Annual Report 2001

The California Breast Cancer Research Program

CALIFORNIA
Breast
Cancer
Research
PROGRAM

Research Highlights

Vitamin A inhibits breast cell growth, and a drug based on Vitamin A could potentially prevent breast cancer. See "Breast Cancer Chemoprevention by Retinoids," page 50 .

Physicians who interpret a high number of mammograms are more likely to find cancers when they are present and less likely to falsely identify a non-cancerous area as cancer. Centralizing mammogram interpretation could save money, increase cancer detection, and reduce biopsy rates. See "Harnessing Technology to Improve Mammography Effectiveness," page 59.

Graduate students are testing a **prototype miniature gamma camera to detect breast cancer** and **methods for reducing breast compression during mammograms**. See "UCLA Biomedical Physics Graduate Training Program," page 66.

Diet and exercise during childhood and adolescence may affect a woman's risk of getting breast cancer as an adult. See "Physical Activity, Diet and Menarche in a Multi-Ethnic Cohort," page 75.

Women who had **high exposure to x-rays in childhood** (in the past, when radiation doses were greater than today) have a higher than average risk of getting breast cancer before age 40, if they also have both benign breast disease and a family member with breast cancer. See "Radiation, Reproductive & Menstrual Factors & Breast Cancer," page 77.

Relatively inexpensive organizational changes can **improve breast cancer care for women at public hospitals.** See "The Breast Care Center: Innovative Care for the Underserved," page 92.

Delivering chemotherapy drugs directly to tumors using microscopic fat particles could potentially **reduce the toxic side effects of chemotherapy**. See "A New System for Breast Cancer Drug Delivery," page 101.

A protein derived from **snake venom** is a potential breast cancer treatment. See "Mechanism of Novel Anti-Angiogenic Therapy for Breast Cancer," page 102.

Extracts of some **Chinese herbs** inhibit cells growth; researchers are trying to isolate compounds that inhibit cell growth from these extracts. See "Treating Breast Cancer with Chinese Herbs: A Pilot Study," page 108. A compound derived from Chinese herbs also greatly enhances the effect of chemotherapy drugs. See "A Novel Drug Induces Apoptosis in Breast Cancer Cells," page 122.

Fish oils decrease breast tumors' ability to spread to other body parts by keeping the tumor from growing blood vessels and decreasing certain crucial proteins. This research strengthens the theory that altering fat in the diet can be used as an additional therapy at any stage of breast cancer. See "Alteration of Dietary Fat to Reduce Breast Cancer Metastasis," page 142.

Advances in Breast Cancer Research 2001

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

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Message from the Director

During 2000, the California Breast Cancer Research Program (BCRP) awarded $16,091,618 for 70 single- and multiple-year research projects at 22 California institutions.

This Annual Report is part of our wide-ranging efforts to make our research available to the public. On these pages, we give brief summaries of the studies we funded this year, along with summaries of studies we funded in previous years that were completed or made progress during 2000. We include results of 58 completed studies and summaries of 51 ongoing studies. We are one of the few research programs in the world to publish annual summaries of studies while they are still in progress.

Designed to push breast cancer research in new, creative directions, the BCRP is funded primarily by a California state tax on tobacco. Since 1995, the BCRP has provided a total of $97,775,174 in research funds.

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

Breast cancer activists have played a leading role in the BCRP from the beginning. They helped write and pass the statewide legis-

lation that created the program in 1993. Women with breast cancer and survivors of the disease are involved in all levels of the BCRP's decision making, including decisions about which projects get funded. With input from these advocates, the BCRP has established a record for funding cutting-edge studies and jump-starting new areas of research. Our goal is to fund the projects that will lead most rapidly to the end of the breast cancer epidemic.

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

About the California Breast Cancer Research Program

Making California a Leader Among States

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

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

Funded primarily by the tobacco tax, and supplemented with taxpayer donations selected on state income tax returns, and private contributions, the California Breast Cancer Research Program (BCRP) has provided a total of $97,775,174 in research funds since 1995. In 2000, the BCRP awarded $16,048,295 for 70 single- and multiple-year grants at 22 California institutions.

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

- Checking the appropriate line on your California Income Tax Return and adding a donation to the California Breast Cancer Research Fund
- Sending a check payable to The Regents of the University of California, with a letter designating the funds for the California Breast Cancer Research Program, to:

300 Lakeside Drive, 6th Floor, Oakland, CA 94612-3550.

Pushing the Research Boundaries

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

To tap the expertise of people most affected by breast cancer, the BCRP has pioneered collaboration between research scientists and nonprofit organizations, including community clinics, organizations serving women with breast cancer, and organizations serving minority communities. The collaborations are available in even wider circles. "Not a Breast Cancer Researcher? Concerned Community Member?" say headlines on the cover of our call for research applications. Inside, the call invites Californians with promising research ideas to team up with professional scientists.

Because the results of basic science research can sit on the shelf for years, with no one in the scientific community being aware of any possible implications for fighting breast cancer, the BCRP also makes "translation" grants. These grants spark collaboration between basic research scientists and scientists who may be able to translate the findings into improvements in breast cancer treatment.

Since the disease is still raging despite increased research efforts, new breakthroughs are likely to come from thinking outside established patterns of scientific thought. So the BCRP brings together scientists from different fields to develop creative ideas outside traditional research channels. An example is 2000's Cancer and Complexity Conference in Berkeley, which brought researchers in breast cancer biology together with experts in new computer modeling technology.

A Structure That Encourages Public Input

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

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

Our 15-member advisory Breast Cancer Research Council includes scientists, clinicians, representatives of industry and non-profit health organizations, and five breast cancer advocates. The Council provides vision, sets research priorities and determines investment strategy. It also conducts one of two reviews every proposal must pass to receive funding. The Council reviews research proposals for relevance to the BCRP's goals, while teams of research scientists and breast cancer advocates from outside California also review all proposals for scientific merit.

In addition, all Californians concerned about breast cancer have opportunities to help set the research agenda via the BCRP's statewide advisory meetings, open to the public. Our bi-annual research symposia bring the scientific and treatment communities into dialog with a broader range of the public than is common at such conferences. We also encourage public review of BCRP-funded research through our website (http://www.ucop.edu/srphome/bcrp/) and this Annual Report.

