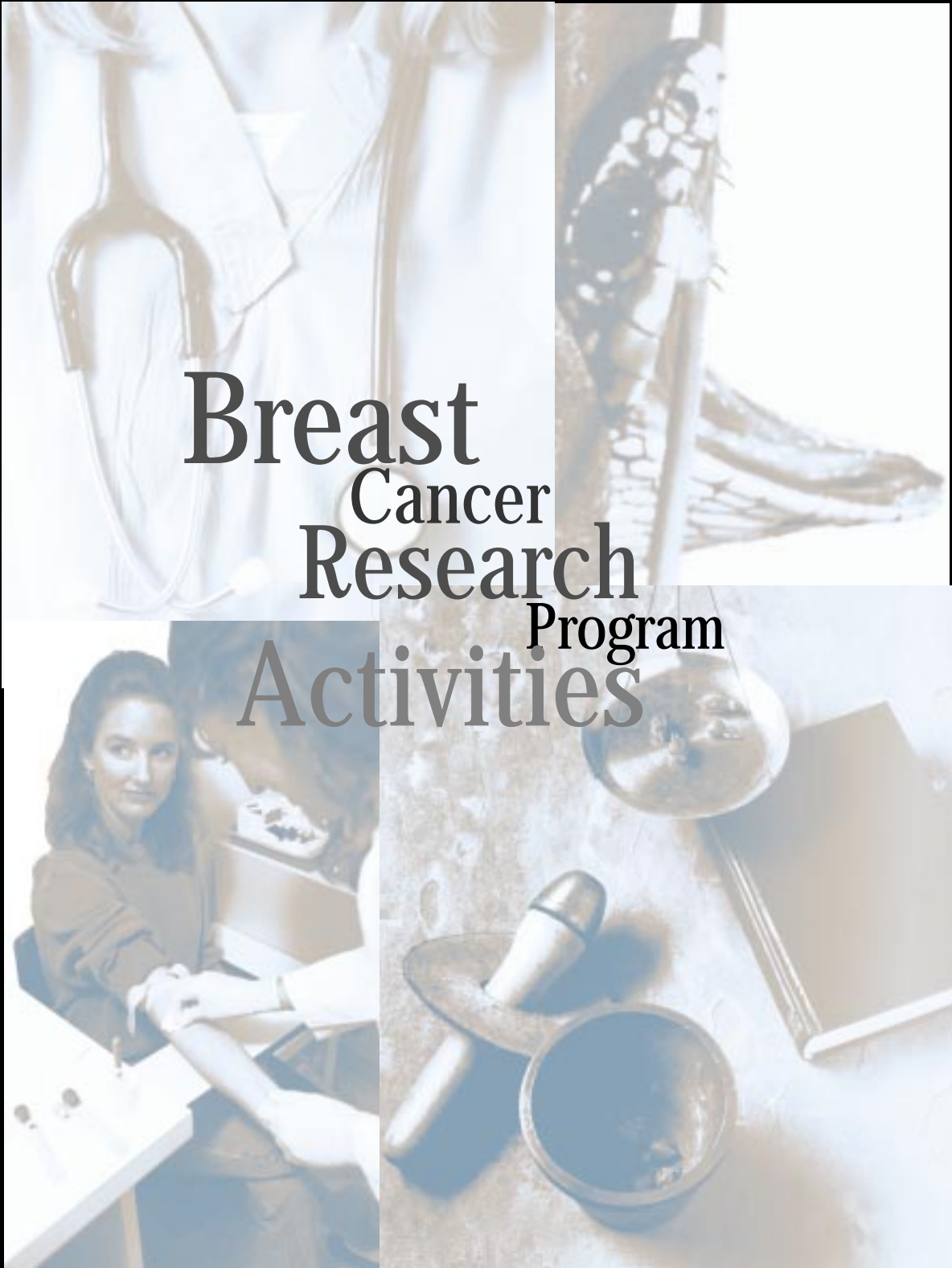


Rates of death due to breast cancer have remained relatively constant in the United States during the last three decades, but have decreased approximately 14% in California since 1985 (about 2% per year). Unfortunately, this decrease has only been consistent and statistically significant for non-Hispanic white women. In addition, although African American women have a lower incidence of breast cancer than white women, the death rate is higher for African American women.

Mammography usage has increased markedly in the past decade, probably accounting in part for both the increased incidence of breast cancer and the decreased mortality. In 1987, only 46.7% of California women aged 40 and over reported ever having had a mammogram. By 1994, this figure had increased to 82.8%. Asian and Hispanic women, less educated women and those reporting a lower income, however, are less likely to have been screened and are therefore at greater risk for being diagnosed with breast cancer at a later stage. While mammography has undoubtedly contributed to the decrease in mortality, no woman diagnosed with breast cancer today, no matter how small the tumor or how early it is detected, can be told that her cancer is cured.

The most promising aspect of this information is that the incidence of breast cancer is no longer increasing, as it did in every decade until the 1990's. Also encouraging is the increased proportion of breast cancers that are diagnosed at an early stage. This should translate into a decrease in mortality in years to come. Most disturbing is the lack of any dramatic changes in breast cancer incidence or mortality, and the increasing burden that breast cancer is placing on different populations of the state.





Breast  
Cancer  
Research  
Program  
Activities

# Strategic Objectives in Research Funding

The mission of the BCRP is to reduce the impact of breast cancer in California by supporting research on breast cancer and facilitating the dissemination of research findings and their translation into public health practice.

The Program is advised and overseen by an advisory council (the Breast Cancer Research Council). The Council is charged with developing the strategic objectives and priorities of the Program, and making final recommendations on which research grants should be funded.

Each spring, the Council meets to determine strategic objectives and funding priorities for the next year. The overall strategic objectives, as specified in statutes, are:

- ♦ To fund research in fields that include, but are not limited to, biomedical science and engineering, the social, economic and behavioral sciences, epidemiology, technology development and translation, and public health.
- ♦ To fund innovative and creative research, with a special emphasis on research that complements, rather than duplicates, the research funded by the federal government.
- ♦ To consider a broad range of cross-disciplinary breast cancer research including, but not limited to, translational and technological research, including research regarding the development and translation of technologies of earlier detection; research regarding the cultural, economic, and legal barriers to accessing the health care system; research examining the link between breast cancer and environmental factors, including both natural and industrial chemicals, estrogen imitators, and electromagnetic fields.

The Council, after careful deliberation, decided that the most effective use of the \$16 million available in funding Cycle IV was to concentrate research funding on a small number of key issues, focusing, to the extent possible, on areas that are not as well-funded by the federal government and other agencies. The priorities established by the Council were based on:

- ♦ the importance of each area to the fight against breast cancer;
- ♦ the Council's sense of the potential impact of funded research on the human and economic costs of breast cancer in the state of California; and
- the funding patterns of the federal government and other agencies.



## Research Priorities:

The following six priorities were adopted:

- ♦ Enhance understanding of the etiology (causes) of breast cancer
- ♦ Enhance understanding of the pathogenesis (development) of breast cancer
- ♦ Develop new approaches to prevent breast cancer
- ♦ Develop more effective techniques for the earlier detection of breast cancer
- ♦ Develop and test innovative models of care
- ♦ Explore innovative treatment modalities

In addition, the Program continued initiatives developed last year:

- ♦ to challenge the research community to propose more innovative approaches to the problem of breast cancer, specifically including fostering collaborations between experienced researchers and community groups; and
- ♦ to provide strong support for collaborative “translational” research, i.e., work whose results can be moved rapidly into practical application, whether through grass-roots organizations or mainstream health care providers.

## The Value of Activist Involvement

- Power to effect large-scale change in public policy.
- Production of written materials that are appropriate for, and responsive to, the community.
- Being reminded of the forest when you are examining the trees.
- Funding and carrying out research that is relevant to the people paying for it.

## Research Training: Maintenance of Needed Human Resources

The relentless rate of deaths due to breast cancer over the last several decades has prompted BCRP to provide for the training of new investigators — the human resources needed to ensure progress in the fight against breast cancer. Through three award types, BCRP endeavors to attract new investigators to breast cancer research. Postdoctoral Fellowship Awards, and New Investigator Awards and Training Program Awards allow researchers early in their careers to receive research training in breast cancer issues. Together, these awards bring new minds into the fight against breast cancer, and ensure the human resources required to eradicate the disease.

## Targeted Research Efforts

The Council identified three specific topics that it felt were (1) especially important to making progress in breast cancer research; and (2) not well supported by other research funding agencies. It set aside \$1.0-\$1.5 million for each of the topics:

**Sociocultural, Behavioral and Psychological Aspects of Breast Cancer** — This Request for Applications encouraged qualitative and quantitative research into sociocultural, behavioral and psychological issues affecting women with respect to the risk or occurrence of breast cancer.

**Basic Breast Biology Relevant to Development of Breast Cancer** — This Request for Applications encouraged studies aimed at achieving a greater knowledge of the normal breast, through all stages of development and change, in order to better understand anomalous changes that may lead to cancer.

**Breast Cancer Prevention, Risk Identification and Risk Reduction** — This Request for Applications encouraged research that will enable more effective and appropriate prevention interventions by increasing our knowledge of modifiable breast cancer risk factors.

# Award Types

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## Innovation in Research

The Council has encouraged researchers to develop and explore innovative and risky concepts in the specific priority areas that it judged as most important in the fight against breast cancer. Innovative Developmental and Exploratory Awards (IDEAs) allow researchers to explore new concepts in breast cancer etiology, pathogenesis, prevention, and earlier detection that could lead to breakthroughs in these fields. Innovative Treatment and Models of Care Awards (ITaMoCAs) encourage development and testing of new treatment modalities or methods of delivering breast cancer care. Through these combined efforts of exploring new concepts and building on existing knowledge, the resulting improvements in prevention, detection and cure of breast cancer will advance the day when we can say with confidence that breast cancer is no longer a threat to the people of California.

## Initiatives in Collaboration

Two award types developed last year were continued and expanded to stimulate and support collaborative research — one for collaborations between experienced research scientists and community members/agencies (the Community-Initiated Research Collaboration (CIRC) Award), and one for collaborations between research scientists in different fields and institutions (the Translational Research Collaboration (TRC) Award). Both types of award were designed to offer a one-year Pilot Award to foster the development of teams and their projects, and (for the first time this year) larger 3-year awards for full projects.

# Special Considerations

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## Innovativeness

In keeping with the intent of the enabling legislation, the Council focuses on funding especially innovative and creative research. This year, we developed a new scoring system to evaluate grant applications. In this new system, every grant application is scored by reviewers on this aspect, which comprises 25% of the total scientific merit score.

## Multidisciplinary Research

The Council encourages researchers to apply ideas from various fields to their research by collaborating across disciplines. This aspect of applications is rated by reviewers and taken into consideration in making funding decisions.

## Translational Potential

A goal of the BCRP is to encourage the translation of scientific findings into practical applications that will make a difference to those at risk for, or diagnosed with, breast cancer. The potential of research findings to be translated into practical applications is rated by reviewers and taken into consideration in funding decisions.

## Focus on the Underserved

Another issue identified by the Council as critically important is the disparity in the incidence and mortality of breast cancer between different groups of Californians. Research that has the potential to reduce these disparities was specifically requested in the Call for Applications, identified by reviewers and considered by the Council in making funding recommendations.

# Strategic Objectives in Research Support



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“Provide for systematic dissemination of research results to the public

and the health care community in order that these findings may be applied to the planning, implementation, and evaluation of breast cancer-related programs.”

“Develop policies and procedures to facilitate the translation of research results into commercial, alternate technological, and other applications”

“Development of appropriate linkages to nonacademic entities, including voluntary organizations, health care delivery systems, industry, government agencies, research entrepreneurs, and public officials.”



## Dissemination of Research Results

medical communities (to facilitate the advancement of the understanding of breast cancer and its treatment among all involved) and to the public (as stakeholders in the Program). To this end, funded research is widely publicized in a variety of ways:

- ♦ Descriptions of new awards are published in the Compendium of Awards
- ♦ The progress report for each project is posted yearly on the BCRP web site
- ♦ Final results of projects are described on the web site and in the annual report
- ♦ A Newsletter reports on new awards, research results and other Program news.
- ♦ Publications are widely distributed and posted on the web site

Researchers also publish final results in peer reviewed scientific journals and present them at scientific conferences; these publications and presentations are tracked by BCRP. The 1997 California Breast Cancer Research Symposium served to disseminate results in a more interactive and visible fashion. A Council Committee, formed in 1997, is examining other means to achieve this aim.

# California Breast Cancer Research Symposium

BCRP held its first Symposium in September, 1997, bringing together individuals with a wide variety of backgrounds, but a common interest in determining the cause of, and cure for, breast cancer. This symposium was distinct from most other scientific symposiums in that it had a strong attendance by breast cancer advocates and the community at large.

The content and the composition of the symposium reflected the goals of BCRP. Over half of the more than 700 attendees characterized themselves as lay people. The activities available to the participants included: listening to keynote speakers, both advocate (Bella Abzug) and scientist (Mina Bissel); viewing artwork by and about people with breast cancer; visiting exhibits by non-profit breast cancer organizations; attending informational seminars about how to be funded to do breast cancer research; and attending talks and posters given by investigators who were funded by BCRP.

In 1998, the Council voted to make the California Breast Cancer Research Symposium a biennial event, and to hold smaller meetings around the state as the opportunity arises in the intervening years. The next California Breast Cancer Research Symposium is now being planned for September, 1999.



Four speakers described different fields of breast cancer research that could produce breakthroughs in explaining or curing breast cancer. Seven more investigators presented their research in poster form. Often emerging research fields seem invisible to the public. The Frontiers in Breast Cancer Research Symposium was a first step in bringing them out into the open.

Meanwhile, BCRP held a regional event in September, 1998 — a collaborative endeavor between the University of Southern California and BCRP. The event combined a legislative breakfast with a half-day presentation on current breast cancer research, geared towards the lay public. The event offered the opportunity to learn about breast cancer research from scientists who are pushing the field forward. Some of the research discussed was already making an impact on how researchers and health care providers view cancer, while others provided glimpses of advances to come.

## Translation of Research Results into Practical Applications



A goal of the BCRP is to encourage the translation of research findings into practical applications that will make a difference to those at risk for, or diagnosed with, breast cancer. Facilitating this process is one of the charges of the Council. One strategy to achieve this goal has been outreach to California biotechnology researchers to encourage applications from those most involved in translational efforts.

In 1997, BCRP launched a new award type (the Translational Research Collaboration Award, or TRC Award) to specifically solicit research proposals for translational research that arises from partnerships of research scientists from different fields and/or institutions (especially encouraging collaborations between academic and industry-based biotechnology researchers). This award type, expanded in 1998, is helping to spread BCRP's principle of translation and collaboration throughout the research community in the state and is resulting in teams across the state who are poised to take research results and use them to develop products, treatments, and services.

# Collaboration with Communities

Close collaboration with organizations and individuals involved in breast cancer issues is a guiding principle of the BCRP. Breast cancer activists participate in all levels of Program activities and decision-making, illustrated in the "Influence Pyramid." Some of this inclusion was built into the Program with the enabling legislation (such as the composition of the Advisory Council). Through active collaboration between breast cancer advocates and the Program administrators, we have made this relationship and inclusion much broader.

At the base of the Influence Pyramid are the people of California, the ultimate recipients of any benefits the Program produces. Efforts to reach these people with the research results funded by the Program fall into two major activities — dissemination and discussion of research results, and translation of research results into services that reach women, both described above.

Active participation of activists in generating ideas and advising the Program on its strategies to make a difference in breast cancer is the second step in the pyramid. The current BCRP Research Priority Issues were developed from recommendations made at the 1996 Public Advisory Meeting. At that meeting, BCRP brought together activists, advocates, survivors, health care providers, health educators, biotechnology industry scientists and academic scientists, who worked together to develop and prioritize the issues they thought most critical to breast cancer research.

At the next level of influence is the review of scientific proposals. Activists have always brought their perspective to assessing the innovativeness, potential impact, significance, and feasibility of individual research proposals submitted to the Program. Breast cancer

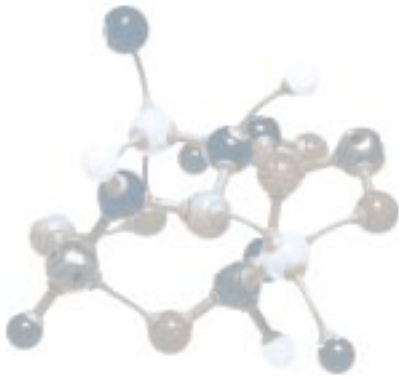
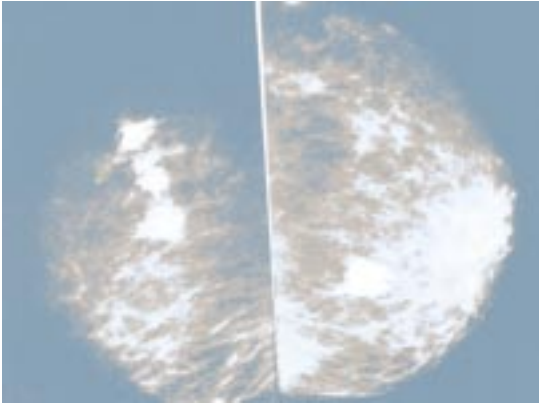
advocates review every proposal submitted for funding, and serve as full voting members of the peer review panels.

Another area in which we have advanced the inclusion of advocates is in actual research. The Community Research Collaboration Award, developed in 1997, requires a partnership between community members (such as a breast cancer advocacy organization) and research scientists. The partnership works together to identify the research question, develop the research plan, carry out the research, interpret the results and disseminate to the community. The result is mutual learning and research that is important to both scientists and communities. This award type, expanded in 1998, is helping to spread BCRP's principle of community involvement and collaboration throughout the research community and is resulting in investigations in areas of research identified by, and important to, communities across the state.

The voices of breast cancer survivors are carried into all major Program decisions by involvement of advocates on the Advisory Council — the body that determines the Program's strategies and funding priorities. With a full one-third of the members being breast cancer activists, a diverse range of activist opinions are heard and brought to bear on all decisions. Finally, the Advisory Council has chosen to ensure that breast cancer survivors are not only seated at the table, but share the leadership of the Council. In all of its five years, the Chair or Vice Chair of the Council has been a breast cancer advocate.

These efforts establish effective dialogue with groups and individuals involved in breast cancer issues. They assure wide dissemination of research results, funding priorities that are important to those most affected by breast cancer, and funded projects that respond to these priorities.

# FUNDED RES



# RESEARCH



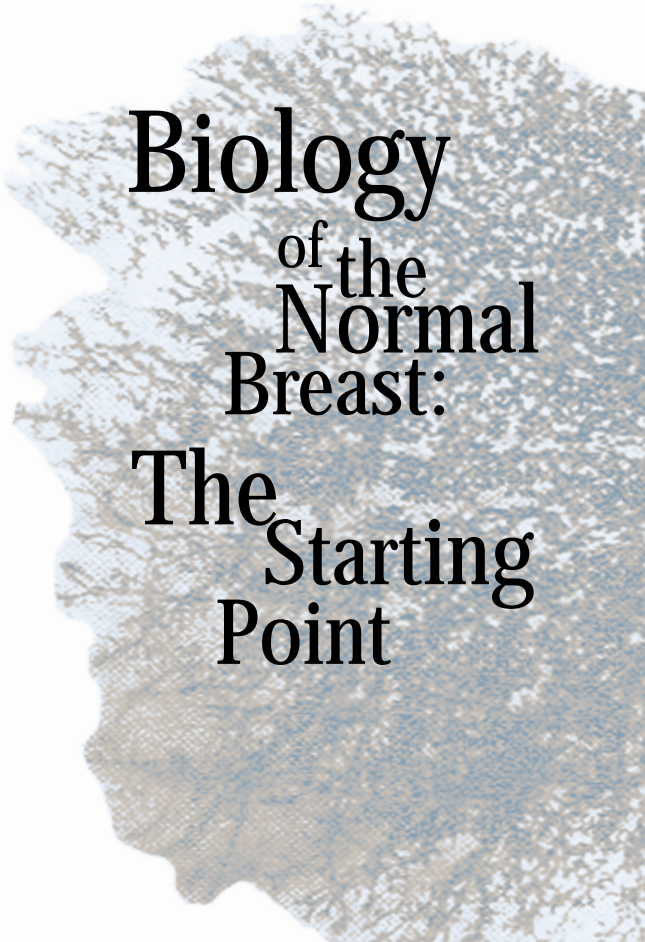
**i**n 1998, a number of research projects funded in 1995 through 1997 were completed. The results of these projects are summarized in this section. Other projects funded in 1995 through 1997 are still underway. The emerging findings based on the annual progress reports submitted to BCRP are also reviewed in this section. Finally, a new portfolio of grants was awarded in these same areas in 1998. These new projects are also summarized in this section.

Abstracts of new projects, and Annual and Final Progress Reports of ongoing funded projects can be found on BCRP's internet web site.





# RESEARCH



Biology  
of the  
Normal  
Breast:  
The  
Starting  
Point

There is a critical, but often overlooked requirement for unraveling the events that lead to breast cancer development – understanding the normal structures and processes of the breast. It is paradoxical that we expend enormous efforts to learn about the biology of breast tumors, but know very little about how the normal breast is structured; how the different cell types contribute to the functioning of the breast; and how to distinguish unusual but normal structures from those whose presence indicates cancer. BCRP identified understanding the biology of the normal breast as an area of research that needs to be emphasized and has funded research investigating this topic for the past two years.

# CONCLUSIONS



The question of what role environmental factors are playing in breast cancer development has been particularly difficult to answer. **Essam Enan, Ph.D.**, at the **University of California, Davis**, finished his project investigating the cellular mechanisms triggered by organochlorine pesticides in breast cancer cells. Most investigators are examining the actions of organochlorine pesticides through their association with the estrogen receptor. Dr. Enan finds that the lindane-like chemical b-HCH and the DDT-like chemical, o,p-DDT can stimulate the proliferation of breast cell lines through a mechanism that does not involve the estrogen receptor. b-HCH regulates several proteins differently in estrogen receptor-positive compared to estrogen receptor-negative cells. Most of these proteins are characterized as second messengers because they carry signals from the cell membrane to the nucleus. The second messengers regulated by b-HCH include cAMP, Src kinase, Protein Kinase A. Additionally, the tumor suppression protein p53 is differentially regulated in the estrogen receptor-positive and negative breast cell lines. This investigation has identified up new ways that for organochlorine pesticides' can affect breast cancer growth.

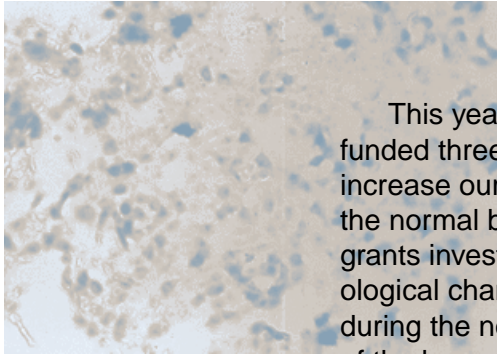
# RESEARCH in Progress

Research in progress in this area is exploring several aspects of breast cells as they relate to tumors, looking at the basic mechanisms that could explain why both normal and cancerous breast cells respond to therapeutic and preventative interventions the way that they do. **Xiao-kun Zhang, Ph.D.**, of **The Burnham Institute**, is investigating the biological basis for retinoid action in breast cancer. He is investigating the cellular suicide and maturation triggers that known and newly developed retinoids have on breast cells. He finds that the pathways employed by different retinoids synergize to produce a greater growth inhibitory effect at lower doses.