California Breast Cancer Research Program's Key Strategies

1) Support the best, most innovative research
2) Build the research talent pool by training new researchers
3) Encourage creativity by financing collaboration across research fields
4) Widely disseminate research results to scientists, health care professionals and the public

To End the Suffering

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

What They're Saying About BCRP

The Best Science

"By harnessing the talents of clinicians and basic scientists and real life experiences of cancer survivors, the California Breast Cancer Research Program ensures that the best science with potential for the greatest benefit to breast cancer patients is funded. In my opinion it is the best conceived, most effective state-based research funding program in the nation and should be copied by other states."

Emmanuel T. Akporiaye, Ph.D.
Professor
Department of Microbiology and Immunology
University of Arizona
Tucson, Arizona

Exciting Research

"Every year, BCRP funds exciting research to test new ideas that would not be funded without their grants. It's extremely important that they fund this risk-taking research."

Kristiina Vuori, M.D., Ph.D.
Assistant Professor
The Burnham Institute
La Jolla, California

Advocates at the Table

"I appreciate the California Breast Cancer Research Program allowing breast cancer advocates like myself to play a role in the peer review process. Having me sit at the table with scientists gives women with breast cancer and survivors a voice in research funding decisions. It also gives me the opportunity to learn more about the ins and outs of breast cancer research."

Sara Williams
3-Year Cancer Survivor
President, Breast Cancer Coalition of North Carolina
Chapel Hill, North Carolina

Lives in the Balance

"At the last BCRP research symposium that I attended in September 1999, I was very much struck by the significant presence and considerable role played by the advocates. I'm a cancer survivor myself. These patients and survivors not only brought back my own experience, but also dramatically underscored the importance of everyone's efforts in fighting this disease. The very personal testimony from these women vividly demonstrated that there are *literally* lives in the balance that depend upon our research to improve the current, largely primitive ways of controlling the disease. I applaud the participation of these advocates and hope they will continue to play a major and interactive role in the research process."

Cary Lai, Ph.D.
Associate Professor
Scripps Research Institute
La Jolla, California

Non-Mainstream Research

"BCRP provided start-up funding for our study into diet and breast cancer, an area that's somewhat hard to get funded by national agencies. They're willing to fund non-mainstream research areas relevant to breast cancer, like social, psychological and dietary factors."

Kent Erickson, Ph.D.
Professor and Chair
Department of Cell Biology, School of Medicine
University of California
Davis, California

Remarkably Efficient

"The thing that really impresses me most about the California Breast Cancer Research Program is the way that it works as an instrument of the citizens of the state of California. This is apparent from the instructions given to the investigators in the requests for proposals, the mandate offered as guidance for the reviewers, and the structure and administration of the grants. By emphasizing the availability and affordability of new treatments and modalities to all people, it has proven itself a remarkably efficient instrument of public health policy."

John Mark Carter, Ph.D.
Director of Chemistry
Acting Director of Environmental Health and Safety
AxCell Biosciences Corporation
Newtown, Pennsylvania

Giant Leaps

"One of the BCRP's best features is that it nurtures new avenues into breast cancer research. Their New Investigator and IDEA grants are immediately relevant to the problems of breast cancer patients, and could yield answers in the very near future. At SRI, BCRP-funded research has generated several new drug candidates that will be further developed for treatment of breast cancer. Several novel drug targets have been studied on BCRP grants. BCRP-funded research has made giant leaps into several research areas of breast cancer, not matched by any federal or state-funded programs in the entire country."

Nurulain Zaveri, Ph.D.
Medicinal Chemist/Project Leader
Pharmaceutical Discovery Division
SRI International
Menlo Park, California

Very Supportive

"I received a postdoctoral fellowship from the BCRP at a critical time in my career. I had done some research on breast cancer as part of my dissertation, and BCRP funding gave me the extra push to continue doing research in this area. BCRP is very supportive of individuals beginning their research careers. Their workshops on how to apply for funding are very helpful. The staff members are pleasant, willing and available to answer questions. My experiences with the BCRP have helped me to become more confident as I continue my research career."

Carol Koprowski, Ph.D., R.D.
Family Environmental Sciences Department
California State University
Northridge, California

Premium on Diversity

"When I served on BCRP's Research Council, I saw that breast cancer advocates really have a say about how the program spends its grant money. BCRP also places a high premium on hearing the voices of diversity—ethnic, racial and socio-economic. Their community-based research efforts give validated scientific methods to community groups to attack the problem of breast cancer. They've done a fantastic job, and supported some really good research that wouldn't have been done if they weren't around."

Marco Gottardis, Ph.D.
Director of Oncology Discovery
Bristol-Myers-Squibb
Princeton, New Jersey

Willingness to Take Risks

"Mary Anne Kreshka, M.A., our partners, and I have been awarded two BCRP Community Research Collaboration grants, to investigate whether a workbook-journal would improve quality of life for rural women recently diagnosed with breast cancer. We have been impressed with BCRP's willingness to take risks in funding research in new areas building on ideas that arise from the community. Their selection of partnerships to receive this funding has supported highly productive teams that accomplish a great deal with limited resources. From the application process onward, BCRP encouraged the researchers involved in our collaboration to listen to the ideas and perspectives of our community partners. BCRP has served as a mentor as well as a potential source of funding. We have appreciated the advice of staff, who encouraged us to initiate this project, who guided us at each step of the application and funding process, and who have always been responsive to our questions and feedback. With BCRP funding support, we researchers have been able to apply our methodological expertise to evaluating the intervention drawn from our community partners' vision."

Cheryl Koopman, Ph.D.
Associate Professor (Research)
Department of Psychiatry & Behavioral Sciences
Stanford University
Stanford, California

Breast Cancer in California

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

During 2000, an estimated 20,000 California women were diagnosed with the disease. Nearly 200,000 women in our state are living with a past or present diagnosis of breast cancer. While many are long-term survivors, some are battling a recurrence and others are fighting for their lives. Today, no woman who has survived breast cancer can be guaranteed that it won't return.

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

Are Rates of Breast Cancer Really Going Down?

The rate of breast cancer was rising in California and in the U.S. about 1% every year throughout most of the last century. In the 1990's, however, cancer registries started reporting that the rate of breast cancer was leveling off, and then that it was beginning to fall. However, while the rates of invasive breast cancer were decreasing, the rates of pre-cancerous lesions called "ductal carcinoma in situ" (DCIS) were increasing.