The response of breast cells to normal intracellular and extracellular signals may indicate how tumor characteristics develop. Many breast tumors, which are resistant to cell death, are also better able to move to distant sites in the body. **Gary Bokoch, Ph.D.**, of **The Scripps Research Institute**, is looking at how a cell growth regulating protein called p21-activated kinase (PAK) is involved in breast cell death and motility. **Nicholas Rampino, Ph.D.**, of **The Burnham Institute**, has begun an investigation into the degree of DNA damage and mutation that occurs in dividing breast cells due to their exposure to estrogens and anti-estrogens.

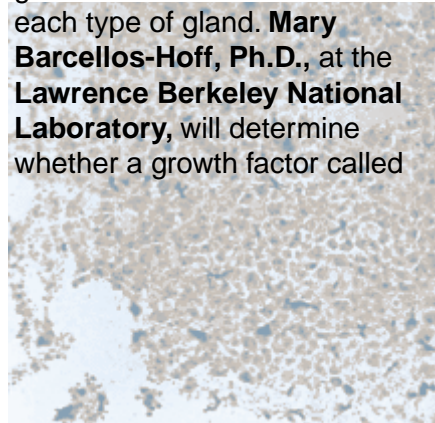
## anti-estrogens

## Recently Initiated Research



glands

This year the BCRP funded three RFA projects to increase our understanding of the normal breast. Two of the grants investigate the physiological changes that occur during the normal progression of the breast through puberty and pregnancy. **Satyabrata Nandi, Ph.D.**, at the **University of California, Berkeley**, will investigate why the mammary glands in rats that have never had offspring are more susceptible to carcinogens than the glands in rats that have (there is a similar pattern in humans) by comparing the genes that are turned on in each type of gland. **Mary Barcellos-Hoff, Ph.D.**, at the **Lawrence Berkeley National Laboratory**, will determine whether a growth factor called



TGF- $\beta$  has a significant role in the development of the breast. TGF- $\beta$  may be important in this process because 1) it is associated with epithelial cell death, which is a necessary step in the maturation of the gland and 2) it is regulated by estrogen and progesterone at different points of breast development. Understanding the role of TGF- $\beta$  in breast development could lead to finding new ways to stop tumor epithelial cells from growing. **Vito Quaranta, M.D.**, at the **Scripps Research Institute**, will determine whether the processing of a component of the extracellular matrix, Ln-5, has a significant effect on the structural integrity of the breast ducts. Loss of structural integrity is believed to be the first stage in tumor cell metastasis. These studies are designed to demonstrate how developing a deeper understanding of the properties of the normal breast can give us insights into how tumors escape their normal constraints.







# RESEARCH

## Etiology: Finding the Cause

Identifying and understanding the factors that lead to breast cancer in individual women and in the population as a whole is crucial. Through this work, we can learn how to prevent breast cancer, for example, by discovering causative factors that can then be eliminated or reduced, or by identifying conditions that predispose a person to breast cancer and for which there may be preventive treatments.



Etiology

36

# CONCLUSIONS



## Environment and gene/ environment interactions: nature and nurture

One cause of breast cancer may be traced to how the body handles carcinogens once it is exposed to them. Certain recognized environmental carcinogens are not able to cause cancer until after enzymes within the body have changed them into their toxic forms. Other enzymes in the body are able to convert these carcinogens to safe forms. **Regina Goth-Goldstein, Ph.D.**, at the **Lawrence Berkeley National Laboratory**, completed an IDEA project to examine the degree to which the ability to activate or detoxify certain carcinogens influences the risk of developing breast cancer. She investigated the genes that regulate the toxicity of a category of carcinogens, called polycyclic aromatic hydrocarbons (PAH) that cause breast cancer in animals. She found that the levels of the products from the activating gene, CYP1A1, were generally higher in the normal breast tissue from breast cancer patients than in healthy individuals. She also found that breast cancer patients tend to be missing the detoxifying gene, GSTM1, more often than further individuals without the disease. These observations are not statistically significant, indicating that further study is necessary; however, they do point out possible avenues where the relationship between genetics and carcinogens can be explored.



# estrogen

At one level, known risk factors for breast cancer can be understood as measures of the cumulative exposure of the breast to estrogen and, perhaps, progesterone—hormones that cause breast cells to grow and divide. Exposure to estrogen and progesterone is thought to be influenced both by genetic differences and environmental exposures. Thus, understanding the role of each of these influences, and how they interact, is essential. **Heather S. Feigelson, Ph.D., M.P.H.**, at the **University of Southern California**, and colleagues are working within a model they developed for breast cancer that includes genes involved in the metabolism of estrogen in the body, such as those that transport estrogen to the breast and those that convert estrogen from less active to more active forms. Dr. Feigelson's current research is based on work in her lab that showed that women who have a particular form of a gene called CYP17 are at a 2.5 fold increased risk of developing advanced breast cancer. Further investigation, with BCRP

support, found that the CYP17 genotype was associated with estrogen and progesterone levels among 83 college-age women. Estrogen measurements during the menstrual cycle showed significantly higher levels among those women with the A2 form of CYP17; progesterone was also significantly higher in these women. These data provide the first direct evidence of genetic control of serum hormone levels. Continuing this research, Dr. Feigelson found suggestive evidence that among cancer-free women, those with the A2 form of CYP17 are less likely than women with the A1 form to report current estrogen replacement therapy use and are less likely to be long term users of estrogen replacement therapy. This may be because CYP17 A2 women do not have as many menopausal symptoms compared to A1 women because of their higher endogenous hormone levels. These data may have important implications for women trying to weigh the risks and benefits of estrogen replacement therapy.

## Hormones and nutrition: understanding the modern woman's lifestyle



# carcinogens

**Stephen Howell, M.D.**, at the **University of California, San Diego**, completed a 2-year Research Project to study the *Molecular Control of Breast Exposure to Selenium*. A novel gene and protein, termed hASNA, is part of a molecular “pump” that determines the concentration of such metal ions as selenium inside cells. It is believed that selenium exerts a protective effect to neutralize the environmental toxic effects of cadmium, arsenite, and nickel on cells. Dr. Howell reported that certain breast tumor samples contained elevated levels of hASNA, and that induction of hASNA production in MCF10-A cells will cause a hypersensitivity to arsenite. The normal breast does not appear to express hASNA. In additional work, it was shown that hASNA interacts with metallothionein-II as detected using a yeast 2-hybrid screen, and a monoclonal antibody was developed to detect and measure the amounts of this protein. The association of certain genes to potential environmental factors opens the door to future work on the genetic epidemiology of this research topic.

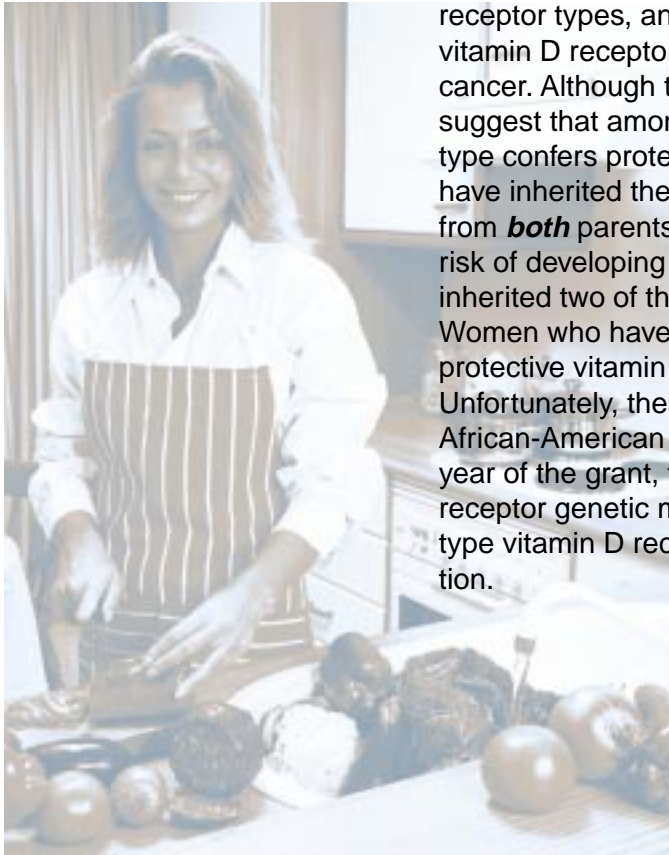
# RESEARCH in Progress

## Environment and gene/environment interactions: nature and nurture

**V**iruses have been shown to cause breast cancer in mice. Is it possible that exposure to a virus found in cows (BLV) could produce a similar effect in humans? In order to do this humans must be exposed to the virus and it must be able to get inside of cells. **Gertrude Buehring, Ph.D.** and her postdoctoral fellow **Linda Kingsbury, Ph.D.**, at the **University of California, Berkeley**, are exploring whether these two criteria are fulfilled. Dr. Buehring is investigating whether humans are actually exposed to the virus and finds that 93% of 200 volunteers appear to be. The next step is to determine whether people are exposed to live virus or inactive virus from sources such as cooked meats. Dr. Kingsbury has determined the best approach for uncovering cell receptors (gateways into the cell) for BLV and is now trying to determine whether human cells have receptors for BLV.

viruses

**Sue Ann Ingles, Ph.D., University of Southern California**, is looking into the genetic basis for the hypothesis that vitamin D may prevent cancer by interacting with vitamin D receptors in the breast and other tissues. The vitamin D receptor plays a key role in this process and occurs in at least two different genetic “types”. Her goal is to develop genetic “markers” that can be used to measure vitamin D



receptor types, and to determine whether women with specific vitamin D receptor types are relatively protected against breast cancer. Although the study is not yet complete, findings to date suggest that among Latinas, one specific vitamin D receptor type confers protection against breast cancer. Women who have inherited the protective type of vitamin D receptor gene from **both** parents appear to have approximately one-third the risk of developing breast cancer compared to women who inherited two of the “non-protective” vitamin D receptor genes. Women who have inherited one protective and one non-protective vitamin D receptor gene are at intermediate risk. Unfortunately, these genetic markers do not work well for the African-American population; therefore, during the second year of the grant, they plan to combine several vitamin D receptor genetic markers to develop a test for the protective-type vitamin D receptor gene in the African-American population.

## Vitamin D

Hormones and nutrition: understanding the modern woman's lifestyle

**James Felton, Ph.D.**, at the **Lawrence Livermore National Laboratory**, is investigating the properties of PhIP, a suspected breast carcinogen found in some cooked meats. PhIP needs to be metabolized before it becomes dangerous. Dr. Felton found that individuals metabolize PhIP into different types and proportions of breakdown products. He is currently analyzing these products and developing an animal model that generates the same breakdown products. Ultimately, he will determine which breakdown products are most closely associated with developing breast cancer.



## Other searches for the causes

**Thomas Balon, Ph.D.**, of the **City of Hope National Medical Center**, is looking at the relationship between breast cancer and nitric oxide, a molecule that regulates cells' ability to produce energy from sugars. So far, he found that when an enzyme that produces nitric oxide is inhibited, it results in decreased sugar transport only in estrogen-dependent breast cancer cells. Regulation of nitric oxide may have a differential effect on how estrogen-dependent cells convert sugars to energy, thereby affecting how they grow and multiply.

There are a number of other very interesting ongoing BCRP studies into the etiology of breast cancer that were funded in the last two years, but which require extensive subject recruitment, data gathering, complex laboratory and statistical analysis before any results can be obtained. Therefore, there are as yet no findings of note for such promising ongoing projects as the work of **Karla Kerlikowske, M.D.**, at the **San Francisco VA Medical Center**, looking at predictors of recurrent breast tumors in women with ductal carcinoma in situ; the work of **Thomas Mack, M.D., M.P.H.**, at the **University of Southern California**, looking at whether mammographic density

## enzymes

(a predictor of risk in White women) is an inherited characteristic, and, if so, whether adult exposures can modify this density; the work of **Anna Wu, Ph.D.**, at the **University of Southern California**, investigating whether individual differences among women in processing (because of polymorphisms or differences in our genetic make-up) certain commonly encountered environmental compounds found in cooked meats, tobacco smoke, etc. are likely to be influencing the risk for breast cancer; the work of **Gerhard Coetzee, Ph.D.**, at the **University of Southern California, Norris Cancer Center**, attempting to explain how variants of the CYP17 actually cause differences in the activity of the enzymes they regulate, and, in turn, how they might be related to the risk of developing breast cancer; and, the work of **Peggy Reynolds, Ph.D.**, at **The Public Health Institute** looking at organochlorine pesticides, which were widely used in the past in industrial processes, and dioxins (a byproduct in the manufacture of petroleum-based herbicides), and whether there may be association between exposure to these compounds and the risk of breast cancer in African American women. Findings from these studies over the next few years should provide more clues to the perplexing problem of the causes of breast cancer.

## exercise

## Recently Initiated Research

**i**n 1998, the BCRP awarded six grants that explore the causes of breast cancer in different ways. One of these is a Training Program Award (**Ronald Ross, M.D.**, at the **University of Southern California**), designed to train graduate students in a multidisciplinary environment that will encourage innovative thinking about breast cancer problems.

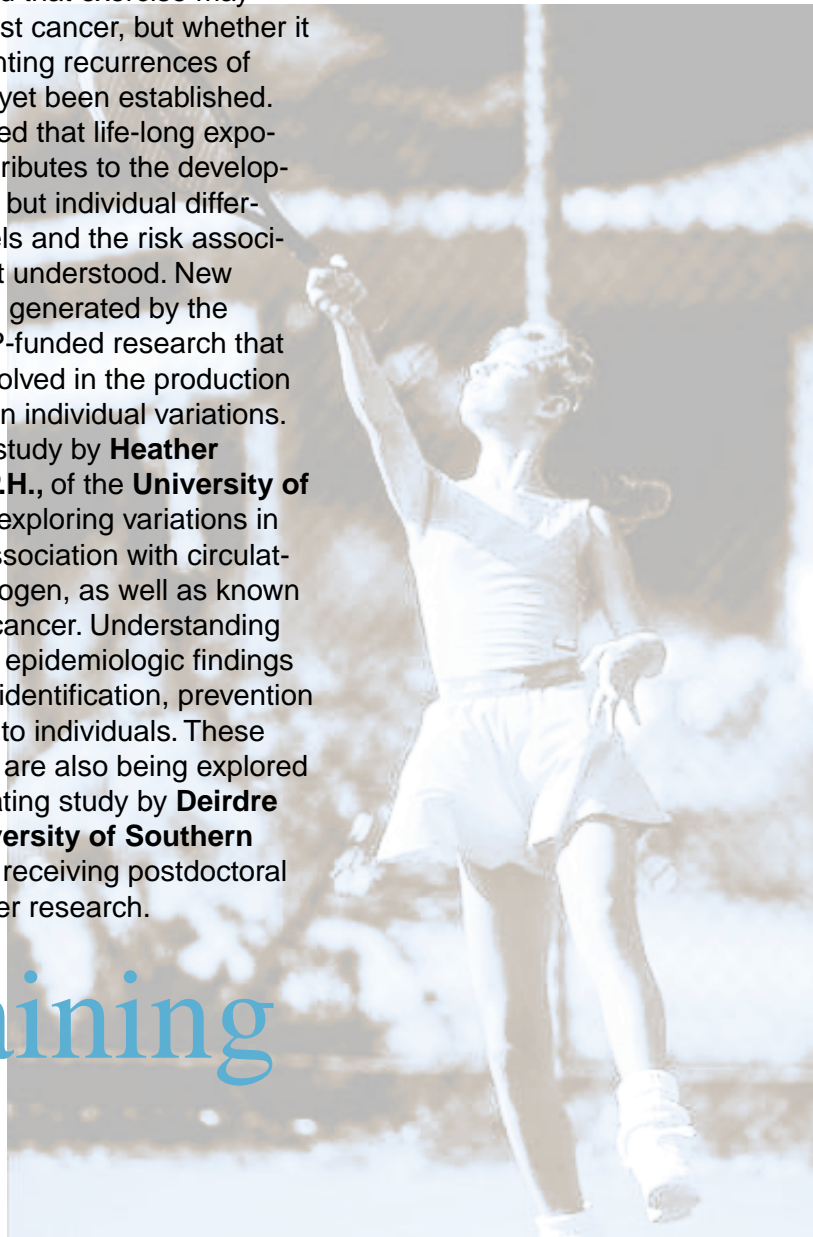
Two of the awards are Community-Initiated Research Collaboration (CIRC) Awards. In a Pilot Award, a team (**Mary Gould of Marin Breast Cancer Watch and Margaret Wrensch, Ph.D.**, of the **University of California, San Francisco**), will explore methods to collect information about adolescent years from older women, with a long-term goal of identifying factors in adolescence that might lead to breast cancer later in life. In a CIRC Full Research Award, **Stephanie Roberts, M.D.**, of **Lyon-Martin Women's Health Services** and **Suzanne Dibble, D.N.Sc.**, of the **University of California, San Francisco**, are working together to explore a commonly believed but unproven hypothesis that lesbians have higher frequencies of some known breast cancer risk factors, leading to a higher risk of breast cancer in this population.



An IDEA grant was awarded to **Lisa Shames, Ph.D., M.P.H.**, of the **University of Southern California**, to explore the role of exercise in breast cancer recurrence. Several studies have suggested that exercise may reduce the risk of breast cancer, but whether it can also help in preventing recurrences of breast cancer has not yet been established.

It is strongly believed that life-long exposure to hormones contributes to the development of breast cancer, but individual differences in hormone levels and the risk associated with these are not understood. New hypotheses have been generated by the finding in earlier BCRP-funded research that variations in genes involved in the production of estrogen may explain individual variations. This has led to a new study by **Heather Feigelson, Ph.D., M.P.H.**, of the **University of Southern California**, exploring variations in two genes and their association with circulating blood levels of estrogen, as well as known risk factors for breast cancer. Understanding the biological basis for epidemiologic findings opens the door to risk identification, prevention and treatment tailored to individuals. These and other risks factors are also being explored in a hypothesis-generating study by **Deirdre Hill, Ph.D.**, of the **University of Southern California** who will be receiving postdoctoral training in breast cancer research.

training







# RESEARCH

Prevention  
and Risk  
Reduction:

Ending the  
Danger  
of  
Breast  
Cancer

t

he BCRP is supporting two main approaches to breast cancer

prevention. The first aims at improving our understanding of risk factors as a basis for lifestyle changes to reduce the impact of these factors. Elucidating the precise role of exercise, diet, early pregnancy and other hormone-affecting events, are important examples of this approach.

The second approach aims at developing products that directly prevent or help repair the early cellular changes that can lead to breast cancer. Here, investigation into natural products offer the prospect of discovering non-toxic, efficacious compounds without adverse side effects, that might relatively quickly become available.

# CONCLUSIONS



hormones

There is a great deal of experimental, clinical and epidemiologic evidence that hormones play a major role in breast cancer. Viewed in this way, the known risk factors for breast cancer can be understood as those affecting the cumulative exposure of the breast to estrogen and, perhaps, progesterone. Thus, many of grants funded by BCRP examine ways this exposure can be beneficially modified. **Catherine Carpenter, Ph.D.**, at the **University of Southern California School of Medicine**, *Physical Activity: Impact on Hormones and Breast Cancer Risk* following up on her previous reports of the benefits of exercise for postmenopausal women, found that breast cancer risk was substantially reduced among women with stable weight (less than 17% gain) who maintained a high level of exercise both before and after age 40. One explanation for this reduction may be that strenuous exercise, by promoting a leaner body mass, may affect hormone levels known to be associated with the presence of excess body fat.

**Satyabrata Nandi, M.P.H., Ph.D.**, at the **University of California, Berkeley**, reported on the *Identification of Pregnancy — Associated Breast Cancer Genes*. In this 1-year IDEA pilot grant, he compared the gene expression of virgin and previously pregnant rats. It is known

that pregnancy in women by the age of 18 provides a significant (30%+) lifetime reduction in breast cancer risk. However, the genetic basis for this protection has not been identified. In this project a novel candidate gene, termed RMT1, was identified and gene was found to be expressed in a majority (74%) of rat tumors compared to normal mammary cells. The RMT1 sequence was not present in DNA/protein databases, and it appears to be mammary gland-specific. Dr. Nandi was funded in 1998 through a 3-year RFA award from the California BCRP to conduct further studies on RMT1 and to search for additional pregnancy-associated breast cancer genes.

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# RESEARCH in Progress



**Pamela L. Horn-Ross, Ph.D.**, of the **Northern California Cancer Center**, conducted a study to address two questions relevant to our understanding of the etiology of breast cancer: (1) whether estrogens found in plant foods reduce breast cancer risk in amounts commonly consumed by non-Asian postmenopausal women; and (2) whether obesity increases breast cancer risk only when a woman's diet does not contain a sufficient amount of these plant estrogens. Preliminary analyses suggest that recent consumption (i.e., within the year prior to breast cancer diagnosis) of foods containing plant estrogens

did not impact breast cancer risk either positively or negatively in the study group of non-Asian postmenopausal women. Consistent with her second hypothesis, she found a slight suggestion that obesity increased a woman's risk of breast cancer only when her diet did not include a substantial amount of plant estrogen-rich foods. However, this association was not statistically significant. While further analyses are underway to verify these initial observations, at present her study suggests that foods rich in plant estrogens do not appear to be useful in breast cancer prevention at levels commonly consumed by non-Asian California women.

foods

How hormone levels may be affected by exercise is being investigated by **Lisa Shames, Ph.D., M.P.H.**, at the **University of Southern California School of Medicine**, who is investigating the relationship of exercise to ovarian function across a range of physical activity—a range that non-athletes might reasonably be expected to maintain. She has to date just finished collecting all of the blood and urine samples necessary and will complete the hormone assays and data analysis during the coming year.

Women who have breast cancer do not die from the primary cancer in the breast but from the consequences of its metastasizing to other parts of the body; how to prevent this is a key question being investigated by **Kent Erickson, Ph.D.** of the **University of California, Davis**. Dr. Erickson has shown that when animals were fed high levels of fish oil, breast tumor growth was slower and the level of metastasis to the lung was decreased when compared to animals fed a diet containing a vegetable oil, safflower oil. The continuation of their work will focus on the possible mechanisms underlying this phenomenon: whether fish oils decrease a tumor's ability to stimulate growth of its own blood vessels, and decrease the specific enzymes necessary for metastasis.