Scientists believe that breast cancer takes years to develop, and that there are many changes that happen on the route from normal breast cell to breast cancer. One of the stages on the path to

Not an Equal Opportunity Killer

When it comes to breast cancer in California, ethnicity makes a difference. White women are most likely to get the disease, followed closely by black women, then Asian/Pacific women, with the lowest rate among Hispanic women. Although the death rate has dropped in the last 12 years, most of the gains have come for white women. Black women have the highest death rate, even though they are less likely than white women to get the disease. Death rates for Asian/Pacific and Hispanic women, although they were lower to begin with, have not improved in recent years.

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

breast cancer is DCIS. DCIS is considered "pre-cancer," rather than cancer, because it does not leave the breast ducts. This was once a very rare diagnosis because DCIS does not form lumps, and cannot be detected by breast examination. More women are being diagnosed with DCIS because more women are receiving mammograms, and DCIS can appear as an abnormality on a mammogram. Although the diagnosis of DCIS was very rare before mammography became widespread, autopsies on women who died of other causes indicate that 5-20% of women probably have undiagnosed DCIS with no symptoms when they die.

In past years, when DCIS was not often detected, an unknown percentage of the women with this condition went on to develop breast cancer. Their numbers added to the numbers of women then being counted as having breast cancer in California. Today, women with DCIS are being diagnosed and treated before they develop breast cancer and these diagnoses are not counted as invasive breast cancer. It turns out that the rate of DCIS has increased over the past 10 years by the same amount that breast cancer has decreased over the same time period. Thus, the rate of invasive breast cancer has decreased, but the rate of DCIS plus breast cancer has remained constant. There has been a shift in the diagnosis of the disease to earlier in the disease process.

This is both good news and bad news. One of our goals must be to detect and treat breast abnormalities before they turn into cancer. And the shift in rates from invasive breast cancer to DCIS indicates that we are beginning to do this. On the other hand, the treatment for DCIS is the same as the treatment for early stage breast cancer (surgery with either removal of the lesion and the surrounding tissue or removal of the entire breast). So the rate of women undergoing surgery for breast cancer or pre-cancer is remaining constant. Thus this shift from invasive breast cancer to DCIS makes little difference in the physical and mental repercussions of diagnosis.

Regardless of whether California's breast cancer rate has changed, the numbers are much too high. If present trends continue, 1 out of 8 California women will have breast cancer at some point in her lifetime. This relentless toll underlines the urgent need for more research into prevention. Keeping breast cancer from happening in the first place is the best way to save lives. This is why the California Breast Cancer Research Program makes prevention research a priority.

Unnecessarily Treating Some to Save Others

The number of precancerous breast conditions being caught through mammogram screening has consequences beyond throwing into question California's breast cancer rate. Early detection also has consequences for California women's lives. It saves some, but leads to others receiving disfiguring and unnecessary treatment.

Catching precancerous breast conditions early saves some women's lives, because it keeps their cancer from progressing to a stage where treatment is less effective. But there's currently no way to tell whether a precancerous condition will turn into cancer. So some women who would have remained cancer-free, and unaware of any problems throughout their lives, are being treated, solely as a result of early detection.

Precancerous conditions are frequently found in more than one place in the breast, so the treatment is often removal of the entire breast. Women who have a small cancer may only have the lump removed, while a woman with DCIS often receives the more disfiguring treatment. It may have prevented her having cancer, or she may not have needed it at all.

Similarly, the breast cancer death rate is going down at the cost of unnecessarily treating large numbers of women, simply because there is no way to identify who will be helped by treatment and who will not. One example is the current treatment for women with Stage 2 breast cancer (breast cancer is classified from Stages 1 to 4, each progressively more serious and life-threatening).

A women under age 50 with a Stage 2 tumor has a 71% chance of surviving without chemotherapy. With chemotherapy, her odds rise to 78%. This means that for every 100 women who get chemotherapy, 22 will die anyway, 71 would have survived without it, and only 7 will be helped. To keep 7 women alive, 93 others receive an often debilitating treatment that does not help them, but can cause long-term health damage.

The Crude State of Treatment

If there were a way to test those 100 women with Stage 2 breast cancer and pinpoint which 7 would benefit from chemotherapy, it would be a big advance. This is just one example of the fairly crude state of today's breast cancer treatment. Individual women with individual cancers are all given the same treatment, although some don't need it and others won't be helped. This is why the California Breast Cancer Research Program funds research into possible new methods for identifying which women will be helped by which treatment, and for more effective new treatments. It's why we encourage researchers to take risks and investigate new approaches. We're working toward a future where any woman who has breast cancer can receive treatment with confidence that the treatment is needed and effective against the disease in her individual case.

References:

Rates of breast cancer and DCIS in California: Kwong SL, Perkins CI, Morris CR, Cohen R, Allen M, Schlag R, Wright WE. Cancer in California: 1988-1998. Sacramento, CA: California Department of Health Services, Cancer Surveillance Section, December 2000.

Survival rates with and without chemotherapy: Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998 Sep 19;352(9132):930-42

Men and Breast Cancer

Breast cancer is rare among men. In California this year, 130 men were diagnosed with the disease, and 35 men died. Breast cancer in men is almost always due to inherited abnormal genes.

Our Funding Strategy

"What critical research can we add to move most rapidly toward prevention and cure?" When the California Breast Cancer Research Program decides what types of research to fund, we always begin with this question.

BCRP is part of a much larger research system. The federal government funds breast cancer research through the National Cancer Institute and the Department of Defense. Non-profit organizations and for-profit corporations also fund breast cancer research. Although we are the largest breast cancer research funder based in our state, our funds make up only a small part of the larger system.

We apply our research dollars to the most promising areas that aren't being covered by the larger funders. Since much of the research in this country investigates cancer in general, we only fund research that specifically investigates breast cancer or applies knowledge about cancer as a whole to breast cancer in particular. We choose projects that can lead to breakthroughs, and projects that can open promising new channels for investigation that the rest of the research system can pick up and develop further. We also identify barriers to good research, and make grants to topple those barriers. For example, in

2000, we offered two new types of awards to encourage cross-disciplinary research collaboration. This type of research is not well funded by other agencies, and we believe bringing expertise from other disciplines into the fight against breast cancer holds strong promise for breakthroughs.