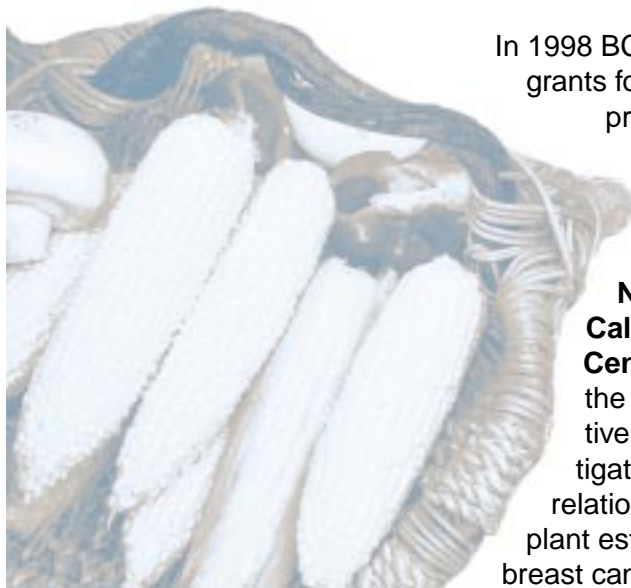
## green tea



**Nurulain Zaveri, Ph.D.**, at **SRI international** is continuing the chemical synthesis of derivatives from a component of green tea, epigallocatechin-3-gallate and testing them for their ability to prevent breast cancer. Several of these newly-synthesized compounds are showing biological activity of cell growth inhibition equal to or greater than the parental compound from green tea. These will be tested in mouse models of breast cancer.

**Gary Firestone, Ph.D.** at the **University of California, Berkeley** is examining how a compound produced in Brussels sprouts, cabbage and broccoli, called indole-3-carbinol (IC3), actually works to inhibit cancer cell growth. He is finding that IC3 causes a decrease in the cellular amounts of proteins that regulate the ability of cells to divide. Interestingly, the growth inhibition appears to be effective in both tamoxifen-resistant and tamoxifen-sensitive cells. IC3 has a low toxicity and, because of its presence in the natural diet, there is a promising potential for its use as a long-term preventative agent.





vegetables

In 1998 BCRP awarded 4 grants for the study of prevention of breast cancer. **Pamela Horn-Ross, Ph.D.**, of the **Northern California Cancer Center** will conduct the first prospective study to investigate in detail the relationship between plant estrogens and breast cancer risk using a recently developed unique

database containing the content of seven different estrogen compounds. She will examine the role of plant estrogens, antioxidant vitamins, and the balance of dietary fat and fiber consumption, among other factors. **Ling Jong (SRI International)** and **Shiuan Chen (Beckman Research Institute of the City of Hope)** will focus on specific dietary components. Dr. Jong's goal is to develop a safe, effective reliable breast cancer preventive agent based on Indole-3-carbinol (I3C), (a dietary component found in cruciferous vegetables such as cabbage, broccoli, and Brussels sprouts), which is

## Recently Initiated Research

currently undergoing Phase I clinical trials. Dr. Chen will investigate the chemopreventive action of grape juice using two animal models, and try to identify the active components in grape juice. He is following up on intriguing laboratory experiments showing that grape juice (in particular red seedless grape juice) stopped estrogen production in cells in a test tube and that tumors implanted in mice fed with a very small amount of grape juice daily for 5 weeks were one-third the size of those in similarly implanted mice not given grape juice.

**Giske Ursin, M.D., Ph.D.**, of **University of Southern California's Norris Comprehensive Cancer Center**, following up on some preliminary indications, will investigate whether women who have a BRCA 1 mutation and who use oral contraceptives have a much higher risk than women without this mutation who use oral contraceptives.





# RESEARCH

Early  
Detection:  
Improving  
the  
Chances  
for a  
Cure

**U**ntil breast cancer can be prevented, detection at the earliest time

possible remains an essential goal. In its first four cycles, BCRP has funded 40 grants aimed at the earlier detection of breast cancer either through improving access and detection technologies or the discovery of biomarkers that could be used to signal the presence of the disease.

# CONCLUSIONS

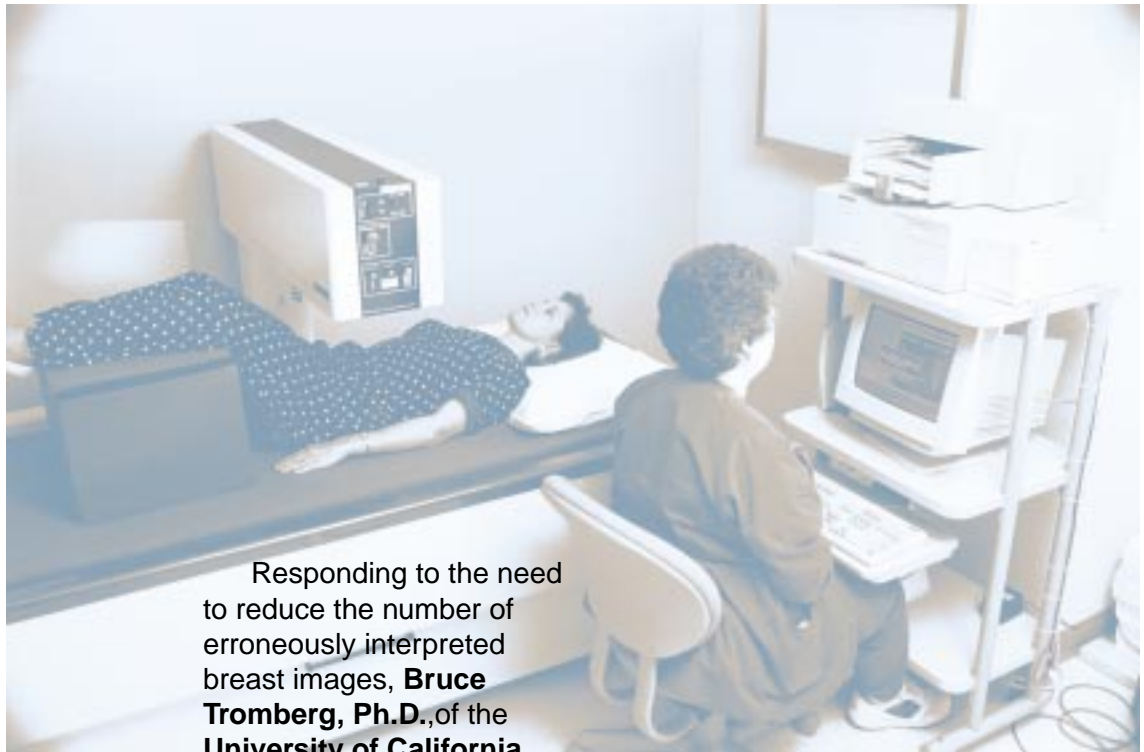
## Developing and improving imaging technologies: better and easier detection



technology

The thrust of research in imaging technology has been toward reconfiguring current imaging devices such as PET and SPECT scanners to a size and configuration more suitable to breast imaging; improving the ability of all techniques to detect abnormal masses at their smallest size; and bringing new technologies such as optical imaging into use.

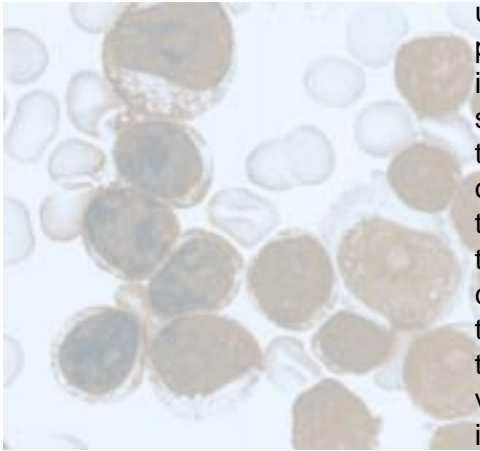
**Edward Hoffman, Ph.D.**, at the **University of California, Los Angeles** has developed a promising small scintillation camera configured to more easily image the breast by combining a NaI(Tl) crystal and a Position Sensitive Photomultiplier. This camera could provide a method of identifying malignant lesions identified as suspicious by mammography and has shown in laboratory studies to be able to detect tumors as small as 0.5 centimeter in diameter. A postdoctoral fellow, **Yiping Shao, Ph.D.**, at the **University of California, Los Angeles** was also funded to design and develop a detector—in this instance a PET scanner—specifically for imaging the breast. He was able to successfully bend optical fibers at large angles with insignificant light loss, thus improving detector performance and exceeding the spatial resolution and count rates (this would lower the radiopharmaceutical dose to the patient) expected in the original proposal. Its predicted performance may result in many significant improvements over conventional clinical PET scanners, and at much lower cost.



Responding to the need to reduce the number of erroneously interpreted breast images, **Bruce Tromberg, Ph.D.**, of the **University of California, Irvine**, undertook research to improve the potential of non-invasive optical imaging using near-infrared light. The promise of optical imaging to provide detailed physiological information on breast tissue has been hampered by the light scattering that blurs small, buried, light-absorbing tumors. His results (from 18 patients) show that pre- and post-menopausal normal breasts exhibit detectable wavelength dependent differences in

both absorption and scattering, and suggests that optical methods are quite sensitive to cellular, molecular and structural differences between normal and malignant breast tissues. Further work is necessary to pin down the precise hemodynamic, oxygen consumption, and structural changes that are encoded within optical signatures. With such information, a new generation of safe, non-ionizing diagnostic tools is possible that could complement existing methods and enhance the overall accuracy, specificity and sensitivity of breast cancer detection.

imaging



## blood vessels

**Robert Brasch, M.D.**, at the **University of California, San Francisco**, completed a 3-year Research Project for the *MRI Detection of Microvascular Status in Breast Cancer*. The blood vessels feeding tumors are increasingly being appreciated as a unique target for therapy. This project explored improvements in imaging tumors in rats with specific attention to selecting the best MRI detection methodology and the use of contrast agents to analyze the tumor blood vessels. A correlation was found between the severity of the tumor and the leakiness of the blood vessels, and an angiogenesis inhibitor (anti-VEGF) was found to decrease this leakiness. Interestingly, differences in the tumor accumulation of chemotherapeutic agents was observed when blood vessel leakiness was altered. These are key insights in technology development for the anticipated uses of chemotherapy and angiogenesis inhibitors, and it presents a rationale for pursuing MRI to evaluate therapy and to measure parameters of tumor leakiness prior to treatment.

**Michael Buonocore, M.D., Ph.D.**, at the **University of California, Davis**, completed a one-year project intended to develop and test new methods of measuring the blood flow through breast tumors, to help determine the presence of abnormal tissue, and to help assess whether the abnormal tissue is malignant or benign (cancerous or non-cancerous). Previous MR studies, using injections of a contrast material (i.e., a drug-like compound that is absorbed by the body's tissues) to improve the ability to see abnormalities, had shown that the blood flow in malignant tumors is higher than that in benign tumors and normal tissue. Using the new methods, he and his team hoped to perform the same type of measurement *without* the use of an injection of contrast material.

He was able to obtain measurements in eight normal subjects without breast lesions and five subjects with palpable and/or mammographically visible breast lesions. He was able to show that his method is reproducible and extremely sensitive to the amount of blood flowing through breast tissue, and is able to detect small differences that exist between abnormal and normal tissue.



## ultrasound

**George Leopold, M.D., and Michael André, Ph.D.,** at the **University of California, San Diego**, undertook a one-year study to examine the suitability of a new ultrasound system for imaging the breast. This system makes cross-sectional image “slices” by transmitting sound waves into the breast from all sides and reconstructing the images in a computer similar to the operation of a x-ray computed tomography scanner (CT or “CAT”). This technology needed to be evaluated for its ability to distinguish between normal tissues and the many types of “lumps” or masses that may occur in the breast.

During the period of study, progress was made in understanding the appearance of different tissues as well as their unique ultrasound “signature”. Preliminary results in very dense breasts, which are difficult to image well with mammography, were also encouraging. The technical quality of the ultrasound CT images and the potential limitations of the method are now better understood.

## Screening



**Tumay Tumer, Ph.D., of Nova, Inc.,** undertook a one-year study to try to improve the technology for producing X ray images of the breast that does not use film as the exposure medium. Traditional mammography systems use phosphor screens to generate light from X rays and photographic film to record the resulting images for display on a viewbox. Image quality is limited by the chemical processing procedure and has a narrow contrast range, and altering this image requires re-exposure of the patient to x-rays to obtain another film. In a digitally recorded mammogram, alterations can be made on the computer.

Specifically, in this project they proposed to develop a two-dimensional array of detector elements on a combination of cadmium, zinc and telluride crystals so that an image of the X rays passing through the patient’s breast could be produced. Directly converting x-ray energy into electrons would provide an image with smaller visible detail, using less radiation, and showing less interference on the image from the imaging device itself (“noise”) than present x-ray films.



The detectors proved more difficult to assemble than anticipated, and at the project's end work was just beginning on lining a narrow column with these detectors to scan underneath the patient's breast. If this study is eventually successful, Nova expects to obtain funding for the development of pixel detectors from this material for a commercial digital mammography system called DigiMAM™.

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## Biomarkers and novel screening approaches: unmasking the hidden signs



**Nicholas Petrakis, M.D.**, of the **University of California, San Francisco**, was funded to expand on his previous research showing that women whose nipple aspirate fluid contained unusual or “atypical” breast epithelial cells had a three-fold risk of breast cancer compared to women with normal findings, and a five-fold increased risk compared to women who did not yield any breast fluid. His BCRP grant investigated whether combining nipple aspirate fluid findings with measures of mammographic density (shown to be predictive of breast cancer risk in White women) would improve the ability to estimate a woman’s risk of developing breast cancer. While this combination did substantially improve the positive predictive value of developing breast cancer, unfortunately the increase was of no clinical value due to the excess number of false positive predictions.

biomarkers

**Per Borgstrom, Ph.D.**, at the **La Jolla Institute for Experimental Medicine**, completed a 1-year IDEA project to study *Platelet Factor 4: a Marker for Malignant Breast Tumors*. A visualization technique of intravital microscopy was used to show that platelet factor 4 that is labeled with fluorescence was associated with regions of tumor cell-induced blood vessel growth (angiogenesis). The breast cancer cell line MCF-7 had the highest level of platelet factor 4, which was consistent with a higher tumor growth rate and concurrent blood vessel growth. Dr. Borgstrom was also able to inject labeled platelet factor 4 into the capillaries of mice with tumors and show that it rapidly localized to the tumor sites and represented a new and potentially useful biomarker for breast cancer.

**Ashraf Imam, Ph.D.**, at the **University of Southern California**, completed an IDEA award investigating the validity of a new prognostic marker for breast cancer called LEA.135. He found that the presence of this marker in human invasive breast cancers strongly correlates with a longer tumor-free and overall survival rate. This finding held up in White and Black women even when other prognostic markers were considered. When Dr. Imam examined the presence of LEA.135 in pre-cancerous cells (ductal carcinoma in situ), he found the presence of LEA.135 indicated a slightly lower risk of developing breast cancer.

## reminder

In order to determine how to take advantage of a tumor marker, it is always helpful to understand how it functions in a normal cell and how its function has changed in a tumor. **Christina Niemeyer, Ph.D.**, at **The Burnham Institute**, completed a postdoctoral fellowship exploring the function of a breast cancer marker (Cripto) in breast cancer formation. She examined the levels of Cripto in the breasts of mice at different stages of development and found that the Cripto levels vary with the physiological state of the gland. Dr. Niemeyer also found that when breast cells were grown in the culture dish, the Cripto levels could be increased by exposing the cells to pregnancy hormones such as prolactin. Cultured cells with high levels of Cripto grew at an increased rate, whereas cells with lower levels grew more slowly. When normal cells with low Cripto were reintroduced into mice they were unable to grow; however, when breast tumor cells with low Cripto levels were reintroduced they still formed tumors. These studies show that Cripto may have its greatest impact on the susceptibility of the pre-cancerous breasts rather than on tumor growth.



## Improved access to screening: reaching every woman

While increasing numbers of women are receiving mammograms and clinical breast examinations, the number of women who obtain screening on a regular basis remains low. **Nicole Howard** at the **CHG Foundation** and **Gregory Talavera, M.D., M.P.H.**, at **San Diego State University**, formed a team to identify interventions that show potential for increasing annual rescreening within the context of a state-funded program. Among women studied, they found that only 32% were receiving annual rescreening. Of those who had been seen for

rescreening, 68.9% had received a reminder from the primary care provider. Of those who had not been seen for rescreening, only 38.7% had received a reminder. Clearly reminders from women's doctors beneficial, but they found that, within the population served by the state-funded program, yearly reminders may miss a significant proportion of women. 27% of women selected for the study could not be contacted (e.g., disconnected telephone, interviewers reached a wrong number). An additional 25.7% of women could not be reached after repeated calls, suggesting that they too may be difficult to reach with standard rescreening reminders. Women who were contacted were more than twice as likely to have been rescreened than women who could not be contacted. Thus, the team suggests that interventions delivered during the 12-month interval between initial and repeat screening may be more effective than standard anniversary date reminders.

camera

# RESEARCH in Progress

Developing and improving imaging technologies: better and easier detection



Among grants to improve to improve existing technologies is the work at the **University of California, Davis** by **John Boone, Ph.D.** and **Anthony Seibert, Ph.D.** Dr. Boone's research is to improve the spatial resolution (the capacity to image small objects) of digital mammography systems. The current technologies that enable the capture of more X rays also "blurs" the visible light produced from these rays. Dr. Boone hopes to use a "hybrid detector" which uses microplate technology (a honeycomb matrix of leaded glass with tiny square pores aligned

with the x-ray source and packed with x-ray phosphor) to channel the visible light toward the light detector and reduce blurring and improve resolution. To date he has manufactured the honeycomb, verified the performance of a necessary x-ray spectrum measuring device, and is conducting computer simulations to study the ability of the system to exclude scattered radiation. Dr. Seibert intends to construct and test a novel digital mammographic imaging detector (a fiber-optic scintillator coupled to a digital camera) that may be useful for more sensitive detection of breast cancer, and which may prove to be a cost-effective solution to the problem of adequately imaging the dense breast. Under study is the alternative phosphor (light producer) cesium oxide. Initial testing of this phosphor in the detector (Complementary Metal-Oxide Semiconductor or CMOS) camera reveals a resolution satisfactory for imaging microcalcifications in the breast. Other functional aspects of the camera are now being tested as a method for correcting image imperfections.

detection

**William Moses, Ph.D.**, of the **Lawrence Berkeley National Laboratory** and **Manbir Singh, Ph.D.**, of the **University of California, Los Angeles** are both working to improve existing detection technologies. Dr. Moses is working to optimize PET cameras (an acronym for Positron Emission Technology) so as to better determine whether suspicious structures observed in mammograms have the increased metabolism associated with breast cancers. These cameras would image the metabolic activity in the breast (to detect a cancer) or the axilla (to detect any metastasis to the lymph nodes). The first phase of the work of improving and adapting three of the basic components (an array of scintillator crystals, a photomultiplier tube, and a photodiode array with one element per scintillation crystal) has been partially completed. The electronics necessary for reading out the photomultiplier tube and the photodiode array have been fabricated and tested, and a prototype detector tested. Work has also begun on the software necessary to operate the camera, acquire data, and reconstruct images from the data.

Dr. Singh will attempt to design a system that will provide, using a newly designed camera configured for the breast, a three-dimensional image from the gamma rays emitted from radiopharmaceuticals. To date, they have successfully conducted computer simulation and experimental studies using the

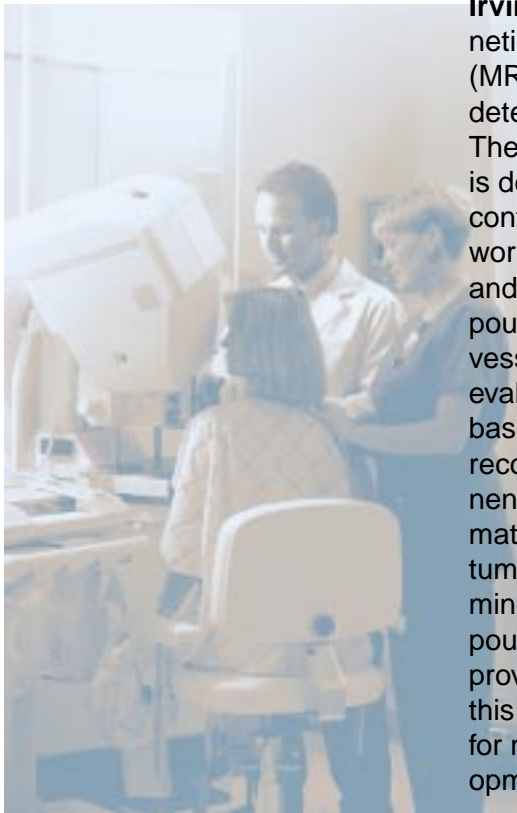
new generation of semiconductor detectors (cadmium zinc-telluride, CZT) arranged either in a cylindrical or hemispherical configuration that does not require breast compression. Results are promising and for the first time suggest the feasibility of using CZT detectors in a SPECT (single photon emission computed tomography) system. Further experiments will be conducted in the next year under a realistic clinical imaging situation.

**Jack Sklansky, Eng. Sc.D.**, of the **Charles R. Drew University of Medicine & Science**, is attempting to develop a computer system to help radiologists use large collections ("databases") of digitized mammograms as aids in determining whether or not to recommend biopsies with the goal of reducing the number of unnecessary biopsies. The first test of this system enabled radiologists to cut approximately in half the number of benign (non-cancerous) biopsies and the number of missed cancers. This test also indicated the potential of radiologists electronically "browsing" a large database to find mammograms that are visually and medically similar to a mammogram under analysis.

Quality

# diagnosis

A key issue in early detection is combining more advanced imaging technology with the ability to analyze the specific characteristics of breast tumors that could indicate a higher potential towards malignancy or invasion. **Orhan Nalcioglu, Ph.D.**, at the **University of California, Irvine**, is combining Magnetic Resonance Imaging (MRI) with specific probes to detect tumor blood vessels. The critical research hurdle is developing an imaging contrast agent that both works for the MRI detection and is selective for compounds present in blood vessels. He is presently evaluating a protamine-based MRI agent that should recognize heparin, a component of the extracellular matrix, which is present in tumor blood vessels. Protamine is a biological compound that is already approved for human use, so this project has the potential for more rapid clinical development.



Two other studies are investigating exciting applications of the new digital mammography technology: one within a medical center, and the other linking the community with a medical center. **Daniel Valentino, Ph.D.**, of the **University of California, Los Angeles**, intends to develop computer systems that enable cost-effective digital mammography in a hospital or community clinic. To date they have: 1) implemented an infrastructure to acquire, archive, and distribute full-field digital mammography images, and have integrated it with the hospital's imaging and information system; 2) established an image database for evaluating systems for processing and display of digital mammography images; 3) developed software to reduce the size of original breast images and restore the compressed image back to its original size, evaluated the ability of radiologists to use these restored images, and determined the limits of useful compression (a factor of 25); 4) developed workstation software for the rapid display and screening of digital mammograms which is now available in a software toolkit called the UCLA Digital Viewbox/Tk™.