As other parts of the research system have adopted aspects of our strategy, BCRP continually moves on, pushing the boundaries of breast cancer research even further.

Each project we fund must fit into two separate sets of categories, our Priority Subject Areas, and also our Types of Awards. BCRP's Subject Areas are broad; our Award Types are narrowly targeted. The broad Subject Areas allow BCRP to have an impact across a wide spectrum of breast cancer research. Our narrowly targeted Types of Award are carefully designed to jump-start under-funded areas of research, encourage creative new thinking, and bring new investigators into the fight against breast cancer.

We apply our research dollars to the most promising areas that aren't being covered by the larger funders.

Priority Subject areas

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

Including Minority Women in Research

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

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

Award Types

Collaboration Awards

- Scientific Perspectives Research Collaboration Awards
- Community Research Collaboration Awards
- Translational Research Collaboration Awards
- Joining Forces Conference Awards

Targeted Awards (RFA's)

- Prevention and Risk Reduction
- Biology of the Normal Breast
- Socio-Cultural, Behavioral and Psychological Issues related to Breast Cancer

Innovative Development and Exploratory Awards

- Type I: One-year
- Type II: Two-year

Career Development Awards

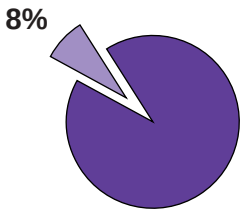
- New Investigator Awards
- Postdoctoral Fellowship Awards
- Training Program Awards

On the following pages, we explain our eight Priority Subject Areas for 2000 and provide statistics on the 70 projects we funded by subject. Then, we explain our Award Types and again provide statistics on the 70 projects, this time by Award Type.

Priority Subject Areas

BCRP made grants in eight Priority Subject Areas for 2000. Each project we fund must fit under one of these subject areas, and also under one of our Award Types, described immediately following the Priority Subject Areas.

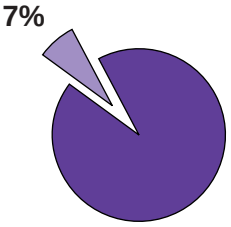
The Starting Point
Biology of the Normal Breast



Understanding the biology of the normal breast may provide important clues about how tumors develop, and point to ways to prevent or stop breast cancer. Yet very little research has been done on normal breast structure and physiology. This is why BCRP makes it a priority to expand knowledge in this area.

Biology of the Normal Breast
Number of projects funded in 2000: **6**
Funds awarded: **$1,366,968**
Percentage of total projects funded: **8%**
Percentage of total funds awarded: **8%**
Types of awards: *3 Two-Year Innovative Developmental and Exploratory (IDEA) Awards, 1 Joining Forces Conference Award, 1 Postdoctoral Fellowship Award, 1 Targeted Award.*

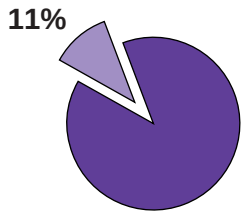
Improving the Chances for a Cure
Earlier Detection



Since there's still no effective way to prevent breast cancer, early detection remains the best line of defense. Present methods of detection are far from perfect. Mammograms miss some tumors, falsely indicate cancer in some cases, and expose women to ionizing radiation. Low-income and minority women are also less likely to have their cancer detected early, when treatment is most likely to succeed. BCRP concentrates funding for detection in areas not well addressed by other funding agencies, such as new detection technology, potential new detection methods (such as blood or urine tests), and ways to lessen the inequality of access to early detection.

Earlier Detection
Number of projects funded in 2000: **5**
Funds awarded: **$1,530,445**
Percentage of total projects funded: **7%**
Percentage of total funds awarded: **9%**
Types of Awards *2 Two-Year Innovative Developmental and Exploratory (IDEA) Awards, 1 Postdoctoral Fellowship Award, 2 Translational Research Collaboration (TRC) Awards.*

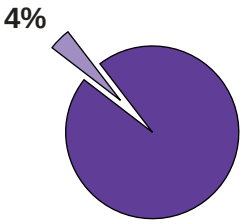
Finding the Causes
Etiology



Discovering the causes of breast cancer can lead to strategies to prevent, treat or cure it. BCRP emphasizes research in areas that haven't received enough study, including possible environmental causes, environment-gene interactions, as-yet-undiscovered genes that affect breast cancer risk, and finding the biological basis behind factors–such as early pregnancy or socio-economic status–that affect risk. We also look into the possible causal role of lifestyle, hormones and nutrition.

Etiology
Number of projects funded in 2000: **8**
Funds awarded: **$1,100,905**
Percentage of total projects funded: **11%**
Percentage of total funds awarded: **7%**
Types of awards: *2 One-Year Innovative Developmental and Exploratory (IDEA) Awards, 2 Two-Year Innovative Developmental and Exploratory (IDEA) Awards, 1 New Investigator Award, 2 Postdoctoral Fellowship Awards, 1 Translational Research Collaboration (TRC) Award.*

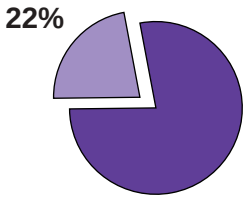
Serving Women's Needs
Health Care Delivery and Health Policy



In California, as in the nation and in the world, inequality increases the suffering breast cancer causes. Low-income women and women from some minority groups face a greater risk, or are less likely to get treatment, or are less likely to survive, or all three. Although BCRP funded only three projects for 2000 in this under-researched area, we encourage more study on how to address the often lethal problem of unequal access to the best in prevention, detection and treatment. We also encourage more work on ethical and legal issues surrounding breast cancer, and on finding the most effective and supportive ways to deliver health care.

Health Care Delivery and Health Policy
Number of projects funded in 2000: **3**
Funds awarded: **$201,389**
Percentage of total projects funded: **4%**
Percentage of total funds awarded: **1%**
Types of awards: *2 Community Research Collaboration Awards, 1 One-Year Innovative Developmental and Exploratory (IDEA) Award.*

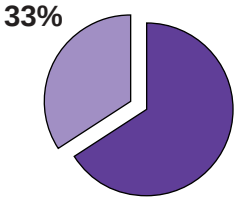
Search for a Cure
Innovative Treatments



Rather than fund more studies on new combinations of standard chemotherapy, BCRP puts our research dollars into alternative and novel medical approaches that hold potential to improve treatment or even point toward a cure.