**H.K. Huang, D.Sc.**, of the **University of California, San Francisco**, is attempting to demonstrate that: 1) telemammography technologies can be developed for routine clinical operation; and 2) real-time telemanagement (i.e., converting a mammogram to a digital image at the examination site and electronically transmitting it to a breast imaging center for immediate expert consultation) can be established for mammography practice. To date, they have been able to complete the telemammography chain with a full field direct digital mammography system (FFDDM) between Mt. Zion Hospital (the breast imaging expert center) and the Laboratory for Radiological Informatics UCSF. Preliminary results using the FFDDM indicate that image quality is at least as good as, if not better than, conventional film mammograms.



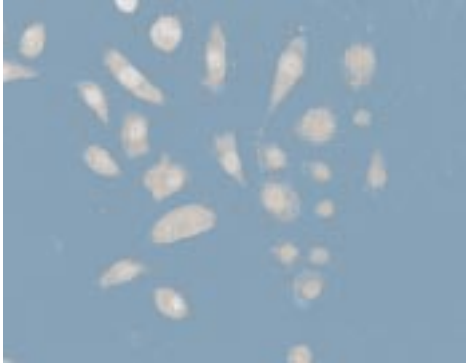
Another study applicable to the use of both digital and conventional mammography is that being conducted by **Laura J. Esserman, M.D.**, at the **University of California, San Francisco**, who is investigating the factors required to achieve high cost-effectiveness in mammography screening in California, and will then develop a plan to promote the provision of the highest quality screening services for the least possible cost. This extremely ambitious, many-faceted research involves quality control studies of mammography and mammographers, an overview of the Northern California market for mammographic screening, identifying strategies for adoption of a low-cost regionalized screening program, estimating the cost of implementing telemammography and its potential benefits, and examining the possible role of publicly funded programs. To date, the quality control studies have been completed and the results are being analyzed and the telemammography study is underway.

In order to help ensure the continued entrance into breast cancer research of promising students in various fields within the imaging technologies discipline, BCRP has funded a biomedical physics graduate training program at the **University of California, Los Angeles**, under the direction of **Carolyn Kimme-Smith, Ph.D.** To date, five students have been enrolled and are making excellent progress in their studies and research endeavors.

## telemammography



## Biomarkers and novel screening approaches: unmasking the hidden signs



# antibodies

**William M. Pardridge, M.D.**, at the **University of California, Los Angeles, School of Medicine**, extending previous BCRP work, is testing 'cationized' HER2 monoclonal antibody in a suitable strain of mice (a strain of mice which do not reject implanted human tumor tissue) developed specifically as part of this study. Dr. Pardridge previously demonstrated that the migration of this antibody across the blood-tumor barrier into the tumor is facilitated when the antibody has been given an electrical charge (cationized). He is now preparing to conduct a comparison study of native (uncationized) and cationized HER2 antibody, both tagged with a radioisotope, to evaluate the extent to which the cationization improves the tumor uptake of the antibody, thus paving the way for future improved early detection and possible treatment of breast cancer in humans.

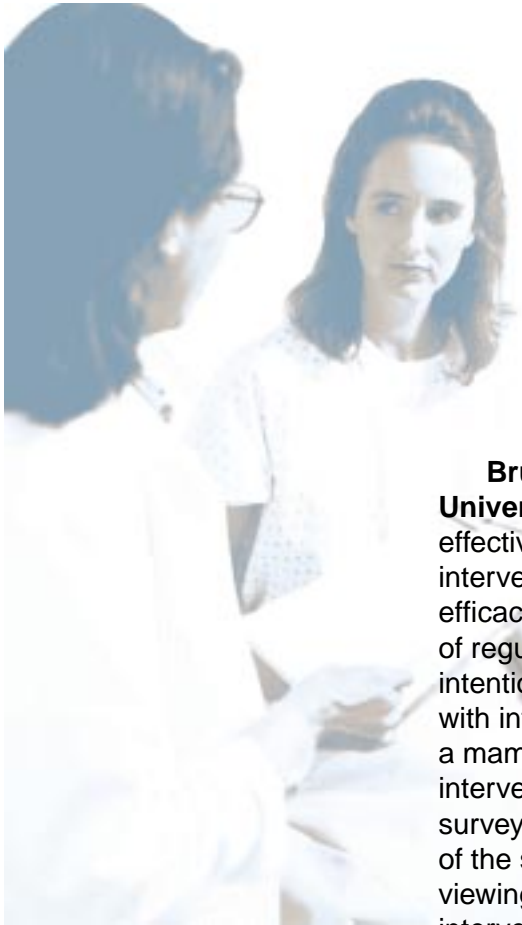
**David Vera, Ph.D.**, at the **University of California, San Diego**, is working toward a similar goal, improved uptake of a radiopharmaceutical, in this case within the lymph nodes. The portion of his work funded by BCRP is to measure the size distribution of a new sentinel lymph node imaging agent and subsequent versions of this agent—a parameter important to the ability of such an agent to rapidly enter the lymph channel and clear the injection site. The first measurements have been made, and next year the size distribution of the final version will be made.

**Malcolm C. Pike, Ph.D.**, of the **University of Southern California School of Medicine**, is investigating whether mammographic densities can be used to predict the risk of breast cancer in African-American and Asian-American as has been found for White women, and in younger as well as in older women. They plan to study the mammograms of 1260 women. To date they have obtained and read a portion of the necessary mammograms, but no findings are available to date.



One goal for detecting breast cancer earlier is to take advantage of tumor biology to identify tissues at risk of becoming invasive cancers. Two investigators are using histological approaches to characterize these tissues. **Susan P. Hawkes, Ph.D.**, of the **University of California, San Francisco** is determining whether a protein called TIMP-3 is a reliable early marker of breast cancer. Dr. Hawkes has developed an assay for TIMP3 that can detect faint traces of TIMP3 in early cancers and is in the process of testing whether it can be used as a non-invasive test for the presence of pre-cancers. **Margaret Huflejt, Ph.D.**, of the **La Jolla Institute for Allergy and Immunology**, is looking at whether a protein called galectin-4 can be used as a breast cancer marker. She has confirmed that galectin-4 is expressed in 100% of breast cancers, but is found in only a few pre-cancerous and noncancerous lesions. She has developed nucleic acid based probes and a new antibody to look at blood levels in patients.

biology



## Recently Initiated Research

### Improved access to screening: reaching every woman

**Bruce Allen Jr., Dr. P.H.** of the **Charles R. Drew University of Medicine & Science** is studying the effectiveness of using a culturally-specific telephone intervention designed to increase participants' self-efficacy, increase their knowledge about the importance of regular mammograms, identify and modify their intentions to undergo screening, and provide women with information to counter their reasons for not having a mammogram. Using input from focus groups, an intervention was designed, and initial work on the survey began in December 1996 with the programming of the survey in a Computer Assisted Telephone Interviewing (CATI) system. The testing of this telephone intervention is expected to continue through September 1998.

biopsy

**Sora Park Tanjasiri, Dr. P.H.** at the **University of California, Irvine**, is investigating the breast cancer knowledge, attitudes and behaviors toward screening of two groups of Pacific Islander immigrants, the Chamorros and the Tongans, and is attempting to elucidate the predictors of their screening behavior. Initial focus group work has been done during the past year and the survey instrument is under development.



Two studies are evaluating various aspects of self-care with respect to breast cancer.

**Jacqueline O'Connor, Ph.D.**, at the **University of California, Davis**, is investigating psychological characteristics that motivate breast cancer early detection practices, and variables that predict continuity and discontinuity in health practices following breast biopsy with a benign (non-cancerous) result. Dr. O'Connor's analyses of her data suggest that, while experiencing a threat to breast health (in this case a breast biopsy) can generate heightened perceptions of personal vulnerability and cancer anxiety that may persist for as long as one year following the event, these psychosocial consequences may not necessarily interfere with subsequent early detection practices. **Noreen C. Facione, Ph.D., R.N.**, at the **University of California, San Francisco**, is studying how English and Spanish-speaking African-American/black, Hispanic/Latina, and Anglo/white women in the San Francisco Bay Area decide whether or when to consult their health care provider about a breast change that may be a signal of breast cancer. Dr. Facione has found that twenty three percent of

## self-care

the women in this community-based convenience sample described themselves as potentially likely to delay seeking a professional evaluation of a breast symptom that worried them. Younger, less well educated, Black and Latina, and lower income women were more likely to say they would delay. Many of these differences were explained by the women's judgments about their access to health care services, perceptions of prejudicial treatment in the health care setting, habits of using self care remedies rather than seeing a health care provider, beliefs that treatment was futile should the symptoms prove to be cancer, prior habits of health care utilization, and eagerness to engage in making difficult decisions.

Many breast cancers are still diagnosed by clinical and self breast examinations using touch. It is the “viscoelastic” characteristics of the breast tissues that enable one to detect irregularities in tissue firmness and consistency. **Michael Buonocore, M.D., Ph.D.**, at the **University of California, Davis Medical Center**, proposes that magnetic resonance imaging (MRI), coupled with a device to mechanically vibrate the tissue, could be used to detect these same tissue characteristics. The advantages of such a device would be greater sensitivity and the capability to “see” deeper within the breast.

After suspicious masses have been detected in the breast, they must often be biopsied to determine whether or not they are cancerous. **Henry Van Brocklin, Ph.D.**, at the **Lawrence Berkeley National Laboratory**, is attempting to develop a pharmaceutical that will carry a radioactive label only to tissue cells that are cancerous. If the proposed pharmaceutical can be developed, it would enable physicians to locate suspicious masses and determine whether they are cancerous in one step.

Most breast cancers that metastasize (spread to other parts of the body) do so through the lymphatic drainage system which radiates out from the breast to nodes in the axilla (armpit). If the node which first receives this drainage (and thus likely the cancer cells) is free of cancer, then it is very likely that the cancer has not spread outside of the breast. Determining whether this first node (called the sentinel lymph node) is free of cancer is important because it most often means that it is not necessary to remove all of the lymph nodes—a procedure that often results in chronic physical problems, discomfort or pain. However, finding this sentinel node can be difficult, even for the most experienced surgeons. Recent techniques using either a blue dye or a radioactive tracer show great promise to dramatically improve the surgeon’s ability to easily find the sentinel lymph node. **David Vera, Ph.D.**, at the **University of California, San Diego**, is proposing to combine a dye and a radioactive tag into a single agent which should allow surgeons to easily and precisely locate the sentinel node. The goal is to develop a sentinel node detection agent that will enable a 100% success rate.









# RESEARCH

## Pathogenesis: Understanding the Disease

**b** CRP's priority issue of **Pathogenesis** focuses on basic science and exploratory research into the *initial development and progression of breast cancer*. We have divided this priority issue into five sub-topics, which define major areas of scientific inquiry. The **spread of breast cancer** in the body continues to be the biggest problem in diagnosis and effective therapy, and there is slow progress towards new strategies. Fortunately, major advances are being made in understanding the process of angiogenesis (development of the tumor's blood supply), and prospects of attacking breast cancer at this level for both primary and metastatic

tumors look very promising. For the topic of **cell growth**, in 1998 there was the first clinical introduction of an effective therapy against the Her-2 growth factor receptor to combat breast cancer. Her-2 continues to be a prime research interest. Associated with cell growth is the topic of **intracellular signaling pathways** that cause breast cancer cells to multiply, accumulate genetic mutations, and survive when attacked by the immune system or current therapies. The BCRP has funded important research on apoptosis, which is programmed cell death. Next, we are accumulating more information at the **genetic level** to discover how specific genes and their protein products serve to differentiate a breast cancer cell from a normal cell. At present, we have an incomplete understanding of these genetic differences. A related topic to cancer genes is the area of **gene regulation**, which involves the proteins and chromosomal regions where

gene activity is controlled. One direction of this research effort is to devise ways to shut down cancer-causing genes within cells. Finally, more information is emerging on the topic of **tumor progression**, which are the events causing normal and pre-malignant cells to transform into full-fledged cancer cells. Several BCRP — funded projects examine the microenvironment of normal and breast cancer cells. Both through human aging and from factors produced by altered cells, these environmental interactions become defective and this creates a permissive opportunity for breast cancer. By understanding the causes of tumor progression, we will be able to influence these factors in normal breast cells to develop ways of preventing the disease.

Pathogenesis

# CONCLUSIONS

Outbreak — how cancer spreads: angiogenesis, invasion, and metastasis

**J**effrey Smith, Ph.D., at The Burnham Institute, finished a 3-year Research Project on *Prevention of Breast Cancer by Blocking Integrin Function*. Breast cancer cells are able to move in the body because of certain cell surface receptors that serve to attach them to the extracellular matrix. In this project, breast cancer cells were mutated to delete a critical adhesion receptor ( $\alpha_v\beta_3$ ). In all respects, except metastasis and adhesion, the cells appeared to be normal. This receptor is an excellent target for therapeutic intervention, since inhibitory drugs are far along in development for diseases other than breast cancer. Dr. Smith has expanded this work to examine the proteins inside of breast cancer and other cells that regulate the binding function of these integrin adhesion receptors.

receptors

**Andre Lochter, Ph.D.**, at the **Lawrence Berkeley National Laboratory**, was funded in a 2-year Postdoctoral Fellowship to study the *Cell Microenvironment and Progression of Breast Cancer*. He examined the process of “epigenetic programming” of breast cancer cells caused by factors outside the cell, a protein meshwork called the ‘extracellular matrix’. An enzyme secreted by breast cancer cells, stromelysin-1, causes degradation of a key cell surface receptor that leads to both cellular and environmental changes associated with the invasive potential of the cells. This invasive behavior was inhibited through blockage of certain ‘integrin’ receptors on breast cancer cells. These observations are key to understanding changes in cell behavior that are independent of DNA mutations in breast cancer. If these microenvironmental perturbations could be reversed, then the early events of certain breast cancers could be prevented.

## Too much cell growth: defective messages and internal signaling

**Daniel Donoghue, Ph.D.**, at the **University of California, San Diego**, investigated *Mechanisms of Aberrant Cell Growth* during a 3-year Research Project. He examined the part of the protein sequence of the oncogene, Her-2, that crosses the cell membrane. This region is critical for relaying the growth signals from outside the cell, primarily by allowing Her-2 to self-associate as homodimers. Dr. Donoghue was able to determine the locations of the critical amino acids in the transmembrane domain that permit receptor dimerization, and he also determined that Her-2 association alone is not sufficient for growth promoting activity. Apparently, the internal portion of Her-2, the kinase domain, requires a specific type of ‘rotational coupling’ to function properly. These studies increase our understanding of growth regulation in breast cancer.

protein

**John Reed, M.D., Ph.D., at The Burnham Institute,** completed a Research Project aimed at understanding *Immune Responses to Breast Cancers: Function of TRAF Protein*. The aim was to uncover ways to make tumor cells more vulnerable to immune attack. This study identified a group of tumor proteins called IAPs that bind to apoptosis proteins and prevent immune-mediated tumor destruction. Additionally, Dr. Reed found that breast cancers sometimes alter their levels of proteins called TRAFs, which are involved in making the cells more sensitive to the signals given by the immune cells. Improper levels of IAPs and TRAFs are at least partially the reason why some breast cancer cells are able to escape killing by the immune system.



## suppressors

**Jamil Momand, Ph.D., at the Beckman Research Institute of the City of Hope,** finished a 3-year New Investigator project to study the *Loss of p53 Tumor Suppressor Function in Breast Cancer*. In this project the relationship between the cellular location of p53 and proteins that p53 interacts with were examined. The tumor suppressor p53 is mutated in some breast cancers and in other cancers it fails to respond to either DNA/cellular damaging chemicals or radiation even when it is not mutated. Dr. Momand first determined that a natural inhibitor of p53, called MDM2, did not appear to function in blocking p53 in certain breast cancer cell lines. It was found that ionizing radiation would cause p53 protein to increase without causing its accumulation in the nucleus of cells. Thus, some functions of p53 appear to be retained under conditions of nuclear exclusion. These results indicate that p53 works in a more complex way in breast cancer than previously believed, and that the cellular location and functionality of its partner proteins will require more study.

**Zheng-gang Liu, Ph.D.**, at the **University of California, San Diego**, finished a Postdoctoral Fellowship to answer the question — *Why Does Normal Cell Death Not Occur in Breast Cancer?* It is known that breast cancer cells do not respond normally to signals that cause normal cells to die — a process called apoptosis. Dr. Liu examined how normal and breast cancer cells respond to the cytotoxic protein, tumor necrosis factor (TNF). The key findings were that c-Jun kinase signaling inside cells is not involved in TNF-induced apoptosis, while in breast cancer cells the activation of the transcription/signaling factor NF- $\kappa$ B will allow the cells to avoid cell death. This information gives tremendous insight into potential ways to restore the normal apoptosis function in breast cancer, which could both block their natural resistance to TNF and make existing chemotherapy work more effectively.

## Mistakes on the master blueprint: molecular genetics and gene regulation

**Helene Baribault, Ph.D.**, of **The Burnham Institute**, was funded for a 2-year Research Project to study *The Role of Bax Gene in Breast Cancer Pathogenesis*. A mouse model system was developed, such that specific genes could be deleted or 'knocked-out' specifically in the mammary gland. This approach is called the Cre-loxP technology, and Dr. Baribault showed that her gene expression (Cre) was restricted to the mammary gland, and all the technical hurdles needed to validate this revolutionary method were developed. Thus, genes that are either known or suspected to be important for mammary cell development, differentiation in pregnancy, and development of breast cancer can be studied in a manner restricted to the mammary gland using this powerful 'knockout' method. This project is being continued to study the apoptosis (cell death) regulator,



Bax. In addition, Dr. Baribault and her postdoctoral fellow were funded in 1998 to apply her Cre-LoxP technology to additional breast cancer genes of interest.

mammary  
gland

**Elizabeth Blackburn, Ph.D.**, of the **University of California, San Francisco**, completed an IDEA grant to examine ways of *Altering Telomerase to Prevent Breast Cancer Progression*. Telomerase is an enzyme that is responsible for maintaining the integrity of chromosomes, thereby allowing the cells to become immortal. Normal cells lack telomerase and can only divide a limited number of times. However, in cancer cells, telomerase expression is one mechanism for a cell to gain unlimited potential for division. This grant explored two strategies for taking advantage of telomerase activity to kill tumor cells by a) using compounds such as AZT to stop telomerase activity, or b) designing compounds that cells with active telomerase would turn into poisons. Dr. Blackburn was able to show that these approaches show promise in test tubes and lower organisms. The long-term goal is to find out whether these approaches are effective in women.

**Utha Hellmann-Blumberg, Ph.D.**, of the **University of California, Davis**, has completed a Postdoctoral Fellowship for *Studies Of Tamoxifen/Toremifene DNA Interactions in Monkeys*. Drugs that interfere with estrogen-stimulated tumor growth have shown great promise for treating and preventing the growth of breast tumors. Physicians already use them for treating breast cancer and are likely to expand their use to reduce breast cancer risk, so it is especially important to identify any toxic effects these drugs might have. These drugs could produce metabolites that bind to DNA and cause uterine tumors. Dr. Hellmann-Blumberg found evidence of DNA binding when tamoxifen metabolites were examined in the test tube, but this was less for toremifene (an alternative to tamoxifen) metabolites. This correlated with the observation that toremifene is less likely to cause uterine tumors in humans than tamoxifen. The animal studies examining DNA damage by these antiestrogens were not conclusive, probably because they required longer exposure to the drugs. These studies indicate that tamoxifen, and possibly toremifene, can cause DNA damage during long-term treatment (chemoprevention), but toremifene may be safer.

telomerase



**John Reed, M.D., Ph.D.**, from **The Burnham Institute**, was funded to investigate *Bax Gene Expression in Breast Cancer*. In this project some of the critical relationships between a cell death (apoptosis) regulatory protein, Bax, and two other proteins, bcl-2 and p53 were established. It was found that Bax was not a good independent prognostic marker for breast cancer. However, the amount of Bax did appear to be increased following chemotherapy. This demonstrates that apoptosis pathways inside breast cancer cells can become initiated, and future research must resolve why these processes are not effective in limiting cell growth.

**Dieter Wolf, M.D.**, at **Stanford University**, completed one year of a Postdoctoral Fellowship to study the *Control of DNA Replication in Breast Cancer*. This project focused on the role of a cell cycle protein, called Cdc6, which activates DNA replication. Defects in DNA replication play a significant role in increased growth potential and for the incorporation of genetic mutations and rearrangements characteristic of breast cancer. Dr. Wolf prepared antibodies to Cdc6, cloned a human gene (hPOP) that regulates Cdc6 stability, and determined the pathway of Cdc6 degradation within human cells. This work has great potential to address the molecular issues associated with changes in ploidy (i.e., abnormal chromosomal duplications).

## Searching the unknown: novel breast cancer genes

**John Groffen, Ph.D.**, at the **Children's Hospital, Los Angeles**, completed a 3-year Research Project to investigate *Two Candidate Breast Cancer Genes on Chromosome 17*. The development of breast cancer is associated with severe alteration in chromosome structure and numbers. Dr. Groffen's initial work was performed on the genes called Crk and Abl. He expanded the study to include another gene called Rac3, which was cloned and analyzed for chromosomal location. For Crk and Abl there was no clear correlation in cell expression, chromosome deletion, and breast cancer samples. Interestingly, Rac3 is still expressed in breast cancer despite the apparent absence of a normal chromosome 17 location. This work is being continued with a focus on signaling proteins/genes, such as Rac3, and their relationship to breast cancer.



chromosome

**David Schott, Ph.D.**, from the **California Pacific Medical Research Center**, completed a Research Project to identify *A Candidate Breast Tumor Suppressor Gene on Chromosome 13*. This gene called Brush-1, is involved in breast cancer development and is lacking in breast cancer cells. When Brush-1 was placed back into breast cancer cells grown in culture, they appeared and behaved like normal cells. Dr. Schott was also able to identify the portion of the Brush-1 gene that was responsible for this activity. The next step was to test whether the presence or absence of Brush-1 affected breast cancer growth in organisms. He found that breast cancer cells with Brush-1 were somewhat less capable of forming tumors, but once tumors did form, they were just as aggressive as tumors without Brush-1.

**Claudia Lin, Ph.D.**, at the **Lawrence Berkeley National Laboratory**, completed a 2-year Postdoctoral Fellowship for the *Targeted Search for New Transcription Factors in Breast Cells*. In this project the nuclear factors in cells that regulate genes for mammary growth and differentiation were studied. Using a technique of yeast 2-hybrid screening, Dr. Lin found a potential transcription factor, ITF-2, and detailed the relationship between the amounts of this protein and mammary growth and differentiation. Since normal breast cell functions are lost in breast cancer, this information could be used to limit the disease by activating normal cell growth limiting and cell death pathways.

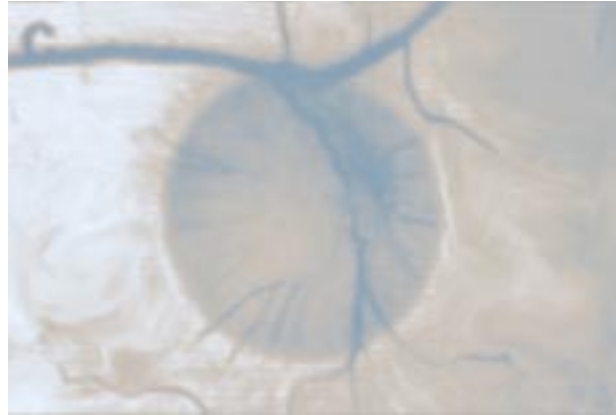
**Michael Lewis, Ph.D.**, at the **University of California, Santa Cruz**, was funded for a 2-year Postdoctoral Fellowship to answer the question: *Homeobox Genes: A New Class of Human Breast Oncogenes?* These genes from fruit flies have counterparts in humans that act to regulate cellular differentiation and body organization. Dr. Lewis' initial work pointed to a family of genes called IRX, which could represent undiscovered examples of either tumor suppressors or oncogenes. His studies that disrupt IRX genes in cells led to cellular changes that resemble neoplastic transformation. This work is being continued to examine expression and amounts of these homeobox genes in breast cancer samples.



cellular

**Manuel Perucho, Ph.D.**, from **The Burnham Institute**, completed a 1-year IDEA project aimed at *Identifying Novel Breast Cancer Tumor Suppressor Genes*. He performed pilot studies using peptide sequences displayed on bacteriophage to demonstrate the feasibility of detecting caspase-3 (an apoptotic enzyme) and the retinoblastoma tumor suppressor. The eventual goal is to introduce phage into cells to block unknown endogenous tumor suppressors in order to identify them. Tumor suppressors are poorly understood, since their loss in many experiments does not lead to carcinogenesis as directly as the presence of oncogenes. This project is a first step in developing the technology to identify novel tumor suppressors.

**Janis Jackson, M.D.**, at the **Scripps Research Institute**, was funded through a 1-year IDEA for the *Analysis of Rac Mutations in Breast Cancer*. This gene is a key player for intracellular signaling that leads to changes in gene expression, growth, and adhesion properties when defects occur. Using a PCR approach Dr. Jackson was able to confirm that a large percentage (17 out of 37) of ductal breast carcinoma samples had detectable mutations in a specific codon of the *rac1* gene. These signaling genes and their mutations in breast cancer are becoming the key links between growth factor receptors (such as Her-2), changes in gene expression, and the lack of a cellular response to the accumulation of genetic mutations.



## Unraveling the path to breast cancer: tumor progression

**Satyabrata Nandi, Ph.D.**, at the **University of California, Berkeley**, completed a 3-year Research Project to develop a *Model of Human Breast Cancer Development and Progression*. His group was able to grow human breast cancer samples in a mouse model and maintain their unique hormonal and growth factor receptor status through several generations of mice. This is called a 'surrogate human breast' model. These animals then become experimental platforms for the study of gene transfer and therapy, drug studies, and hormonal modification. Such issues as pregnancy, contraceptive use, and hormonal replacement therapy can be studied in this mouse model. This system has better relevance to human cancer, compared to the more commonly used laboratory breast cancer cell lines.

**Steven Frisch, Ph.D.**, from **The Burnham Institute**, investigated *Reprogramming Breast Cancer Epithelial Cells*. In this 1-year IDEA project he examined the mechanism by which the adenovirus E1a gene could revert cancer cells to normal cells. E1a is a nuclear gene regulatory protein. Dr. Frisch identified the critical regions of a partner protein, called p300/CBP, that appears to mediate the E1a effects. The eventual goal is to better understand and use this system to overcome the 'silencing' of normal adhesive functions present in epithelial cells, but lost in cancer cells. The ability to 'activate' these latent functions would serve to limit the invasiveness of breast cancer and restore normal functions.

**Robert Ochs, Ph.D.**, at **The Scripps Research Institute**, was funded through a 1-year IDEA award to investigate *Autoantibodies in Breast Cancer*. He found that about 50% of breast cancer patients appear to develop autoantibodies, which are directed at breast cancer proteins. This observation was consistent in the three samples of patients analyzed. However, at present there appears no definite relationship between the presence of autoantibodies and various clinical parameters associated with diagnosis and disease progression. Dr. Ochs plans to continue this work by a more detailed analysis of the specific proteins recognized by the autoantibodies. Continued efforts to understand the immune response to breast cancer and make it more effective in combating the disease remains a major interest of BCRP.



**Valerie Weaver, Ph.D.**, at the **Lawrence Berkeley National Laboratory**, finished a Postdoctoral Fellowship to study *Vitamin D and Breast Cancer Prevention: Cell Death vs. Growth*. The focus of this study was the relationship between breast cancer cells and their immediate microenvironment, called the extracellular matrix. This association becomes perturbed in cancer, and understanding how this can be restored could reverse the early stages of breast cancer. Vitamin D treatment serves to arrest the growth of breast cancer cells and enhance their attachment to the extracellular matrix. Interestingly, treatment of cancer cells with antibodies to the  $\beta_1$ -integrin adhesion receptors caused them to revert to a more normal phenotype. Maintaining the connection between breast epithelial cells and the extracellular matrix appears to be critical to limiting both their growth potential and the ability of cells to accumulate mutations that eventually lead to cancer.

# RESEARCH

## in Progress



### Outbreak: how cancer spreads

In order to become life threatening, a breast tumor has to acquire the ability to invade the tissues surrounding it. **Pierre-Yves Desprez, Ph.D.**, of the **California Pacific Medical Research Institute**, has two BCRP-funded projects to study the enzymes, called metalloproteinases (MMPs), which cause invasiveness. First, he has confirmed that a protein found in some tumor cells, Id-1, correlates with cellular invasiveness. This observation holds in cell lines and in humans. Secondly, he has discovered novel proteinases that could be utilized for both diagnosis and treatment. Enzymes present outside of the cell can be critical in determining a tumor's degree of invasiveness, in terms of not only their presence or absence, but also the form they take. **Alex Strongin, Ph.D.**, of the **La Jolla Institute for Experimental Medicine**, has shown that MMP2 controls tumor migration, invasion and metastatic potential when it is in a form that is bound to the outside of the tumor cells. Finally, **David Rose, D.V.M., Ph.D.**, at the **Scripps Research Institute**, has found that intracellular signaling proteins can modulate the affinity of a cell surface integrin receptor, and these results are being extended to breast cancer.

invasiveness

## Too much cell growth: defective messages and internal signaling

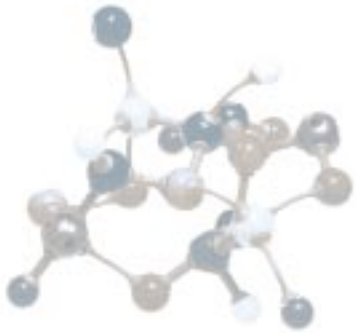
Breast cancer cells must pass critical checkpoints in order to divide, and the proteins that regulate this process (called cyclins) are potential targets for breast cancer therapy. **Kevin Sato, Ph.D.** at the **Scripps Research Institute** has reported success in being able to block the activity of the DNA replication cyclin E by using of an 'antisense' technique. This caused the delay of DNA synthesis, but did not entirely block cell division. Still, cyclin E is elevated in breast cancer, and this technique is a novel approach for selective inhibition. **Juan Zapata, Ph.D.**, at **The Burnham Institute**, finds that a Tumor Necrosis Factor signaling protein, called TRAF-4, is reduced in breast cancer, and this loss is permissive for continued growth. This work is being extended to the study of an inhibitor of TRAF-4, called I-TRAF, which will be studied in an animal model.



The pathogenesis of a tumor can provide clues regarding why treatments are effective, or ineffective. With the recent interest in anti-estrogen therapy as a risk reducing agent in addition to a therapeutic one, it is especially important to learn about the underlying mechanisms for its action. **Ruth Lupu, Ph.D.**, at the **Lawrence Berkeley National Laboratory**, is concentrating on the function of the newly discovered estrogen receptor, ER- $\beta$ . She is using antibodies to determine whether ER- $\beta$  is regulated differently by estrogen and tamoxifen than traditional estrogen receptors. Studying the pathogenesis of tumors can also lead to the discovery of new agents to use in the fight against breast cancer. **Michael Stallcup, Ph.D.**, of the **University of Southern California**, has been studying peptides, GRIP1, GRIP2 and GRIP3, that mediate the action of estrogen. He determined that although two of these peptides (GRIP 2 and 3) are not found in nature, they provide promising starting points for novel peptides that could inhibit estrogen receptor action.

agents





## molecules

The epidermal growth factor and members of the epidermal growth factor receptor family play a significant role in breast cancer development, therefore it is important to understand how the receptors are regulated.

**Gordon Gill, M.D.**, of the **University of California, San Diego**, finds specific proteins

(SNX1, but not SNX2) that guide EGF receptors to the part of the cell where they are destroyed. Dr. Gill has identified the function of distinct regions of SNX, for example the SNX of a specific receptor.

**Ichiro Maruyama, Ph.D.**, of the **Scripps Research Institute**, is examining the structure of the EGF receptor and how it moves in the cell membrane in order to determine how the receptor is turned on. Dr. Maruyama has preliminary evidence that upon binding to EGF the receptor molecules rotate or

twist around the axis perpendicular to the plane of the cell membrane and become active. Finally, **Wanda Reynolds, Ph.D.**, of the **Sidney Kimmel Cancer Center**, is investigating the regulation of Her-2, another receptor in the EGF receptor family. She is specifically looking at areas on the Her-2 gene, called Alu repeats, where hormone receptors can bind and possibly affect their expression. The Alu repeats could also be sites of DNA mutations.



## Mistakes on the master blueprint: molecular genetics and gene regulation

It is appreciated that breast cancer cells are genetically different from normal cells. One important aspect of this is due to the expression of different genes. **Philippe Pujuguet, Ph.D.**, at the **Lawrence Berkeley National Laboratory**, is determining how the immediate microenvironment of breast cancer cells becomes defective and sends the wrong signals inside the cell. He is finding that histones, which package DNA into chromatin, are one important level of transcriptional control in breast cells and breast cancer. **Robert Oshima, Ph.D.**, at **The Burnham Institute**, is studying a mutant form of a protein, called Ets2, which regulates gene expression. **David Zaring, Ph.D.**, at the **Pangene Corporation**, is developing a novel method for detecting mutant genes in cancer cells using circularized DNA probes. In addition, he is examining a protein called Rad51, which is involved in DNA repair and can interact with the tumor suppressors, p53 and BRCA1. Finally, **Mark Chapman, Ph.D.**, of **The Salk Institute for Biological Studies**, is trying to determine how BRCA1 functions in cells. One hypothesis is that BRCA1 interacts with other proteins to regulate the production of growth stimulating factors. He has identified several proteins that bind to BRCA1 and BRCA2 and provide clues to how these genes protect normal cells from becoming tumor cells.

# genetics

## Searching the unknown: novel breast cancer genes

Breast cancer appears to always involve genetic differences between abnormal and normal cells. One research goal is to find and catalog these changes. **Sergei Malkhoysan, Ph.D.**, at **The Burnham Institute**, is using a technique called AP-PCR to identify chromosomal regions that both unmask tumor-causing genes (oncogenes) and cause the loss of tumor-inhibitory genes (tumor suppressors). In a more defined manner, **Terumi Kohwi-Shigematsu, Ph.D.**, at the **Lawrence Berkeley National Laboratory** is studying the global ways DNA is organized in breast cancer. There exist specific DNA segments and associated proteins that attach the chromosomes to the supporting matrix in the cell's nucleus. She is focusing on a protein called p114, which is selectively present in breast cancer cells. This protein could modulate gene expression through its function of regulating DNA structure.

Heregulin is a protein that binds to and stimulates the HER-2/neu growth factor receptor. **Fabiana Guerra-Vladusic, Ph.D.**, of the **Lawrence Berkeley National Laboratory**, is identifying genes that are regulated by heregulin. She caused a cell line that normally does not produce heregulin to make it and found that the cells were growth-inhibited, had lost their capacity to spread in culture, had increased cell size, and showed signs of apoptosis of (cell death). She is now looking for the genes that mediate this effect.



## retinoids

### Unraveling the path to breast cancer: tumor progression

**Judith Campisi, Ph.D.**, at the **Lawrence Berkeley National Laboratory**, is investigating the nature of the critical changes, both genetic and environmental, that allow breast cancers to become established. She is creating breast cells that contain subtle mutations, but still appear normal. The idea is to expose these minimally altered cells to factors known to cause cancer. Her key interest is cell senescence that causes changes in the microenvironment of breast cells, and this could stimulate cancer when cells have already accumulated otherwise 'silent' mutations. **Anissa Agadir, Ph.D.**, of **The Burnham Institute**, is determining which molecular events are responsible for the physiological effect of retinoids, which are derivatives of retinoic acid that inhibit tumor progression. She is also investigating the mechanism of synthetic retinoids such as retinyl methyl ether (RME) in inhibiting tumor growth and progression. She has found that RME-activated retinoid receptors specifically interfere with AP-1 (factors that turn on growth genes) activity in the cell and inhibit cell invasion induced by a tumor promoter.

## Recently Initiated Research

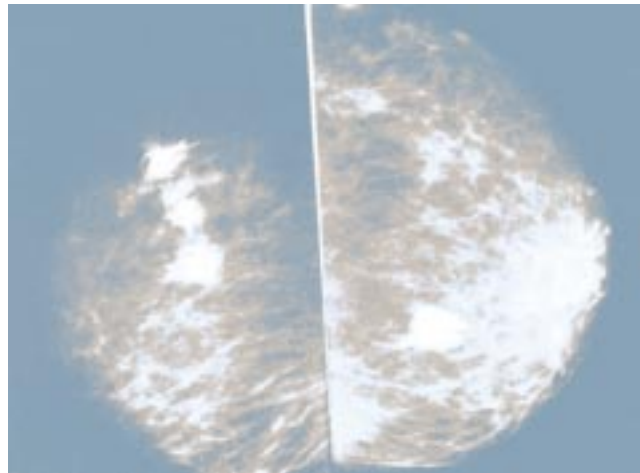
### Outbreak - how cancer spreads: angiogenesis, invasion, and metastasis

Five new grants were awarded in this topic area.

**Sonoko Narisawa, Ph.D.**, at **The Burnham Institute**, will examine how breast cancer spreads to the bone, the most common site of metastasis. Her plan is to discover new cell receptor proteins for breast cancer cells that are on the endothelial cells in bone, and these methods should directly indicate the active protein regions where metastasis inhibitors might be developed. **Pragada Sriramarao, Ph.D.**, at the **La Jolla Institute of**

**Experimental Medicine**, will investigate the properties of newly formed tumor blood vessels with respect to binding circulating lymphocytes. These potentially tumor-fighting lymphocytes circulate adjacent to breast tumors, but for unknown reasons they fail to recognize the regions of tumor growth. **Earl Sawai, Ph.D.**, from the **University of California, Davis**, is funded to study the molecular linkage between uncontrolled breast cancer cell growth and metastasis. A key intracellular

protein, phosphatidylinositol 3-kinase, will be studied in a unique animal model. Closely related to metastasis is the process of cell-cell adhesion that links the normal breast epithelial cells together and limits their growth. **Karin Zeh, Ph.D.** is a Postdoctoral Fellow working with her mentor, **Helene Baribault, Ph.D.**, at **The Burnham Institute**, to produce transgenic mice to study cell surface adhesion receptor-associated intracellular proteins. They plan to make whole animal mutations in these cytoskeletal proteins, called  $\gamma$ -catenin and plakoglobin, to study their role as regulators of mammary development and cancer.



# Inhibitors

## Too much cell growth: defective messages and internal signaling

The BCRP continues to support innovative and career development grants in this topic.

**Glenn Rosen, M.D.** at **Stanford University** is funded to investigate the molecular mechanism of action for a compound derived from a traditional Chinese herb, which sensitizes breast cancer cells to apoptosis. **Koji Itahana, Ph.D.** from the **Lawrence Berkeley National Laboratory** will be examining mutant p53 (a tumor suppressor protein) for its possible role in promoting breast cancer, beyond the loss of its normal function. Another tumor suppressor protein, retinoblastoma, will be investigated for its interaction with associated proteins using the technique x-ray crystallography by **Kathryn Ely, Ph.D.** from **The Burnham Institute**. Finally, **Cary Lai, Ph.D.** from the **Scripps Research Institute** will study a possible regulatory binding protein, related to neuregulin, which could activate the Her family of breast cancer growth receptors.

## Mistakes on the master blueprint: molecular genetics and gene regulation

Research funded in this topic includes some of the same proteins as described earlier, but the focus is more on gene regulation. **Shu-ichi Matsuzawa, Ph.D.** from **The Burnham Institute** will investigate a family of p53 target proteins, called Siah, as downstream mediators of tumor suppressor function and apoptosis. p53 mutations are common in breast cancer, and some of these mutations could serve to disrupt other pathways inside the cell. **Heinz Ruffner, Ph.D.** at the **Salk Institute for Biological Studies** is funded to study the modification (phosphorylation) of BRCA1 by looking for specific intracellular kinases.

## Searching the unknown: novel breast cancer genes

**Fumiichiro Yamamoto, Ph.D.**, at **The Burnham Institute**, will examine a novel set of genes that are believed to be associated with breast cancer development because they have a different number of methyl groups attached when compared to normal genes. Another aspect of chromosomal structure will be investigated by **Paul Kaufman, Ph.D.**, from the **Lawrence Berkeley National Laboratory**, who will study the association of Chromatin Assembly Factor (CAF)-I with breast cell senescence (aging).



## Unraveling the path to breast cancer: tumor progression

Studies of tumor progression are providing an important link between Pathogenesis and another BCRP priority issue, the Biology of the Normal Breast. **Martha Stampfer, Ph.D.**, at the **Lawrence Berkeley National Laboratory**, will be using a novel molecular approach to look for genes showing loss-of-function (tumor suppressor genes) and also permissive for cell immortalization. **Kunxin Luo, Ph.D.**, also at the **Lawrence Berkeley National Laboratory**, plans to study a portion of a normal growth factor in mammary cells that could have a tumor suppressor function. **Henrik Ditzel, M.D., Ph.D.**, at the **Scripps Research Institute**, is funded to examine a breast cancer protein that stimulates this 'medullary breast tumor' T-lymphocyte infiltration, and could serve as the future basis for a vaccine. Finally, **G. Shyamala, Ph.D.** at **Lawrence Berkeley National Laboratory** will be investigating the relationship of the progesterone receptor with the activity of matrix metalloproteinases, presence of a matrix protein called laminin, and a cell surface adhesion receptor called E-cadherin.



# RESEARCH



Innovative  
Treatments:  
Search  
for  
the Cure

**P**re-clinical and early clinical studies are the bases for generating radically different ways to treat breast cancer. These BCRP funded projects are exploring how newly discovered technologies and products can be used to treat breast cancer in more effective, less toxic ways.



# CONCLUSIONS

## Gene therapy and other treatments: new frontiers



**S**enyon Choe, Ph.D., at **The Salk Institute for Biological Studies**, completed a 2-year project that investigated *Targeting Breast Cancer Using Diphtheria Toxin*. This study was designed to develop the potential for diphtheria toxin as a breast cancer therapeutic. Dr. Choe determined the X-ray crystallographic structure of diphtheria toxin under conditions when it is attached to its natural partner, the 'EGF precursor' protein. He was able to identify the critical atoms for both diphtheria toxin and the 'EGF precursor' that regulate this binding function. In future work, the structure of diphtheria toxin will be modified to make it specific for heregulin, a growth promoting protein found on breast cancer cells. This is possible, because the 'EGF precursor' and heregulin are very similar in structure. Thus, the toxic effect of diphtheria toxin could be re-directed selectively to breast cancer as a novel therapeutic approach.

toxins



# diagnosis

**Silvia Formenti, M.D.**, at the **University of Southern California**, completed an ITaMoCA grant to investigate the utility of radiosurgery for replacing the six weeks of the radiation therapy normally required to treat breast cancer. Radiosurgery delivers a radiation dose in a single session (lasting approximately one hour) that may be biologically equivalent to what is received over six weeks of daily treatments. Dr. Formenti performed a preliminary study to work out the logistics of the technique. Although the optimal radiation dose for killing the tumor still needs to be found, the study was able to demonstrate that radiosurgery is feasible and that patients tolerate the treatment well.

**Orhan Nalcioglu, Ph.D.**, at the **University of California, Irvine**, completed a 3-year Research Project for the investigation of *Improved Drug Delivery in Breast Cancer*. This project examined the permeability of the blood vessels in experimental mouse breast tumors using the technique of magnetic resonance imaging (MRI). These tumor vessels are more permeable or 'leaky' compared to the normal microvasculature. Dr. Nalcioglu was able to determine the level of leakiness by constructing MRI 'contrast agents' of different sizes. Differences in permeability were correlated to the aggressiveness of the tumor with respect to spread in the body. Vasomodulators and other drugs were able to alter the tumor leakiness. These experiments set the stage for the application of MRI for diagnosis in human breast cancer, and to develop ways for the selective delivery of drugs to tumors based on the permeability characteristics of their blood supply.



**Ke Shuai, Ph.D.**, at the **University of California, Los Angeles**, was funded for 3 years as a New Investigator to study *Growth Inhibition of Breast Cancer Cells by Interferons*. His initial experiments examined an interferon regulator from fibroblasts, Stat1, but these experiments indicated that this antiproliferative pathway was not operable in breast cancer cells. Next, it was shown that a transcription factor, NF- $\kappa$ B, was activated by interferon, but this did not account for antiproliferative activity. Finally, Dr. Shuai found that specific cytokine signaling factors, called SOCS1 and SOCS3, appeared to protect breast cancer cells from the antiproliferative activity of interferon. Thus, further studies on these factors could lead to possible strategies to make interferon a more effective anti-breast cancer agent.

## isozymes

## Hormone and chemotherapy targets: improving today's arsenal

Cells that are drug resistant tend to have a higher overall activity of an enzyme called protein kinase C, but not enough is known about the role of the different forms of protein kinase C (isozymes) in drug resistance. **Yuefeng Lu, Ph.D.**, at the **Stanford University**, completed one year of a post-doctoral fellowship investigating how the six different protein kinase C isozymes found in breast cancer are involved in the development of drug resistance. Protein kinase C may function either by excluding drugs from cells or by causing the cells to undergo programmed cell death. Different forms of protein kinase C behave differently and even oppositely on these processes. Dr. Lu interfered with the function of specific isozymes and found that certain isozymes ( $\beta$ -PKC) appear to be more involved in protecting cells from programmed cell death than other isozymes ( $\delta$ -PKC and  $\epsilon$ -PKC). Isozyme-selective inhibitors of these protein kinase C isozymes may serve as models for designing agents that would make chemotherapy more effective.

**Silvia Formenti, M.D., Peter Danenberg, Ph.D., and Franco Muggia, M.D.**, at the **University of Southern California**, have completed a pilot Translational Research Collaboration Award. The purpose of the study was to determine whether there are biological factors in tumors that could be used to predict their response to chemotherapy. In order to perform the study they examined the response of primary tumors to paclitaxel. The researchers found that the paclitaxel unresponsive tumors had very high levels of certain types of  $\beta$ -tubulin (a component of cellular structural proteins) while those that responded well to paclitaxel had the lowest levels. Findings from this pilot study justified a larger translational research project aimed at finding the biological factors that determine the response to paclitaxel and paclitaxel plus radiation. The ultimate aim of these investigations is to spare patients with resistant tumors from exposure to unnecessary toxicity and to optimize the treatment of patients with potentially responsive tumors.