Innovative Treatments
Number of projects funded in 2000: **16**
Funds awarded: **$4,030,703**
Percentage of total projects funded: **22%**
Percentage of total funds awarded: **25%**
Types of awards: *1 One-Year Innovative Developmental and Exploratory (IDEA) Award, 9 Two-Year Innovative Developmental and Exploratory (IDEA) Awards, 1 New Investigator Award, 2 Postdoctoral Fellowship Awards, 1 Scientific Perspectives Research Collaboration (SPRC) Award, 2 Translational Research Collaboration (TRC) Awards.*

Understanding the Disease
Pathogenesis

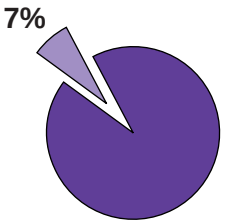


Using the tools of molecular biology, scientists can discover the gene and protein interactions that make breast cancer cells grow and spread. These discoveries may lead to new treatments, they may be dead ends, or their implications for breast cancer may only become apparent after further discoveries.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

Pathogenesis
Number of projects funded in 2000: **24**
Funds awarded: **$4,565,122**
Percentage of total projects funded: **33%**
Percentage of total funds awarded: **30%**
Types of awards: *1 One-Year Innovative Developmental and Exploratory (IDEA) Award, 11 Two-Year Innovative Developmental and Exploratory (IDEA) Award, 4 New Investigator Awards, 8 Postdoctoral Fellowship Awards.*

Ending the Danger

Prevention

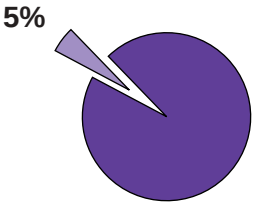


According to current science, at most one in five cases of breast cancer is due to inherited abnormal genes. The other four are caused by environment and lifestyle. So changing our environment or lifestyle has great potential to prevent cancer. However, the question is, which changes? BCRP funds research into promising areas, including diet and ways women can take preventive action, especially women among under-researched communities. We also fund studies on the immune system and potential vaccines.

Prevention
Number of projects funded in 2000: **5**
Funds awarded: **$2,113,934**
Percentage of total projects funded: **7%**
Percentage of total funds awarded: **13%**
Types of awards: *5 Targeted Awards*

The Human Side

Socio-Cultural, Behavioral and Psychological Issues



California women with breast cancer, and those at high risk, get treatment or don't get treatment, make critical decisions or miss their chance to make them, and cope with the disease–all in a social and cultural context. This context has great impact on well-being and even survival. For this reason, BCRP encourages research on enhancing quality of life for women with breast cancer, improving doctor-patient interaction, and non-medical factors leading to long-term survival.

Socio-Cultural, Behavioral and Psychological Issues
Number of projects funded in 2000: **4**
Funds awarded: **$1,106,915**
Percentage of total projects funded: **5%**
Percentage of total funds awarded: **7%**
Types of awards: *1 Targeted Award, 2 Two-Year Innovative Developmental and Exploratory (IDEA) Awards, 1 New Investigator Award.*

Award Types

BCRP made ten types of awards in 2000. Two of our collaboration awards are new this year. Every project we fund must fit under one of these Award Types, and also under one of our Priority Subject Areas, described on the preceding pages.

Collaboration Awards

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

Scientific Perspectives Research Collaboration (SPRC) Awards

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

Scientific Perspectives Research Collaboration (SPRC) Awards
Number of projects funded in 2000: **1**
Funds awarded: **$147,001**
Percentage of total projects funded: **1%**
Percentage of total funds awarded: **1%**
Subject area: *Innovative Treatments*.

Community Research Collaboration (CRC) Awards

We believe communities should take an active part in research about themselves. So this award brings community organizations or members of communities together with experienced scientists. The teams investigate breast cancer problems that are important to that community, using culturally-appropriate research methods. This award allows cancer service organizations, breast cancer advocates, organizations serving minority groups and community clinics to enrich the breast cancer research process with new expertise and ideas.

Community Research Collaboration (CRC) Awards
Number of projects funded in 2000: **2**
Funds awarded: **$161,598**
Percentage of total projects funded: **3%**
Percentage of total funds awarded: **1%**
Subject areas: *2 Health Care Delivery and Health Policy.*

Translational Research Collaboration (TRC) Awards

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

Translational Research Collaboration (TRC) Awards
Number of projects funded in 2000: **5**
Funds awarded: **$2,137,875**
Percentage of total projects funded: **7%**
Percentage of total funds awarded: **13%**
Subject areas: *2 Earlier Detection, 2 Innovative Treatments, 1 Etiology.*

Joining Forces Conference Awards

Creative thinkers working in fields far removed from breast cancer research may have concepts, methods and discoveries that could lead to breakthroughs. By bringing breast cancer researchers into dialog with experts from another field, the Conference Award is aimed at kindling new research across disciplines. In 2000, we held the first Joining Forces Conference. It brought breast cancer researchers together with experts in new computer modeling technology.

Joining Forces Conference Awards
Number of projects funded in 2000: **1**
Funds awarded: **$14,160**
Percentage of total projects funded: **1%**
Percentage of total funds awarded: **1%**
Subject area: *Biology of the Normal Breast*

Targeted Awards

In three of the eight subject areas we fund, little research funding is available nationwide. Yet these areas are crucial to progress against breast cancer. So we set aside $1 million to $1.5 million each to encourage creative research in:

- Prevention of breast cancer
- Biology of the Normal Breast
- Socio-Cultural, Behavioral and Psychological Issues related to breast cancer

Targeted Awards
Number of projects funded in 2000: **7**
Funds awarded: **$3,164,835**
Percentage of total projects funded: **9%**
Percentage of total funds awarded: **19.5%**
Subject areas: *1 Biology of the Normal Breast, 5 Prevention, 1 Socio-Cultural, Behavioral and Psychological Issues.*

Innovative Developmental and Exploratory (IDEA) Awards

Innovative Developmental and Exploratory (IDEA) Awards

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

Two-Year Innovative Developmental and Exploratory (IDEA) Awards
Number of projects funded in 2000: **29**
Funds awarded: **$7,282,889**
Percentage of total projects funded: **41%**
Percentage of total funds awarded: **45%**
Subject areas: *3 Biology of the Normal Breast, 2 Earlier Detection, 2 Etiology, 9 Innovative Treatments, 11 Pathogenesis, 2 Socio-Cultural, Behavioral and Psychological Issues.*

One-Year Innovative Developmental and Exploratory (IDEA) Awards
Number of projects funded in 2000: **5**
Funds awarded: **$442,499**
Percentage of total projects funded: **7%**
Percentage of total funds awarded: **2.5%**
Subject areas: *2 Etiology, 1 Health Care Delivery and Health Policy, 1 Innovative Treatments, 1 Pathogenesis.*

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

New Investigator Awards

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

New Investigator Awards
Number of projects funded in 2000: **7**
Funds awarded: **$1,505,223**
Percentage of total projects funded: **10%**
Percentage of total funds awarded: **9%**
Subject areas: *1 Etiology, 1 Innovative Treatments, 4 Pathogenesis, 1 Socio-Cultural, Behavioral and Psychological Issues.*

Postdoctoral Fellowship Awards

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

Postdoctoral Fellowship Awards
Number of projects funded in 2000: **14**
Funds awarded: **$1,160,301**
Percentage of total projects funded: **23%**
Percentage of total funds awarded: **7%**
Subject areas: *1 Biology of the Normal Breast, 1 Earlier Detection, 2 Etiology, 2 Innovative Treatments, 8 Pathogenesis.*

Training Program Awards

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

Training Program Awards
Number of projects funded in 2000: **None;** however, we currently fund two training programs through 3-year grants made in previous years.

Sharing Our Research with Scientists and the Public

Funding good research isn't enough. If the research is going to have an impact in the fight against breast cancer, a wide range of people need to know the results. The scientific community needs to know, to make progress against the disease. The medical community needs to know, to improve prevention and treatment. Women with breast cancer need the opportunity to learn about new treatment options. Breast cancer activists need information about research results to help shape the fight against the disease. Communities affected by breast cancer need to know what's been proven to work in other communities. And the taxpayers of California need to know what their taxes are funding.

The scientists whose projects we fund publish the results in peer-reviewed scientific journals and present them at scientific conferences. However, the California Breast Cancer Research Program is committed to making the research we fund available to a much wider public. We publish and distribute our research widely, in print and over the Internet. We are one of the few research funding programs in the world to publish annual summaries of research while the studies are still in progress. BCRP does this so scientists and other interested people can make use of the information as soon as possible. We get out the word about our research results and research progress in a variety of ways:

Research Symposia Every other year, we host a Research Symposium, a statewide conference presenting the results of the research we fund. Our Symposium draws more breast cancer advocates and members of the public than is usual for such a scientific meeting. Our researchers present their findings in language geared toward the general public, and the meeting creates an opportunity for dialog between research scientists and breast cancer activists. During 2000, we laid the groundwork for our next Symposium, in Oakland, September 2001.

Website Our website (http://www.ucop/srphome/bcrp/) is open to the public. It has summaries of all completed research projects and annual progress reports for ongoing projects, in language accessible to the general reader. For anyone who

wants a more detailed description, our summaries are linked to PubMed Abstracts, a public access website for all published scientific studies. Our website also contains a list of each year's awards and information on applying for grants.

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

We are one of the few research funding programs in the world to publish annual summaries of research while the studies are still in progress.

Summary of Awards To make it easy for scientists and the public to follow BCRP-funded research from the beginning, we publish a summary of new projects funded for the year. The summary is free to the public and is also posted on our website.

Newsletter Our newsletters, also available free to the public and posted on our website, report on new awards, research results and other program news.

Special Outreach BCRP makes special efforts to share our research results; during 2000 we made a special effort with staff members of the statewide California Breast Cancer Early Detection Program. This state government program provides breast cancer screening to low-income women in our state and is funded by the same tax on tobacco that provides the majority of funding for the BCRP. Staff members at local early detection sites told us they needed more information on research progress in early detection. So BCRP provided a summary of early detection studies we've funded and brought a panel of early detection research experts to speak at a state-wide meeting for Early Detection Program lead staff. We plan to continue and expand this effort.

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

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

Collaborating with Breast Cancer Activists and California Communities

Women with breast cancer and survivors of the disease have played a leading role in the California Breast Cancer Research Program from the beginning. We've been in the forefront of a nationwide trend among research funding agencies toward a greater voice for the people breast cancer affects most. Moreover, we still set a standard for having advocates at all levels of leadership.

A Wide Role for Advocates

Breast cancer advocates help shape our funding priorities, decide which research to fund, and take part in conducting some research projects.

We developed our current funding strategy from recommendations made at our statewide Public Advisory Meeting in 1996. That meeting brought together research scientists from universities and the biotech industry, health care providers and health educators, and breast cancer activists and survivors. Together, they set the course for a half-decade of BCRP grant-making.

Breast cancer advocates are one-third of our Advisory Council, the body that recommends the research proposals that best fit our funding strategy. Throughout our six-year history, an advocate has also served as the Council's

Chair or Vice-Chair. All research proposals are reviewed for scientific merit by out-of-state research scientists; out-of-state breast cancer advocates are full voting members of these review panels. And a California advocate observes each panel.

Advocates also mount exhibits about their work at our bi-annual Symposia.

Having breast cancer advocates in a wide variety of leadership posts allows us to fund research important to the people who face the disease in their day-to-day lives.

Pioneering Community-Based Research

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

Projects we've funded over the years include:

- A community-based workbook for helping rural cancer patients;
- Breast cancer risk factors of lesbians and heterosexual women;
- Breast cancer screening in Hmong-American communities;
- Culturally-appropriate care for Samoan-American and Korean-American women;
- Breast health access for women with disabilities;
- The effectiveness of "peer navigators"—breast cancer survivors who volunteer to help newly-diagnosed women make decisions about treatment and coping with the disease.

Empowering Communities

During 2000, we conducted a formal evaluation of our Community Research Collaboration Awards. Based on recommendations from the evaluation, we've improved these awards by providing community members with more training, support and information. We added smaller grants to develop promising ideas by providing funds to build a better research team or design a better research proposal. We also corrected some problems with the timing of the awards and payments.