## retinoids

## Immune therapy: mobilizing the body's defenses

Many researchers believe that the immune system can successfully deal with cancer in the same way that it deals with viral infections. A logical extension of this theory is that vaccines can be used to combat cancer growth. One hurdle in developing a cancer vaccine is making it general enough to address the high genetic variability between individuals as well as between tumors, but still making it specific enough to kill only tumor cells. **Alessandro Sette, Ph.D., and Esteban Celis, M.D., Ph.D.**, at **Epimmune, Inc.**, completed an ITaMoCA award to develop a cancer vaccine by training a particular type of immune cell, the cytotoxic T-lymphocyte, to recognize common "self-antigens" in addition to the proteins that are often found in tumors. This approach increases the possibility that the vaccine will be useful for a broad segment of the population. Drs. Sette and Celis were successful in developing cytotoxic T-lymphocytes that could recognize various tumor markers (HER2/neu, CEA, MAGE2/3, and p53) in cells with a variety of "self-antigens" present. This is a hopeful step toward the development of a cancer vaccine.

# RESEARCH

## in Progress



### New drug design: creative science

targets

Harnessing the power of retinoids (vitamin A) to stop cells from dividing is an avenue of investigation that holds promise for breast cancer therapy. The types of retinoids that have been tested until now have had some undesirable side effects. **Magnus Pfahl, Ph.D.**, at the **Sidney Kimmel Cancer Institute**, used his ITaMoCA award to test a new class of retinoids that make cancer cells commit suicide. He found that the new retinoids were able to cause breast cancer cells to die within 24 hours of exposure, and that they turned on a different combination of receptors than traditional retinoids. The new retinoids were too potent to use in combination with chemotherapy as was originally hoped; however, these studies did lead to the discovery of a new compound, MX871, that effectively treats advanced estrogen receptor-negative cancer in the laboratory. Clinical trials of MX871 are now being developed.

## Gene therapy and other treatments: new frontiers

Current breast cancer treatments generally inflict terrible side effects on patients. This is often because of an inability to target the treatment selectively to the cancer. The same issue applies to gene therapy — we need better ways of delivering therapeutic genes to cancer cells. **Robert Debs, M.D.**, at the **California Pacific Medical Center, Geraldine Brush Research Institute**, is encapsulating his gene therapy agent inside lipid particles to protect them in transit in the blood and deliver them to cancer cells. He is finding that his technique will target the blood vessel lining cells (endothelial cells) in the tumor blood vessels. Many of our funded projects are finding the tumor's blood supply is a better target than the tumor itself. This strategy is being pursued in a Translational Research Collaboration Pilot grant to **Marc Shuman, Ph.D.**, **Randall Hawkins, M.D.**, and **Laura Esserman, M.D.**, at the **University of California, San Francisco**. This cross-disciplinary group of scientists is developing the clinical potential of a monoclonal antibody against an

angiogenesis-stimulating protein vascular endothelial growth factor (VEGF). They are using both an advanced form of magnetic resonance imaging (MRI) and positron emission tomography (PET) to directly visualize the effects of anti-VEGF treatment. Combining new non-invasive detection technology with emerging state-of-the-art therapy is the strength of this project. Finally, **Qing Zhou, M.D.**, at the **University of Southern California**, is working with his postdoctoral mentor, **Francis Markland, Ph.D.**, to deliver an angiogenesis-inhibiting snake venom protein directly to the tumor blood vessel cells by gene therapy techniques. Their hypothesis is that this approach will disrupt the tumor blood supply. Since the blood vessel cells are not cancer cells, they are unlikely to develop resistance to this treatment.

Breast cancer patients can develop side effects from the removal of the primary tumors. Alternative, less invasive ways of removing the tumor are highly desirable. **Boris Rubinsky, Ph.D.**, at the **University of California, Berkeley**, finds promise in an alternative to surgery — freezing the primary tumors. Dr. Rubinsky has found that by injecting cultured breast cells or surgical specimens with certain “anti-freeze proteins” and then freezing them, he can achieve complete destruction of the target tissue regardless of how far the temperature is lowered. He is currently in the process of testing this approach in animals.

Breast cancer patients suffer severe effects from the presence of tumor cells that

## bone loss



have spread in the body. This is especially true in bone, where the cancer cells cause bone loss and elevated calcium levels in the blood. **Herve LeCalvez, Ph.D.**, at **The Burnham Institute**, is investigating a bone cell protein, called meltrin- $\alpha$ , which is critical for the fusion of cells to form the bone-destroying osteoclasts. He is studying meltrin- $\alpha$  in experimental cell systems with the aim of developing strategies to block its function. This could have applications both for breast cancer and in treating osteoporosis.



## Hormone/chemotherapy targets: improving today's arsenal

Several ongoing BCRP grants are investigating the Her-2 growth factor, which is present on the surface of breast cancer cells in about 30% of patients. A monoclonal antibody against Her-2 was approved for treatment in 1998, but this topic remains an intense area of interest. **Cara Marks, Ph.D.**, of the **University of California, San Francisco**, is using monoclonal antibodies and X-

ray crystallography to study how Her-2 self-associates into a dimer and how this relates to growth signaling within cells. In a different approach to neutralize the Her-2 receptor, **Joel Gottesfeld, Ph.D.**, at the **Scripps Research Clinic**, is developing a novel method to 'turn off' the gene for this protein. He is investigating pyrrole-imidazole polyamides, which are molecules that bind to specific regions chromosomal DNA and can 'lock' genes in an inactive state. **Dr. Richard Pietras** of the **University of California, Los Angeles** is addressing the problem of estrogen independence in Her-2 expressing cells. He has found that there is cross-communication between Her-2 and estrogen receptors, which provides a biologic basis for the clinical observation of tamoxifen resistance in patients with breast tumors rich in Her-2 receptors. Resistance of these cancer cells to tamoxifen can be reversed by treatment with an antibody that counteracts the ill effects of Her-2.

Chemotherapy treatment remains a common approach for breast cancer, despite the fact that it is ineffective in many cases. Cells become resistant to chemotherapeutic compounds in a variety of ways, and research is underway to understand the basis for this resistance. **Daniel Mercola, M.D., Ph.D.**, of the **Sidney Kimmel Cancer Center**, is researching ways to inactivate an intracellular signaling protein, called Jun kinase, in order to restore the sensitivity of cancer cells to the DNA-damaging drug — cisplatin. When Jun kinase becomes inhibited, the cells lose growth potential and become more sensitive to cisplatin.

antigens



## Immune therapy: mobilizing the body's defenses

Breast cancer does not appear to stimulate as strong an immune response as some other cancers (e.g., melanoma), so research in this topic often examines the ability of breast cancer cells to avoid this natural mechanism of defense. Several different immune cell types can be recruited in order to train the body to recognize cancer cells and destroy them. One cell type, the dendritic cell, is especially good at processing antigens so that the body can see them. Two BCRP researchers are making progress in taking advantage of this dendritic cell characteristic, **Michael**

**Roth, M.D.**, of the **University of California, Los Angeles**, targeting Her-2 and **Jeffrey Weber, M.D., Ph.D.**, of the **University of Southern California**, targeting CEA. They are removing the dendritic cells from patients, exposing them to the antigen of interest and then returning them to the patient. Ideally, this process will allow the immune system to recognize and attack the breast tumors.

Researchers are also using other cell types in the immune system to train the body to see tumor cells. **Jeffrey Smith, Ph.D.**, at **The Burnham Institute**, is using T cells to target and kill the cancer cells. Dr. Smith is using a process called protein loop grafting, which allows him to change the function of a protein. He is now fusing a part of the T cell that recognizes the T cell receptor to the part that recognizes cancer proteins in order to target the killer cells more specifically to the tumor cells. He has begun to examine whether these new constructs are properly displayed on the surface of immune cells – one of the first steps toward developing an effective immune therapy.



# vaccine

Antibodies are another component of the immune system that BCRP investigators are using to specifically kill tumor cells. **Sherrie Morrison, Ph.D.**, at the **University of California, Los Angeles**, has begun to develop a cancer vaccine by fusing an immune cell growth factor, IL2, with the antibodies to CEA or HER-2. She has made several versions of these fused antibodies and is now testing their effectiveness in mice. **Jerry Peterson, Ph.D.**, at **The Cancer Research Fund of Contra Costa**, has made a novel type of molecule call Ifabs, which are combinations of antibodies and radioactive agents (radioconjugants). He finds that by using parts of the antibodies that target BrE3 and Mc3 proteins as



agents

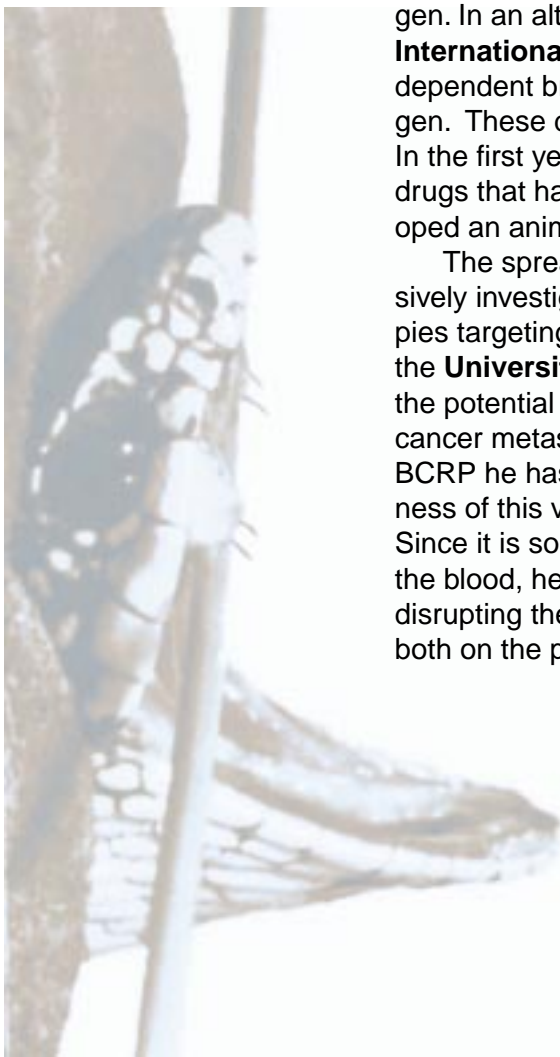
radioconjugants, he is able to target human tumors. **Yoko Fujita-Yamaguchi, Ph.D.**, of **The Beckman Research Institute**, is using antibodies to interfere with IGF-I stimulation of tumor cell growth. Her approach is to block IGF-I binding to its receptor by introducing an antibody that gets in its way. They have learned that stable expression of antibodies against the IGF-I receptor inside of cells is probably lethal to cancer cells. Next, the breast cancer cells expressing insoluble antibodies against the IGF-I receptor will be used to test synergistic effects of chemotherapy and anti-growth factor antibodies.

## New drug design: creative science

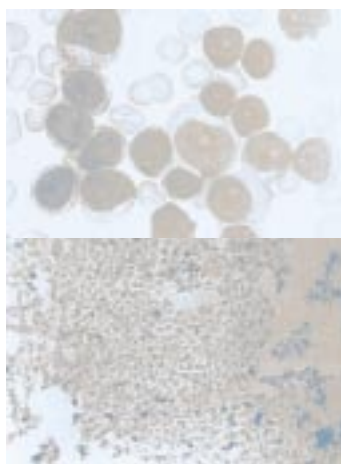
Breast cancer cells grow in response to estrogen. Tamoxifen works by blocking the tumor cells' access to estrogen. In an alternative approach, **Masato Tanabe, Ph.D.**, of **SRI, International**, is designing a new drug to treat estrogen-dependent breast cancer by inhibiting the production of estrogen. These drugs inhibit the production of estrone sulfatase. In the first year of his project, Dr. Tanabe has designed several drugs that have shown promise in cell culture and has developed an animal model in which to test the compounds.

The spread of breast cancer (metastasis) is being intensively investigated for opportunities to develop new drug therapies targeting this process. **Francis Markland, Jr., Ph.D.**, at the **University of Southern California**, continues to develop the potential of a protein from snake venom to inhibit breast cancer metastasis and angiogenesis. Using support from the BCRP he has purified, cloned, and established the effectiveness of this venom protein in breast cancer animal models. Since it is so difficult to block breast cancer cells in transit in the blood, he is developing his novel drug with the aim of disrupting the blood supply. This approach would be effective both on the primary tumor and places in the body (e.g., bone

and lung) where breast cancer commonly spreads. Two other investigators, **Renata Pasqualini, Ph.D.**, at **The Burnham Institute**, and **Joseph Konopelski, Ph.D.**, at the **University of California, Santa Cruz**, are working towards developing therapies directed against the proteins that breast cancer cells use for attachment during invasion and metastasis. Dr. Pasqualini is studying a polymeric form of a protein called fibronectin to block tumor angiogenesis. Dr. Konopelski is using computer modeling to design protein-based derivatives of a fragment of laminin, a cell attachment protein.



# snake venom



Under this priority issue, BCRP awarded 12 grants in 1998. In most cases, the funded projects are a *link between the basic science laboratory and the clinic*. At this stage there is a need for refinement of the mechanisms of action of new treatments and validation of their potential before they are used in humans. These projects make strong use of both animal model systems of breast cancer and clinical samples. There is an increased awareness that more relevant model systems are needed to test potential treatments for breast cancer. This year our awards are clustered in three topic areas (i) metastasis and angiogenesis, (ii) immunotherapy and drug delivery approaches, and (iii) surgery, tumor markers, and drug efficacy.

Angiogenesis has recently emerged as a promising target for attacking breast cancer. The size, invasive-

## Recently Initiated Research

ness, and spread (metastasis) of tumors can be limited by treating the local blood supply. The blood supply of tumors is poorly organized or 'leaky', which allows tumor access for new forms of drug delivery and targeting. **Francis Markland, Jr., Ph.D.**, is exploring the delivery and formulation of a novel protein from snake venom that affects the adhesive properties of both endothelial and breast cancer cells. Similarly, **Keith Laderoute, Ph.D.**, has identified a new drug that disrupts the internal cytoskeleton of cells, and also targets both the blood vessels and breast cancer cells in tumors. Finally, dietary agents could offer more long-term, preventative affects on tumor angiogenesis. **Kent Erickson, Ph.D.**, is investigating conjugated linoleic acid as a potential angiogenesis inhibitor to treat women at risk for developing metastasis following the diagnosis of breast cancer.

# immune system

Immunotherapy and associated treatment strategies commonly focus on the breast cancer cell oncogene Her-2, which is present in about 30% of women diagnosed with breast cancer. Her-2 is a cell surface receptor that leads to unregulated cell growth. Women having tumors with the Her-2 marker experience a poorer clinical outcome. One possible approach to treatment is to use antibodies to Her-2 to directly target breast cancer cells. **Daryl Drummond, Ph.D.**, is attaching Her-2 antibodies to liposome particles to deliver chemotherapy drugs directly to the interior of breast cancer cells. In contrast, **Malcolm Mitchell, M.D.**, is trying to find portions of the Her-2 protein that will stimulate a cytotoxic T lymphocyte recognition of breast cancer cells. The idea is to generate a cell-mediated immune response, rather than just antibodies. **Joseph Lustgarten, Ph.D.**, will attach an immune-enhancing cytokine to Her-2 antibodies to 'mark' tumor cells for attack by the immune system. From a totally different perspective, **Gordon Louie, Ph.D.**, is using the diphtheria toxin x-ray crystal structure as a way to model a novel molecular interaction with a natural ligand for the Her oncogene family, called heregulin.

Several new innovative treatment awards are strongly in the clinical realm. Surgeons need more advanced molecular markers to use in diagnosing breast biopsies. **Shanaz Dairkee, Ph.D.**, will study the molecular pathology of breast samples to see if defects are present even when the visual histological appearance is normal. There is evidence to suggest that the stage of the menstrual cycle can effect the outcome of breast cancer surgery. **Hillary Klonoff-Cohen, Ph.D., Helena Chang, M.D., Ph.D., and Hungyi Shau, Ph.D.**, will approach this issue by examining the differential effect of surgery during different phases of the menstrual cycle on disease outcome. The key strength here is collaborative association of oncologists and epidemiologists brought together in the Translational Research Collaboration (TRC) funding mechanism. Physicians and surgeons are confused and frustrated that, while so many breast cancer 'markers' are known, we are lacking in follow-up studies to see how effective they are in predicting clinical outcome and survival. **Shelley Enger, Ph.D., Michael Press, M.D., Ph.D., and Jon Greif, Ph.D.**, are assembling a team (TRC Pilot) and developing a strategy for collecting and evaluating information on Her-2, p53 (a tumor suppressor gene) and Bax (which regulates apoptosis, or normal cell death) from a sample of patients, and analyzing this information with respect to the therapy provided and subsequent survival status. Finally, we know that only a portion of women actually respond to any given therapy, and this is most frustrating for those women considering chemotherapy. **Silvia Formenti, M.D., Peter Danenberg, Ph.D., and Franco Muggia, M.D.**, will be studying whether they can identify tumor markers that will predict the response of a tumor to the drug, Paclitaxel, with or without radiation before actual treatment begins.





# RESEARCH

Health  
Care  
Delivery  
and Health  
Policy:

Meeting  
a woman's  
needs

One goal of BCRP is to contribute to finding effective prevention, detection and treatment modalities for breast cancer. Achieving this goal alone, however, is not sufficient to end the breast cancer epidemic. Research has demonstrated over and over again that access to and utilization of medical interventions are not uniform in our population. Until effective prevention, detection and treatment is available and acceptable to all, breast cancer will remain a threat to the people of California. For this reason, BCRP has committed to investing in research on health care delivery and health policy.



# CONCLUSIONS



statistic

Success in increasing the portion of breast cancers that are detected at their earliest possible stage depends not only on technology, but also on the ready availability of technology in appropriate health care settings optimally located for ready access. This is especially important for the large numbers of women for whom health care access is difficult for socioeconomic and other reasons. Planning for such services depends on accurate, appropriate statistics. **David J. Delgado, Ph.D., M.P.H.** at the **University of Southern California**, undertook a study to stabilize or “smooth” race/ethnicity and age-specific incidence rates, using a statistical technique called constrained empirical Bayes (CEB). Such smoothing is useful in instances where comparisons are made based on relatively few numbers (of late-staged breast cancer) between geographic areas or time periods, and thus could be misleading (e.g., a change from 2 to 4 while very small, is a change of 100% and would show as a doubling of a rate, in this case the incidence rate — in statistical terms, such rates are considered “unstable”). Dr. Delgado used Medical Service Study Areas (MSSA) in Los Angeles County to test the usefulness of this technique.

# RESEARCH in Progress



Among the findings was that among White women, there were increases in late-stage incidence among areas of low-socioeconomic status that, on average, were larger than increases observed in middle and upper socioeconomic areas when comparing time periods 1976-1983 and 1984-1991. Among Latinas, there were both increases and decreases in incidence that varied according to area. Color maps outlining the distribution of these incidence rates for 87 areas in LA county

were produced, focusing on race/ethnicity, age distribution and time period. His findings could be used to augment other information to help policy makers with issues of resource allocation, program planning and especially breast cancer program evaluation.

**Cyllene Morris, D.V.M., M.V.P.M., Ph.D.**, of the **Public Health Institute**, is doing research into possible factors associated with the apparent underutilization of Breast Conserving Surgery in California. Breast Conserving Surgery followed by radiation therapy is an equally effective alternative to mastectomy and is recommended for most women with stage I or II breast cancer. Nevertheless, even though Breast Conserving Surgery utilization has increased in California, only 54.1% of women with early stage breast cancer received Breast Conserving Surgery in 1995. Preliminary findings (based on all first primary breast cancers diagnosed in the state from 1988 to 1995) show that there is a clear and statistically significant trend towards the use of Breast Conserving Surgery in California. Overall during the eight-year period, 44,079 (41.8%) out of 105,466 women with breast cancer received Breast Conserving Surgery. The percentage receiving Breast Conserving Surgery increased from 27.8% in 1988 to 53.4% in 1995. Dr. Morris's analysis indicates that women of Asian or Hispanic race/ethnicity, diagnosed at a later stage, at older age, or those residing in less affluent areas were less likely to be treated with Breast Conserving Surgery. On the other hand, African-American women were the most likely to receive Breast Conserving Surgery during the study period. Despite these differences, Breast Conserving Surgery utilization is increasing in all groups examined and at a very similar rate regardless of the patient's race/ethnicity or the income level in their area of residence.

In the next year, Dr. Morris will be comparing survival for patients who had Breast Conserving Surgery to those who had mastectomy. **Jay Harness, M.D.** at the **Northern California Cancer Center**, is looking at whether the establishment of Breast Care Centers in two of the Bay Areas county hospitals can make a difference in the care received by indigent women.

While Breast Care Centers have been established and evaluated in several university-based care programs to facilitate delivery of care to women with breast cancer (and other clinical breast conditions), they have never been implemented or evaluated as a technique for improving both health care delivery and adherence to clinical recommendations by indigent women in public facilities.

In Dr. Harness' study, the experience of women with breast cancer treated at the two county hospitals which have, or are establishing, breast centers (the study hospitals) is being compared with that at two other Bay Area county hospitals which do not have such centers (control hospitals). Dr. Harness plans to use interview surveys completed by the patients, medical record data documenting clinical characteristics of the disease and clinical recommendations, and administrative data recording care received (and failed appointments) for this evaluation.

## care

To date, the format for the initial interview has been developed, approved and pilot tested with satisfactory results, and the first post-treatment interview has been drafted. Data managers for the participating hospitals have either been hired and are now being trained, or are now going through the hiring process. Data collection from interviews of patients at all of the sites begun.

Indigent women with breast cancer have been found repeatedly to be less likely than more affluent women to receive full courses of optimal care and to be more likely to experience poorer outcomes. At least some of these undesirable differences can be traced to information and other aspects of care being delivered in ways that are inconvenient, difficult for the women to understand, or otherwise not supportive to the patients needs.

It is hoped that the results of this study will provide information to help all women receive the best possible care.

# Recently Initiated Research



access

Three projects were funded to develop and test educational and screening programs for communities that are not served by current methods: (i) women with disabilities, (ii) Samoan Americans, and (iii) older women.

Women with disabilities have been neglected in breast cancer statistics and in local, state, and national initiatives aimed at earlier breast cancer detection. Although numerous obstacles may limit the access of disabled women to screening services, nothing is known about the extent of the problem and little research has examined the issues involved. With scientific partners, Breast Health Access for Women with Disabilities (BHAWD), a coalition of community-based agencies formed in 1995 in San Francisco's East Bay region, proposes to address this research gap.

To obtain data on the extent and nature of the problem, **Mary Smith, M.S., C.R.C.**, of the **Disabled Community Health Clinic** at **Alta Bates Medical Center** and **Carol D'Onofrio, Ph.D.**, of the **Northern California Cancer Center** will undertake original analyses of data from a large national survey of the general population and a related follow-back survey of respondents with disabilities. A complementary telephone survey of 1,000 women with physical disabilities who live in Alameda or Contra Costa County will be conducted to determine whether results from the national survey describe issues at the local level, to explore barriers to screening in greater depth, and to evaluate BHAWD efforts to improve screening access. While the survey work is in progress, BHAWD partners will draft, revise and distribute a manual to share what has been learned to date from their community-based project and to advise others on how to organize similar initiatives. Throughout the project, interested

individuals will be able to review findings from this project and BHAWD materials on a special website. This and other aspects of the research design are intended to strengthen and expand the BHAWD collaboration.

**Pat Luce-Aoelua, M.S.**, of the **National Office of Samoan Affairs** and **Shiraz Mishra, M.D., Ph.D.**, of the **University of California, Irvine**, will implement and evaluate an innovative, theory-based, culturally sensitive and linguistically appropriate breast cancer control educational program (“intervention”) specially developed for Samoan women. The intervention consists of three components: specially developed English — and Samoan — language educational materials; skills building exercises; and, interactive group discussions. The intervention, designed in four modules, address different aspects of breast cancer (i.e., risk, severity, susceptibility, screening and early detection exams). The materials and the skills building exercises necessary to model and role play new behaviors will supplement group discussions. The study will be conducted in two contiguous Southern California counties, Los Angeles and Orange. Samoan-speaking churches located in these two counties will form the study sites. This collaborative research project has several benefits. It addresses a crucial community identified cancer

control need of Samoan women. Due to the unique study design, Samoan women have an opportunity to make an impact on various aspects of the study as program developers, implementers and evaluators. Furthermore, the research project will provide crucial insights into the applicability and appropriateness of the behavior change theory and research methods for this community. Lastly, the behavior change theory, educational program, evaluation protocol and associated methods will be presented in a didactic monograph designed to be used as a guidebook for other cancer control programs through relevant community-based organizations that work with minority, hard-to-reach populations.

A project by **Arthur Coleman, M.D.**, of **Bayview Hunter’s Point Health Care Task Force**, and **Daramola Cabral Evins, Dr.P.H.**, of the **San Francisco Department of Public Health** is exploring the individual and institutional barriers that prevent women from receiving appropriate follow-up of abnormal mammograms.

# intervention









# RESEARCH

Socio-cultural,  
Behavioral  
and  
Psychological

Issues  
Relevant  
to  
Breast  
Cancer: The  
Human  
Side

**W**hile most re-  
search on  
breast cancer is  
focused on the

biology of the disease, we cannot forget the social and cultural context in which women who are faced with breast cancer live and make decisions. These aspects of human life influence health-related behavior, quality of life, and the biological response to breast cancer. It is the goal of this Priority Issue to explore these social-cultural factors to allow us to impact the human and economic cost of breast cancer.

# CONCLUSIONS



retreat

**S**hoshana Levenberg, B.S.N., of the **Charlotte Maxwell Complementary Clinic**, and **Ellen Levine, Ph.D., M.P.H.**, of the **California Pacific Medical Center Research Institute**, received one of the first Community-Initiated Research Collaboration Pilot Awards. This investigation explored the benefits of a retreat for low-income women with breast cancer. The aims of the project were to identify the needs of low-income women with breast cancer that are not being met by the community at large (e.g., medical care, social support services, transportation, food, child care), and to determine the acceptability and impact of a retreat designed for low-income women with breast cancer on mood, helplessness/hopelessness, feelings of self-efficacy, and self-determination. The first phase of the project was to delineate the problems and challenges faced by low-income women with breast cancer. This was accomplished through a working group of low-income women with cancer, who defined the problems that they faced. After these problems were defined, a three-day retreat was designed by this group of women. The second phase of the project included the retreat itself. Forty-six women participated in a three-day retreat designed by low-income women with breast cancer. The retreat included workshops and experiences with

alternative therapies. At the end of the retreat, women felt that they were more able to cope with problems related to their cancer. The women felt less psychologically distressed (e.g., less anxious, depressed, confused, fatigued), at the end of the retreat than they had at the beginning of the retreat. These differences were statistically significant. The women were contacted two months after the retreat, and asked about their ability to cope with the problems defined initially, and about their mood state. Two months after the retreat, the women felt that their problems were less than before the retreat, and the increased positive mood continued.

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# RESEARCH in Progress



One well-known study of supportive/expressive group therapy showed an extended survival of about 18 months in metastatic breast cancer patients, doubling the survival time of a matched (control) group of patients not receiving this therapy. **Janine E. Giese-Davis, Ph.D.**, at **Stanford University**, set out to try to understand the possible therapeutic and physiological mechanisms underlying this surprising finding. She wanted to deter-

emotions

mine if change in emotional expression, amount of talk-time, or emotional control are therapeutic mechanisms related to survival, immune and endocrine function, and well-being in metastatic breast cancer patients who participate in a year of this group therapy.

Dr. Giese-Davis developed an extensive system of coding the study patients' emotional responses, and measured a hormone (cortisol) to judge levels of stress. Preliminary results indicated that long moments of indirect or constrained anger expressed during the first few months of group therapy strongly predicted an earlier death—the mean survival time was doubled for women who do not constrain anger (3.7 years compared with 1.8). This was the first behavioral study in a relatively naturalistic setting which linked bottling up anger with shorter survival.

Preliminary results also suggested that women who have a healthy, responsive, stress-hormone level when they enter the study appear to live longer if they increase the duration of moments of genuine positive emotional expression over time; or increase the duration of moments of expressing fear, direct anger, and sadness. Furthermore, women who have a flat or unresponsive stress hormone (cortisol) level do not increase their survival through emotional expression in the group. They appear rigid in their emotional coping style in a way not modified by the group. These results indicate that these women may benefit from an additional or quite different kind of therapy and that future research should select those with poor stress-hormone responsivity and test whether such women's survival time could improve using an intervention suited to their rigid coping style.

Women with breast cancer require immedi-

## support

ate and continuing education and emotional support as part of their comprehensive treatment. A woman newly diagnosed with breast cancer is faced with difficult decisions about her treatment. Often she must make these decisions quickly and with a lack of information about the long-term effects of these choices, and at the same time cope with the awareness of a life-threatening illness. As a woman nears the end of her treatment for breast cancer, she faces the prospect of living day-to-day with the uncertainty of whether her cancer will return. To address such concerns, support groups have been created with breast cancer survivors or cancer treatment centers in many California communities. In rural counties, however, many women who would like to participate in support groups often live too far away or do not have reliable transportation. In response, La Loba, a grass roots breast cancer support group in Nevada County, initiated with **Sierra Nevada Memorial Hospital Cancer Center (Mary Anne Kreshka, M.A.)** a study funded by a CIRC Pilot Award in partnership with researchers from the **Stanford University School of Medicine (Cheryl Koopman, Ph.D.)**.



## counseling

The Sierra-Stanford Partnership responded to the needs of rural women with breast cancer by developing and piloting an innovative community-based intervention which is inexpensive, accessible to rurally isolated women, and effective in reducing psychosocial distress and improving coping skills. This user-friendly work-book journal created by community members includes personal experiences of rural women diagnosed with breast cancer, together with sections on exploring and making sense of feelings, strengthening family and social supports, developing partnerships with doctors, and taking charge of treatment decisions. Information about local, state and national resources, such as books, organizations and public agencies helps direct women in their search for education about breast cancer and its treatment. To date, 87 women have been recruited into the project and interviewed at baseline and 60 3-month follow-up interviews have been conducted. Participation rate and follow-up compliance has been high with none of those initially interviewed refusing to complete follow-up assessment. Results from initial findings reveal the success of the work-book journal in reaching women in rural areas and suggest that it may have an impact on reducing traumatic stress by increasing fighting spirit and reducing negative social support and disengagement in coping with breast cancer.

In 1998, BCRP awarded 4 grants to study aspects of breast cancer that affect women personally. A team of scientists (**Joan R. Bloom, Ph.D., Marion Lee, Ph.D., and Susan L. Stewart, Ph.D.**, from the **University of California, Berkeley** and **San Francisco** campuses, and the **Northern California Cancer Center** respectively) will test a telephone counseling strategy for women who are at higher than average risk for breast cancer. In the first phase of the project, a telephone counseling protocol will be field tested with 400 women. The women involved are sisters of a population-based group of women diagnosed with breast cancer at age 50 or younger, of whom approximately 30% are Asian, Latina, or African American. In the second phase of the project, the telephone risk counseling protocol will be implemented in the Cancer Information Service (CIS) of Northern California and Nevada with 400 women calling about breast cancer who are not diagnosed patients.

high risk

## Recently Initiated Research

**Rose C. Maly, M.D., M.S.P.H.**, in the **Department of Family Medicine, University of California, Los Angeles** will look at older women's illness experience of breast cancer, exploring how it differs from younger women's in the way they are evaluated and treated by the health care system, and in their personal reactions to and needs resulting from the diagnosis. The study is designed to assess older breast cancer patients' illness experience, specifically in terms of psychosocial, informational, and health needs arising from the diagnosis, how and whether these needs are met by health care practitioners, and how health, functioning, and quality of life are associated with the degree to which these needs are met. On the basis of these findings, the study will continue with development and feasibility testing of potential interventions to improve emotional, social, and informational support given to newly diagnosed older breast cancer patients by physicians and their staff.

**Nangel M. Lindberg, Ph.D.**, in the **Department of Psychiatry** at the **University of California, Los Angeles School of Medicine** will look at some of the difficult issues facing women at familial risk for breast cancer. For these women, early detection and adherence to medical recommendations are particularly critical; however, studies have shown that family history of breast cancer is associated with emotional reactions that may interfere with desirable health practices, including non-participation in prevention and screening programs. The proposed study seeks to: (1) examine the factors associated with attendance to multidisciplinary preventive programs such as the UCLA High Risk Clinic; (2) examine the factors that may affect adherence to medical recommendations and beneficial health behaviors; and (3) assess compliance and Clinic attendance for different groups of at-risk women. The ultimate goal of the proposed study is to aid in the development and modification of programs that would facilitate and improve access to services for women at familial risk for breast cancer, fostering the development of beneficial health behaviors, including preventive measures and early detection screenings.

## evaluation

Finally, a team of agencies that provide psychosocial support services to women with breast cancer (**Mitch Golant, Ph.D.**, of **The Wellness Community**, **Carol Kronenwetter, Ph.D.**, of the **Cancer Support Community** and **David Spiegel, M.D.**, of **Stanford University**) will study three different models of support groups in an attempt to understand how the various elements of these services help women and to understand their physiological effects. The study is designed to evaluate the strengths and weaknesses of two different community-based support group interventions for breast cancer patients. The interventions will be compared with a model developed in the university setting. The team will study which aspects are most effective, and who benefits the most. This proposal is based on a year-long collaborative effort with The Wellness and Cancer Support Communities, two major cancer support programs providing group interventions.



Careful methods will be applied to understanding the effectiveness of two well-established support group programs in Northern California. This will allow the team to refine and improve group interventions, and better match specific ones to those who will most benefit.

There is a growing body of evidence that participating in support groups improves the quality of life of breast cancer patients. The existence of community support programs provides a means of offering such effective support rapidly and inexpensively, making it available to diverse populations of breast cancer patients. The combination of this community-based effort and university research program provides the potential for improving all of these programs and providing evidence to support health policy changes. This could lead to programs of group support throughout the state of California, offering comfort, guidance, and support to all women coping with breast cancer.

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# Federal and State Funding



One of BCRP's mandates is to "fund innovative and creative research, with a special emphasis on research that comple-

ments, rather than duplicates, the research funded by the federal government and other entities."

A major accomplishment of BCRP towards this goal in 1998 was the creation and convening of the nationwide Breast Cancer Research Funders Network.

Until 1998, there had never been a meeting of the many agencies throughout the U.S. that fund breast cancer research. In fact, it was difficult to keep track of how many programs existed, and even more so to track what each agency was funding. The lack of information and communication was a barrier for BCRP in one of its primary goals – to emphasize research that complements, rather than duplicates, the research funded by other entities. While we have presented in past reports an analysis of research funded by BCRP as compared to other agencies, these analyses have lagged at least a year from actual funding due to the slow release of public information, and have not included all of the agencies funding breast cancer research.

To remove this barrier, not only for BCRP but for all agencies involved in breast cancer research funding, BCRP proposed forming a network of these agencies to share information, ideas, and resources. The idea was enthusiastically received and, in July, 1998, the first ever gathering of breast cancer research funding agencies from around the country was held. The meeting, co-sponsored by the California Breast Cancer Research Program and the Department of Defense Breast Cancer Research Program, was attended by representatives from 12 research funding agencies:

- American Cancer Society
- Canadian Breast Cancer Research Initiative
- Department of Defense Breast Cancer Research Program
- Illinois Department of Public Health
- National Cancer Institute
- New Jersey Commission on Cancer
- New York State Department of Health
- Massachusetts Department of Public Health
- Pennsylvania Department of Health
- The Breast Cancer Fund
- The Susan G. Komen Breast Cancer Foundation

The meeting provided participants with the opportunity to learn about the structure, history, priority issues, award mechanisms, and funding decision protocols of national, private, and state-run breast cancer research funding agencies. It was hoped that this information sharing would allow each to contribute to breast cancer research in the most meaningful and informed way possible.

The following conclusions were reached:

The research priority emphases of the different programs vary, as do the types of funding that the programs offer. Some programs emphasize specific areas of breast cancer research, while others prioritize their funding based entirely on the scientific merit of the proposals they receive. Several programs target socio-cultural issues and prevention as funding priorities. A few programs emphasize research into the biology of the normal breast. All of the programs include some funding mechanism or review criterion that rewards innovation in a proposal.

There was general agreement that advocacy has an important role in breast cancer research funding. All of the agencies include advocates in some level of their decision-making processes and most of the agencies use advocates in the grant review process.

The definition of translational research differs between the programs. The level of translation, the strictness with which it is applied, and the degree to which other elements such as infrastructure development and diffusion of results are considered all play into how each program designed its translational awards. Most agencies want to build the facilitation of translational research into their priorities, but few have successfully developed a means to do so.

The vision for smaller versus larger funding organizations was generally the same. No particular area of the breast cancer research landscape can only be served by a funding agency of a given size; however, due to limited funds the smaller agencies have to target their resources differently. Because of these limitations, smaller agencies generally provide seed funds for research projects, post-doctoral/new investigator awards, and IDEA type grants.

Attendees unanimously agreed that a method for rapid exchange of information was critical for any program that wished to avoid duplication of efforts with other programs. For this reason, the BCRP developed a private e-mail list-serve that allows agencies to communicate effectively and to exchange confidential (or not yet public) information. This e-mail network has resulted in sharing of resources, policies, procedures and ideas, and has made each program more effective.

BCRP is now working to create a universal research classification scheme that will encourage agencies to report their funding in a uniform manner. This will permit agencies and the public to compare the research portfolios of the different agencies in a more meaningful way. Such reporting and analysis will be a major advance in developing research strategies, and help ensure that each dollar spent on breast cancer research, in California and throughout the country, is used in the best possible way.





# Research on Women and Minorities

**I**n accordance with statute (AB2055, 1991), BCRP reports on the extent to which state-funded research projects address medical issues of particular concern to women and minorities. Breast cancer is a disease that strikes women almost exclusively; therefore, all of the research funded by BCRP addresses an issue of particular concern to women. Minority women in general are under-represented in medical research and are underserved in medical practice.

BCRP's advisory Council again



made research that addresses the needs of underserved women a priority in 1998 because of documented disparities in the morbidity and mortality of breast cancer among these women. Applicants were required to explain how their proposed research would address the needs of underserved women and the reviewers who evaluated grant applications were asked to rate them on this criterion. The Council considered this criterion in arriving at its recommendations regarding the grants that should be funded.

Of the 53 grants that BCRP awarded in 1998, 32 (60%) were investigations that included human study samples. Women were the sole source of these samples in all of these clinical studies. 11 (21%) of the grants used human tissues or samples, while 21 (40%) used human subjects as participants. Of these 21 clinical studies, four had a major focus on minority women, five had a major focus on other underserved women, while an additional 18 studies included, but did not specifically focus on, minority or underserved women.

The following studies had a primary emphasis on minority and/or underserved women:

- ♦ Does Mobile Mammography Increase Screening in Older Women?
- ♦ Prediction of Compliance and Retention in High Risk Women
- ♦ Exercise and Risk of Breast Cancer Recurrence
- ♦ Multi-ethnic Study of Genetic Control of Plasma Hormones
- ♦ Breast Cancer Risk Factors: Lesbian and Heterosexual Women
- ♦ Increasing Breast Health for Women with Disabilities
- ♦ Samoans and Breast Cancer: Evaluating a Theory Based Program

# BCRP Staff

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

**Laurence Fitzgerald, Ph.D.**  
Research Administrator

**Katherine McKenzie, Ph.D.**  
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**Walter Price, Dr. P.H.**  
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**Brenda Dixon-Coby**  
Administrative Coordinator

**Deshawn Boyd**  
Administrative Assistant

**Garland Giles**  
Assistant to the Director



# Breast Cancer Research Council

The overall objectives, strategies and priorities of BCRP are set by the Breast Cancer Research

Council, which actively participates in overseeing the program and making final recommendations on the research projects funded. In each Grant Cycle, BCRP awards grants based on the Council's recommendations, which are based on peer reviewers' evaluations, program priorities and available funds.

The Council currently consists of 16 members; five representatives of breast cancer survivor/advocacy groups; five scientist/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.



**Robert Erwin, Chair**  
July 1, 1996 — June 30, 1999



**Suzette Wright, Vice Chair**  
July 1, 1996 — June 30, 1999



**Barbara Brenner**  
**Advocate**  
July 1, 1998 — June 30, 2001



**Floretta Chisolm**  
**Advocate**  
August 27, 1997 — June 30, 2000



**Arlyne Draper**  
**Advocate**  
July 1, 1996 — June 30, 1999



**Carol Pulskamp**  
**Advocate**  
July 1, 1995 — June 30, 1998



**Michell Rakoff**  
**Advocate**  
July 1, 1998 — June 30, 2001



**Beverly Rhine**  
**Advocate**  
July 1, 1996 — May 25, 1998  
Deceased



**Liana Lianov**  
**Ex-officio**  
Feb. 15, 1994 — Ongoing



**Jacquolyn Duerr**  
**Ex-officio**  
Feb. 15, 1994 — Ongoing



**Marco M. Gottardis**  
**Industry**

March 3, 1996 — June 30, 1999



**Kevin Scanlon**  
**Industry**

February 10, 1998 — June 30, 2001



**Bobbie Head**  
**Medical Specialist**

January 15, 1997 — June 30, 2000



**Judith Luce**  
**Non-Profit Health Organization**

August 12, 1997 — June 30, 2000



**Holly Mitchell**  
**Non-Profit Health Organization**

July 1, 1998 — June 30, 2001



**Carol J. Voelker**  
**Non-Profit Health Organization**

July 1, 1995 — June 30, 1998



**Mary Ann Jordan**  
**Scientist/Clinician**

July 1, 1998 — June 30, 2001



**Susan M. Love**  
**Scientist/Clinician**

July 1, 1996 — June 30, 1999

**Shelley Adler**  
**Scientist/Clinician**  
July 1, 1996 — June 30, 1999



**Maria Pellegrini**  
**Scientist/Clinician**  
July 1, 1996 — June 30, 1999

**Anne Wallace**  
**Scientist/Clinician**  
August 27, 1997 — June 30, 2000



## Chair and Vice Chair

### **Robert Erwin, Chair**

July 1, 1996 — June 30, 1999

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Mr. Erwin (Industry Representative), is a founder and serves as President and Chief Executive Officer of Biosource Technologies, Inc., founded in 1987. As a co-founder of Sungene Technologies Corporation, he served as Vice President of Research and Product Development from 1981 through 1986. Mr. Erwin has served on the Biotechnology Industry Advisory Board for Iowa State University and the Executive Committee of the California Tissue Culture Association. He is currently a Director of the Independent Institute, the Marti Nelson Cancer Research Foundation and Large Scale Biology Corporation. Mr. Erwin's biotechnology experience includes research in molecular biology at Abbott Laboratories and at the University of Alabama Medical School. He received his M.S. degree in genetics from Louisiana State University.

### **Suzette Wright, Vice Chair**

July 1, 1996 — June 30, 1999

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Suzette Wright, M.S.P.H., is a five year survivor and advocate of breast cancer. As a member and current president of Save Ourselves/Y-ME Breast Cancer Organization in Sacramento, she was active in lobbying and testifying for the Breast Cancer Act of 1993. Suzette balances her advocacy work with teaching mathematics at the Learning Skills Center at UC Davis and spending time with her family. She strongly hopes that her twenty-one year old daughter will never personally experience breast cancer.

## Advocates

Barbara Brenner

### **Advocate**

July 1, 1998 — June 30, 2001

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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.

## Advocates (cont'd)

Floretta Chisolm

**Advocate**

August 27, 1997 — June 30, 2000

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Floretta Chisolm brings her years of experience in committee work and team building to the BCRC. She is currently the Director of Health and Human Services in Oakland, CA. She also serves on a variety of health and social service committees such as the Healthy Start Advisory Board; the City of Oakland Commission on Homelessness; the City of Oakland Health Commission; the Community Action Agency Advisory Board; and the Ann Martin Children's Center. She became active in the fight against breast cancer as a member of the Breast Cancer Fund Board. The welfare of her daughter provides Ms. Chisolm with her strong motivation for eradicating breast cancer.

Arlyne Draper

**Advocate**

July 1, 1996 — June 30, 1999

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Breast cancer has been a part of Arlyne and her family's lives for the past 20 years. Arlyne Draper has survived two breast cancers and, for the past five years, has dedicated herself to fighting this disease by promoting education, increasing awareness, and encouraging others to speak up and demand attention. She is founder of the Women's Cancer Task Force (WCTF), a grassroots organization and a chapter of Y-ME, which works for changes in breast cancer education, research, diagnosis and treatment. She also co-founded the California Breast Cancer Organizations (CABCO) where she serves as president and representative to the National Breast Cancer Coalition (NBCC) working board. She has participated in numerous breast cancer conferences and committees at the state and federal levels.

## Advocates (cont'd)

Carol Pulskamp

**Advocate**

July 1, 1995 — June 30, 1998

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Carol Pulskamp is a life-long activist and (since 1990) breast cancer survivor/advocate. She is a former educator of the deaf, and a staunch and outspoken advocate for health care reform, rights of disabled persons, etc. She is a founding member and the executive director of the Northern California Coalition for Cancer Survivorship, an association member of the National Coalition for Cancer Survivorship.

Beverly Rhine

**Advocate**

July 1, 1996 — May 25, 1998

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Beverly Rhine was a breast cancer survivor and vice president of the Women of Color Breast Cancer Survivors Support Project. She was dedicated to providing support, counseling and psycho-social assistance to African American women faced with breast cancer. Beverly was also a member of the Breast and Cervical Cancer Early Detection Program Advisory Council. Beverly Rhine passed away on May 25, 1998.

Michell Rakoff

**Advocate**

July 1, 1998 — June 30, 2001

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Michell Rakoff is a breast cancer survivor and advocate. Shae is a Board Member of the Los Angeles Breast Alliance (LABCA) and the California Breast Cancer Organization (CABCO). Ms. Rakoff has participated in the Department of Defense (DOD) Breast Cancer Research Program and the California Breast Cancer Research Program (BCRP) 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.