Overall the evaluation of our Community Research Collaboration Awards was positive. The program reached communities not often reached in research, such as minority women, disabled women, rural women and lesbians. BCRP also provided constructive feedback on proposals we did not select for funding, and we supported applicants through re-writing and re-applying. This is extremely helpful for bringing new types of researchers into the research process. These grants also facilitated relationships between community groups and some of the most community-sensitive researchers in California. More importantly, our Community Research Collaboration Awards have given communities of women affected by breast cancer the power to formulate and conduct research on questions that concern them.

We still set the standard for having women with breast cancer and survivors of the disease at all levels of leadership.

Unmet Need

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

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

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

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

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

- Services BCRP provides funding for community-based organizations to test services for women with cancer, but once those services have been shown to help women with breast cancer cope or survive, we are unable to provide continued funding.

- Grant Proposals We Do Not Fund During 2000, BCRP turned down 75 grant applications, for a total of $26.1 million. While some of these applications lacked merit, the majority contained good ideas. With technical assistance from BCRP, the majority of these applications could become good, creative projects that could help enlarge the scope of breast cancer research.

Since BCRP's major source of funding, the state tobacco tax, is decreasing every year, it is unlikely that we will be able to meet these critical needs without additional funding from other sources.

Research Progress and Results

On the following pages, we present the results of research funded by the California Breast Cancer Research Program that was completed during 2000. We also present summaries of research in progress, and of new research started this year.

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

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

Biology of the Normal Breast: The Starting Point

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Biology of the Normal Breast: The Starting Point

As any woman who performs her monthly breast self-examinations knows, the normal breast is a constantly changing organ. The breast's normal changes can obscure the more ominous changes associated with cancer. Researchers have worked hard to determine what constitutes a cancerous change in the breast, but the lack of a thorough understanding of the normal breast makes this work more difficult. Because a relatively small amount of research is being done in this area, the California Breast Cancer Research Program earmarks funds especially for it. In 2000, we funded researchers who are studying the development, structure, hormonal regulation and genetic control of the normal breast. Our hope is that these studies will provide a strong foundation for distinguishing the difference between benign and malignant breast changes.

Research Conclusions

Cancer and Complexity: Questions for a New Millennium

Mary Helen Barcellos-Hoff, Ph.D., Mina Bissell, Ph.D., and G. Shyamala, Ph.D., of the **Lawrence Berkeley National Laboratory,** Berkeley hosted a highly successful conference on March 31, 2000 in Berkeley. It brought together industry researchers, academic researchers and health care professionals from two different scientific disciplines: breast biology and computational science. They discussed how to develop dynamic computer models of cell behavior in the breast. In the first session, "Dynamic Interactions in Carcinogenesis," Drs. Don Coffey, Allan Balmain and Harry Rubin discussed the paradoxes of human cancer and the complexity of genetic progression in cancer development. In the second session, "Heterogeneity of Target Genes and Target Cells" Drs. G. Shyamala, Satyabrata Nandi and Robert Cardiff described what is known about breast pathology and the role of hormones in breast biology and breast cancer. Drs. Mina Bissell, James Baish and Stuart Newman in the "Cell and Tissue Interactions" session talked about breast structure. They outlined how new techniques can play a role in understanding the interactions and functions of different cell types. These techniques include informatics, which uses computer technology to process and make sense of large amounts of information with many variables, and analytical tools, such as complex mathematical equations called fractals. In the final session, "Integration of Complex Processes: Tools for a New Millennium," Drs. Ed Liu, Sylvia Spengler, Adam Arkin, and Joe Gray described informatics-based tools that can be used for deciphering breast cell function and the cells' relationship to their environment. The conference generated lively discussion. Hopefully, it will lead to collaborative research projects between breast biologists and computational scientists.

Research in Progress

Breast Development

The breast changes at the structural and cellular level as a woman goes through puberty, pregnancy, breast-feeding, and weaning. A better understanding of the factors that control breast development through these different stages can provide clues to how tumors develop.

- **Hox Genes in Normal Breast Development and Breast Cancer. Carmen Hagios, Ph.D.,** at the **Lawrence Berkeley National Laboratory,** Berkeley is finding that when a developmental gene called HoxA1 is deactivated in tumor cells, they behave more like normal cells.
- **Hormonal Regulation of TGF-β during Mammary Development.** The reproductive organs of female mice go through the estrus cycle, where periods when pregnancy is possible alternate with periods when it isn't. Levels of the hormones estrogen and progesterone rise and fall in a pattern during the mouse estrus cycle, as they do during the human menstrual cycle. **Mary Helen Barcellos-Hoff, Ph.D.,** at the **Lawrence Berkeley National Laboratory,** Berkeley genetically engineered a mouse that lacks the growth factor TGF-β1. Growth factors are proteins that stimulate the cell from outside to cause the cell to divide, mature or go through some other growth process. Dr. Barcellos-Hoff examined mammary glands in normal mice and mice lacking TGF-β1 during various stages of the estrus cycle. She found that estrogen and progesterone each have a different influence on TGF-β1's ability to regulate epithelial cell growth and death. This study is discussed in *Breast Cancer Research* (2000;2:92-99).
- Two investigators are studying factors that make the breast and cells within it mature (differentiate). **Identification of Pregnancy-Associated Breast Cancer Genes. Satyabrata Nandi, Ph.D.**, from the **University of California, Berkeley** is continuing a project to identify and study breast cancer-related genes associated with pregnancy. A full-term pregnancy reduces a young woman's lifetime risk of breast cancer

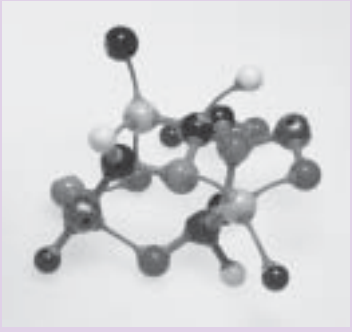
Epithelial Cells
Several studies in this section deal with epithelial cells. In the bodies of humans and animals, epithelial cells cover most surfaces, form glands and line most cavities. The breast (or the mammary gland in mice, rats and other mammals) is composed of several types of epithelial cells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

by about 30%. Dr. Nandi has identified a novel gene, called RMT1, which appears to be turned on at high levels in the breast cells of virgin rats. This gene also appears to be turned on at higher levels than normal in breast cancer in rats. Dr. Nandi is exploring the type of breast cell where RMT1 is found, along with its gene sequence and hormonal regulation. The rationale and background for this project has been published in the *Proceedings of the National Academy of Sciences, USA* (1999;96(5):2520-5).