## Ex-officio Members

Liana Lianov

**Ex-officio**

Feb. 15, 1994 — Ongoing

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Liana Lianov, M.D., M.P.H. is currently medical advisor to the Cancer Detection Section at the California Department of Health Services. Over the past seven years, she has developed and implemented the Breast and Cervical Cancer Control Program, which is federally funded, and the Breast Cancer Early Detection Program, which is funded by 50% of the tobacco tax raised by the Breast Cancer Act. These programs offer screening, diagnostic and educational services to low income women. Dr. Lianov is a physician board certified in both Internal Medicine and Preventive Medicine and Public Health and was trained at Good Samaritan Medical Center in Phoenix, Arizona and Baylor Medical Center in Dallas, Texas. She received her Masters Degree in Public Health from the University of California, Berkeley in 1990 and her medical degree from the University of Nevada in 1985.

Jacquolyn Duerr

**Ex-officio**

Feb. 15, 1994 — Ongoing

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Jacquolyn Duerr, M.P.H. is Chief of the Breast Cancer Early Detection Program in the Cancer Control Branch of the California Department of Health Services. In this position, she is responsible for the design and development of a statewide program for the expansion of breast cancer screening services to low-income, underserved, older women. She has overseen the creation of local partnerships comprised of providers and consumers to create a network for case management, and to monitor and improve the quality of these services. She has extensive training and experience in community health education and outreach.

## Industry

Marco M. Gottardis

**Industry**

March 3, 1996 — June 30, 1999

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Marco M. Gottardis, Ph.D. is a Research Investigator in the Dept. of Endocrine Research at LIGAND Pharmaceuticals in San Diego, California. His research group is currently developing new classes of breast cancer hormonal therapies (which include novel retinoid and anti-hormonal agents) that have greater target selectivity and less side-effects than current days. Dr. Gottardis has studied the molecular and biological mechanisms of resistance to breast cancer hormone therapies for the last 15 years. He has trained in several of the preeminent breast cancer research laboratories. He serves on several standing and ad hoc research grant study sections for the American Cancer Society, U.S. Army Breast Cancer Research Program and National Institute for Environmental Health Sciences.

Kevin Scanlon

**Industry**

February 10, 1998 — June 30, 2001

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Kevin Scanlon, Ph.D., is an Industry Representative. He is Vice President and Head of the Cancer Research Department of Berlex Biosciences in Richmond, CA. Dr. Scanlon did his post-graduate work at the Department of Biochemistry at the University of London in the United Kingdom. He was a postdoctoral associate in the Department of Pharmacology at Yale University, School of Medicine and a scholar in the Leukemia Society of America. Dr. Scanlon was awarded the 1988 Paul Martini Internal Medical Research Prize in Germany. He has published over 85 papers on Cancer research and currently serves as co-editor for Cancer Gene Therapy, and the Internet Book of Gene Therapy. His extensive experience as a member in the National Institutes of Health, Cancer Study Section provides the council with insight into the traditional review process.

# Medical Specialist

Bobbie Head

## **Medical Specialist**

January 15, 1997 – June 30, 2000

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Bobbie Head, M.D., Ph.D. specializes in caring for women with breast cancer in her private practice in Marin County, California providing education and information to women who have been diagnosed with breast cancer. Her practice caters to the emotional, physical and spiritual needs of women and provides access to complimentary care modalities to assist women with making informed decisions about treatment options. Dr. Head chairs the Breast Health Committee at Marin General Hospital and the California Healthcare Systems Science Committee, which evaluates new trials for 3 Bay Area Hospitals. She also serves on the Board of Directors of the Hospice of Marin. Bobbie Head is active in clinical research and teaching and she participates in national and pharmaceutical company trials that utilize new cancer therapies.

Judith Luce

## **Medical Specialist**

August 12, 1997 — June 30, 2000

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Judith Luce, M.D., has demonstrated her dedication to the fight against breast cancer in her volunteer and her professional work. She has been an active member of American Cancer Society for over 15 years. She has served as president of the San Francisco Unit of the ACS, as well as both member and Chairperson of the California Division Breast Health Task Force. Dr. Luce is a faculty member at UCSF and the Director of Oncology Services at San Francisco General Hospital. She is also the principal investigator on several clinical trials including a study on breast and cervical cancer intervention, and a multi-center breast cancer prevention trial. Her proudest achievement of her volunteer/research life has been her work with others in the Department of Public Health to offer breast and cervical cancer screening to underserved women in San Francisco. "We started this work in 1988, and today have highly successful programs in BCCCP (we were one of the first in the state) and BCEDP, as well as a new program to do targeted outreach to every woman in our patient population who has not been screened. We have worked with a variety of others to accomplish this, and I am certain that we are seeing the results of these efforts in better health for women in our city."

## Non-Profit Health Organizations

Holly Mitchell

**Non-Profit Health Organization**

July 1, 1998 — June 30, 2001

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Holly Mitchell is past Executive Director of the California Black Women's Health Project (CBWHP), a women's health advocacy organization that is committed to improving the health of Black women in California. She has recently taken a new position as Legislative Advocate at Western Center of Law and Poverty. She has been actively involved in public policy and service through her former positions as a graduate fellow in the Coro Foundaton; a senior consultant to the Senate Committee on Health and Human Services for State Senator Diane Watson; and as a project director for the California Women's Health Project, a program of the California Elected Women's Association for Education and Research (CEWAER). A local activist and staunch supporter of women's rights, Ms. Mitchell volunteers with numerous community-based organizations and serves on several boards of directors including: Planned Parenthood of Sacramento Valley; The Center for Community Health and Well Being (home of the nationally recognized Birthing Project); Save Ourselves, a breast cancer advocacy, education and peer support organization; and the Dangerfield Institute, a foster care

Carol J. Voelker

**Non-Profit Health Organization**

July 1, 1995 — June 30, 1998

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Carol J. Voelker, Ph.D., was appointed to the BCRC in July, 1995, as a representative of a non-profit health organization. A sixteen year member of Soroptimist International of the Americas, whose focus in the health area is breast cancer awareness, Dr. Voelker is also a member of the National Breast Cancer Coalition and the Orange County Chapter of the Susan G. Komen Breast Cancer Foundation. She also works as a legislative advocate to obtain funding at both the state and national levels for breast cancer research.



## Scientist/Clinician

Shelley Adler

**Scientist/Clinician**

July 1, 1996 — June 30, 1999

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Shelley Adler, Ph.D. is a medical anthropologist specializing in sociocultural gerontology at the University of California, San Francisco. Some of her current research includes "Women's Breast Cancer Treatment Choices by Cohort and Ethnicity;" "Older Women's Interactions with Their Physicians Regarding Breast Cancer;" and "Alternative Breast Cancer Treatments." She is a member of the American Anthropological Association, the Society for Medical Anthropology and the American Society on Aging.

Mary Ann Jordan

**Scientist/Clinician**

July 1, 1998 — June 30, 2001

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Mary Ann Jordan, Ph.D., earned her B.A. 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 performed 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.

Susan M. Love

**Scientist/Clinician**

July 1, 1996 — June 30, 1999

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Susan M. Love, M.D. is an author, teacher, surgeon, researcher and activist. She is an Adjunct Professor of Surgery at UCLA and former Director of the Revlon/UCLA Breast Center. She is one of the co-founders of the National Breast Cancer Coalition and serves on their Board of Directors. She also serves as a co-chair of the Biological Resources Task Force of the National Action Plan on Breast Cancer. She is the author of many books and articles including an *Atlas of Techniques in Breast Surgery* and *Dr. Susan Love's Breast Book* (second edition June 1995), which has been termed the 'bible' for women with breast cancer. Her second book, *Dr. Susan Love's Hormone Book: Making Informed Choices about Menopause*, was published by Random House in February of 1997.

## Scientist/Clinician (cont'd)

Maria Pellegrini

**Scientist/Clinician**

July 1, 1996 — June 30, 1999

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Maria Pellegrini, Ph.D., is currently Dean of Research in the College of Letters Arts and Sciences at the University of Southern California in Los Angeles. Dr. Pellegrini's research interests have included studies of the structure-function relationships within proteins and the regulation of gene expression. She is the recipient of an Alfred P. Sloan Foundation Fellowship and a Dreyfus Foundation Teacher-Scholar Award and has received several research and training grants from the National Institutes of Health. Since 1977, Dr. Pellegrini has been Professor of Biological Sciences at USC. Dr. Pellegrini has served on a number of National Institutes of Health grant review panels, including a current assignment on the NIH Training Grant Study Section. She is a breast cancer survivor and a co-founder of Reprogen, Inc., a biotechnology company focused on developing new products relating to women's reproductive health.

Anne Wallace

**Scientist/Clinician**

August 27, 1997 — June 30, 2000

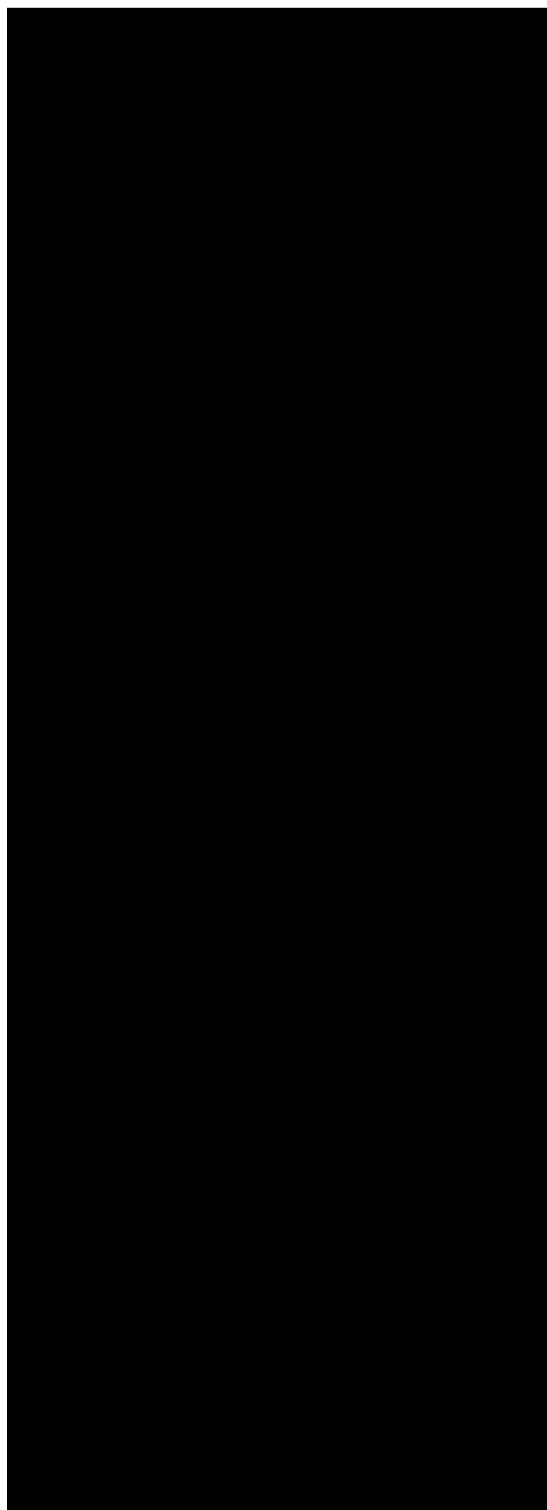
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Anne Wallace, M.D., has substantial experience with breast cancer patients, basic research, and clinical research. She is a surgeon at the University of California, San Diego whose practice consists primarily of breast cancer patients. Dr. Wallace has experience in research at many levels. She heads the National Surgical Adjuvant Breast and Bowel Project (NSABP) for UCSD, a large scale clinical study that has increased in efficiency and in the patient participation under her direction. She is a member of the UCSD Cancer Center Protocol Review Committee, which is a body that evaluates the protocols for grant applications from the entire Cancer Center. She also collaborates on research projects that investigate the basic biology of breast cancer. She has a profound interest in funding forward thinking research that is maximally beneficial to breast cancer patients.





Summary  
of  
New  
Awards  
by  
Institution



	Duration	Direct Costs	Indirect Costs	Total
<b>Alta Bates Foundation</b>				
Smith, Mary				
Increasing Breast Health Access for Women With Disabilities	3	\$494,776	\$ 9,367	\$504,143
<b>Beckman Research Institute of the City of Hope</b>				
Chen, Shiuan				
Breast Cancer Prevention with Phytoestrogens in Grape Juice	3	\$306,438	\$232,893	\$ 539,331
<b>The Burnham Institute</b>				
Baribault, Helene				
Role of Gamma-catenin in a Breast Cancer Mouse Model	2	\$149,704	\$142,219	\$291,923
Ely, Kathryn				
Role of Rb Protein and Cell Cycle Defects in Breast Cancer	2	\$145,321	\$138,055	\$283,376
Matsuzawa, Shu-ichi				
Siah-family Genes: Effectors of p53 in Breast Cancer	2	\$ 69,820	\$ 5,586	\$ 75,406
Narisawa, Sonoko				
Understanding Breast Cancer Cell Metastasis to Bone	3	\$224,210	\$213,000	\$437,210
Yamamoto, Fumiichiro				
Alteration of Developmental Genes in Breast Cancer	2	\$150,000	\$142,500	\$292,500
Zeh, Karin				
Cell Adhesion Signaling Defects in Breast Cancer	2	\$ 70,000	\$ 5,600	\$ 75,600
<b>Total</b>		<u>\$809,055</u>	<u>\$646,960</u>	<u>\$1,456,01</u>
<b>California Pacific Medical Center Research Institute</b>				
Dairkee, Shanaz				
Molecular Mapping of Surgical Margins	2	\$199,964	\$ 88,028	\$287,992
Drummond, Daryl				
A New System for Breast Cancer Drug Delivery	2	\$ 69,991	\$ 5,331	\$ 75,322
<b>Total</b>		<u>\$269,955</u>	<u>\$ 93,359</u>	<u>\$363,314</u>
<b>Kaiser Foundation Research Institute</b>				
Enger, Shelley				
Breast Tumor Markers and Response to Adjuvant Therapy	1	\$ 73,934	\$ 6,358	\$ 80,292
Sternfeld, Barbara				
Epidemiology of Physical Activity and Ovarian Function	2	\$149,482	\$ 39,063	\$188,545
<b>Total</b>		<u>\$493,371</u>	<u>\$138,780</u>	<u>\$632,151</u>

	Duration	Direct Costs	Indirect Costs	Total
<b>La Jolla Institute for Experimental Medicine</b>				
Sriramarao, Pragada Leukocyte Recruitment, Angiogenesis and Breast Cancer	2	\$ 148,969	\$155,844	\$ 304,813
<b>Lawrence Berkeley National Laboratory</b>				
Barcellos-Hoff, Mary Helen Hormonal Regulation of TGF Beta During Mammary Development	3	\$4 40,960	\$319,928	\$ 760,888
Itahana, Koji Novel Binding Functions of Mutant p53 in Breast Cancer Cells	2	\$ 70,000	\$ 0	\$ 70,000
Kaufman, Paul Chromatin Regulation of Breast Cancer Cell Senescence	2	\$ 150,000	\$ 82,054	\$ 232,054
Luo, Kunxin TGF-Beta Receptor Signaling and Breast Cancer	3	\$ 224,246	\$139,014	\$ 363,260
Shyamala, G. Progesterone Receptor and Remodeling of Basement Membrane	1	\$ 75,000	\$ 49,412	\$ 124,412
Stampfer, Martha Genes Involved in Immortalization of Human Mammary Cells	2	\$ 150,000	\$103,314	\$ 253,314
VanBrocklin, Henry Development of EGFR-Based Imaging Agents for Breast Cancer	1	<u>\$ 50,000</u>	<u>\$ 31,325</u>	<u>\$ 81,325</u>
<b>Total</b>		<u>\$1,160,206</u>	<u>\$725,047</u>	<u>\$1,885,253</u>
<b>Lyon-Martin Women's Health Services</b>				
Roberts, Stephanie Breast Cancer Risk Factors: Lesbian and Heterosexual Women	3	\$ 141,185	\$ 28,238	\$ 169,423
<b>National Office of Samoan Affairs</b>				
Luce-Aoelua, Pat Samoans and Cancer: Evaluation of a Culturally Appropriate Program	2	\$ 319,172	\$ 89,368	\$4 08,540
<b>Northern California Cancer Center</b>				
Horn-Ross, Pamela Diet & Breast Cancer in the California Teachers Study Cohort	2	\$ 110,933	\$ 38,161	\$ 149,094
Stewart, Susan Risk Notification for Women at High Risk for Breast Cancer	3	<u>\$ 499,007</u>	<u>\$148,975</u>	<u>\$ 647,982</u>
<b>Total</b>		<u>\$ 609,940</u>	<u>\$187,136</u>	<u>\$ 797,076</u>

	Duration	Direct Costs	Indirect Costs	Total
<b>SRI International</b>				
Jong, Ling				
Dietary Indole Analogs for Breast Cancer Prevention	3	\$224,995	\$209,919	\$434,914
Laderoute, Keith				
Novel Anti-vascular Agents for Breast Cancer Therapy	2	<u>\$199,998</u>	<u>\$152,065</u>	<u>\$352,063</u>
<b>Total</b>		<u>\$424,993</u>	<u>\$361,984</u>	<u>\$786,977</u>
<b>Salk Institute for Biological Studies</b>				
Louie, Gordon				
Heregulin-specific Diphtheria Toxin as a Cancer Therapy	3	\$225,000	\$195,975	\$420,975
Ruffner, Heinz				
Biochemical and Functional Characterization of BRCA1	2	<u>\$ 70,000</u>	<u>\$ 5,600</u>	<u>\$ 75,600</u>
<b>Total</b>		<u>\$295,000</u>	<u>\$201,575</u>	<u>\$496,575</u>
<b>San Francisco Department of Public Health</b>				
Evins, Daramola				
Study of Inadequate Follow-up of Mammography Abnormalities	1	\$ 74,980	\$ 8,643	\$ 83,623
<b>Scripps Research Institute</b>				
Ditzel, Henrik				
Targets of B Cell Infiltrate in Medullary Breast Cancer	2	\$159,937	\$119,953	\$279,890
Lai, Cary				
The Role of a Newly Discovered Neuregulin in Breast Cancer	1	\$ 49,984	\$ 37,488	\$ 87,472
Quaranta, Vito				
Regulation of Breast Epithelial Cell Motility by Proteases	3	<u>\$265,160</u>	<u>\$198,870</u>	<u>\$464,030</u>
<b>Total</b>		<u>\$475,081</u>	<u>\$356,311</u>	<u>\$831,392</u>
<b>Sidney Kimmel Cancer Center</b>				
Lustgarten, Joseph				
Antibody-IL-2 Fusion Protein for Breast Cancer Immunotherapy	3	\$224,100	\$201,444	\$425,544
<b>Stanford University</b>				
Rosen, Glenn				
A Novel Drug Induces Apoptosis in Breast Cancer Cells	2	\$150,000	\$ 81,490	\$231,490
Spiegel, David				
Do Community Cancer Support Groups Reduce Physiologic Stress?	3	<u>\$496,143</u>	<u>\$232,729</u>	<u>\$728,872</u>
<b>Total</b>		<u>\$646,143</u>	<u>\$314,219</u>	<u>\$960,362</u>



	Duration	Direct Costs	Indirect Costs	Total
<b>University of California, Berkeley</b>				
Nandi, Satyabrata				
Pregnancy Genes Associated With a Risk for Breast Cancer	3	\$373,725	\$0	\$373,725
<b>University of California, Davis</b>				
Buonocore, Michael				
Measurement of Breast Tissue Viscoelasticity Using MRI	1	\$4 9,984	\$0	\$4 9,984
Erickson, Kent				
Reduced Breast Cancer Metastasis by Conjugated Linoleic Acid2		\$199,629	\$0	\$199,629
Sawai, Earl				
Intracellular Signaling Pathways in Metastasis	1	\$ 50,000	\$0	\$ 50,000
<b>Total</b>		<u>\$299,613</u>	<u>\$0</u>	<u>\$299,613</u>
<b>University of California, Irvine</b>				
Mishra, Shiraz				
Samoans and Breast Cancer: Evaluating a Theory-Based Program	2	\$168,955	\$0	\$168,955
<b>University of California, Los Angeles</b>				
Lindberg, Nangel				
Prediction of Compliance and Retention in High Risk	2	\$ 69,600	\$0	\$ 69,600
Maly, Rose				
Improving Health-Related Quality of Life in Older Women after breast cancer	3	\$417,677	\$0	\$417,677
Reuben, David				
Does Mobile Mammography Increase Screening in Older Women?	3	\$499,982	\$0	\$499,982
<b>Total</b>		<u>\$987,259</u>	<u>\$0</u>	<u>\$987,259</u>
<b>University of California, San Diego</b>				
Klonoff-Cohen, Hillary				
Timing of Breast Cancer Surgery, Menstrual Cycle & Prognosis	3	\$520,075	\$0	\$520,075
Mitchell, Malcolm				
Breast Cancer Immunotherapy Using CD4+ Lymphocytes	2	\$200,000	\$0	\$200,000
Vera, David				
Sentinel Node Detection via Targeted Fluorescence	1	\$ 41,282	\$0	\$ 41,282
<b>Total</b>		<u>\$761,357</u>	<u>\$0</u>	<u>\$761,357</u>

	Duration	Direct Costs	Indirect Costs	Total
<b>University of California, San Francisco</b>				
Dibble, Suzanne				
Breast Cancer Risk Factors: Lesbian and Heterosexual Women	3	\$ 186,214	\$ 0	\$ 186,214
Wrensch, Margaret				
Marin County Breast Cancer Study of Adolescent Risk Factors	1	<u>\$ 77,407</u>	<u>\$ 0</u>	<u>\$ 77,407</u>
<b>Total</b>		<u>\$ 263,621</u>	<u>\$ 0</u>	<u>\$ 263,621</u>
<b>University of Southern California</b>				
Feigelson, Heather				
Multi-ethnic Study of Genetic Control of Plasma Hormones	3	\$ 214,254	\$ 136,404	\$ 350,658
Formenti, Silvia				
Biologic Determinants of Response to Paclitaxel & Radiation	3	\$ 498,315	\$ 318,302	\$ 816,617
Hill, Deirdre				
Radiation, Reproductive & Menstrual Factors & Breast Cancer	2	\$ 70,000	\$ 5,600	\$ 75,600
Markland, Francis				
Mechanism of Novel Anti-Angiogenic Therapy for Breast Cancer	2	\$ 200,000	\$ 124,300	\$ 324,300
Ross, Ronald				
NCCC Breast Cancer Research Training Program	3	\$ 314,877	\$ 25,190	\$ 340,067
Shames, Lisa				
Exercise and Risk of Breast Cancer Recurrence	2	\$ 149,979	\$ 95,795	\$ 245,774
Ursin, Giske				
Oral Contraceptives, Hormonal Risk Factors and BRCA1	3	<u>\$1,041,683</u>	<u>\$ 659,008</u>	<u>\$1,700,691</u>
<b>Total</b>		<u>\$2,489,108</u>	<u>\$1,364,599</u>	<u>\$3,853,707</u>