- **Identification of Novel Id-1 Regulated Genes in Breast Cells.** Id-1 is a gene that keeps cells from maturing. It also allows cells to multiply and move into the bloodstream through blood vessel walls. **Jarnail Singh, Ph.D.,** at the **California Pacific Medical Center,** San Francisco is finding genes that Id-1 regulates. Dr. Singh has found that Id-1 causes a protein called clusterin to decrease. Clusterin protein tends to be high in cells that are producing milk in culture and in animals.

Other Processes in Breast Biology

- **Mechanisms of Fluid Transport in Human Mammary Epithelium. Sheldon Miller, Ph.D.,** at the **University of California, Berkeley** is investigating how epithelial cells regulate the movement of fluid into the ducts of the breast. The regulation process is critical for milk production; deregulation leads to breast cystic disease. Dr. Miller has identified the proteins that regulate the movement of fluids and ions (electrically charged molecules) across mammary cell membranes in mice. In the coming year, he will determine whether the same proteins are at work in human cells.



Research in Progress

- **Regulation of Breast Epithelial Cell Motility by Proteases.** Breast epithelial cells are surrounded by a complex structure containing support components (the extracellular matrix) and other types of cells. The interaction between epithelial cells and other cell types in their surrounding environment plays an important part in dictating how epithelial cells behave. This interaction can be regulated by hormonal interaction between cells or by their physical relationship to one another. These factors also tend to be activated when a tumor achieves the ability to move from the breast to a distant organ. The structural components of the breast include proteins called laminin. To move around and reorganize (or in the case of cancer, spread to other parts of the body), the epithelial cells need to digest the structural proteins supporting them. **Vito Quaranta, Ph.D.,** at **The Scripps Research Institute,** La Jolla is investigating how an enzyme, MT1-MMP, digests a laminin protein, Ln-5, and is determining the physiological result of this process. He has found the section (site) of Ln-5 that allows MT1-MMP to digest it. Over the next year, he will use genetically altered mice to determine the physiological consequence of having breast cells that are missing Ln-5 or not able to bind Ln-5.
- **The Role of Nitric Oxide and Arginine in the Breast.** Exposure to molecules containing oxygen (oxidation) has ramifications for both normal and tumor breast cells. Arginine is an amino acid that can be converted to nitric oxide. **Carol MacLeod, Ph.D.,** at the **University of California, San Diego** has found a molecule, CAT2, which can transport arginine into cells and increase their production of nitric oxide. She is finding that genetically altered mice that are deficient in CAT2 are less likely to develop hyperplasias and dysplasias, which are abnormal tissue structures that are more likely than normal tissues to later become cancer. CAT2-deficient mice also have a lower tumor burden than mice with normal CAT2.

- **Genetic Repair of Oxidative Damage: Effect of Estrogen. Nicholas Rampino, Ph.D.,** of **The Burnham Institute,** La Jolla is also studying oxygenation in cells. He exposed cells that are sensitive to the hormone estrogen to molecules containing oxygen. Then, he exposed the cells to the drugs raloxifene and tamoxifen, and also to pure estrogen inhibitor IC 182,780. The cells exposed to raloxifene had lower mutation rates than cells exposed to the other two substances. This indicates that raloxifene may be a superior agent for preventing breast cancer.

Breast Cell Aging and Death

- **Breast Cancer Chemoprevention by Retinoids. Xiaokun Zhang, Ph.D.,** at **The Burnham Institute,** La Jolla is also exploring the effect of agents that have the potential to prevent breast cancer. He is investigating how Vitamin A (retinoic acid) inhibits breast cell growth. Dr. Zhang has identified a new mechanism through which Vitamin A acts within breast cells. The protein in cells that takes in Vitamin A acts through a part of the cell called the mitochondria. This discovery provides a new basis for potentially developing a breast cancer-preventive drug based on Vitamin A. Results from this study have been published in *Molecular and Cell Biology* (2000;20:957-970); *Cancer Research* (2000;60(12):3271-3280); and *Science* (2000;289(5482):1159-1164).
- **Cloning of Senescence Genes in Mammary Epithelial Cells.** Investigators have made progress in understanding how normal cells age and eventually stop reproducing (senesce). **Hong Zhang, Ph.D.,** at **Stanford University**, Palo Alto is using a technique

(random homozygous knock-out, or RHKO) to generate immortal clones from normal human breast epithelial cells. Using these cells, he is trying to find the senescence genes that cause normal cell aging. In the first year he made an RHKO human breast epithelial cell library of about 25,000 independent sections of genes, and started to search for the gene(s) that cause cells to age normally.

- **The Role of PAK2 in Breast Cancer Cell Death. Gary Bokoch, Ph.D.** at **The Scripps Research Institute,** La Jolla has found that an enzyme, p21-activated kinase (PAK), removes the protein that triggers cell death, BAD, from action. PAK stops BAD's action by attaching a phosphate molecule to it. By identifying the regulators of this process, investigators are hoping to find the keys to how tumor cells, which often gain the capacity to grow continually, circumvent it.

Breast Development

- **Pregnancy and Breast Cancer: an Immunological Connection?** A full term pregnancy at an early age protects a woman against developing breast cancer. But what changes occur in the breast to explain it? Many theories concentrate on hormones. **Michael Campbell, Ph.D.,** of the **University of California, San Francisco** will investigate whether the immune system plays a part. Dr. Campbell will examine the sera (a part of blood) from women who have had multiple pregnancies. He is looking for antibodies that specifically recognize breast tumors. At the end of the study, he hopes to have a panel of antibodies and antigens that are normally present and can protect against tumor development.

Other Processes in Breast Biology

- **The Role of NCo-R During Normal Mammary Gland Development.** The relationship between hormones such as estrogen and breast development has been firmly established, however the mechanism for this regulation is still unclear. **Sung Hee Baek, Ph.D.,** of the **University of California, San Diego** will look at the role of a protein, N-CoR, in the growth and development of the normal mammary gland. N-CoR is a molecule inside the nucleus that is involved in estrogen regulation of cell growth. Using mice with cloned genes transferred into their DNA, she is analyzing the mammary gland growth patterns when N-CoR is either absent or present at elevated levels.
- **A Vascular Restriction of Mammary Tumor Progression. Robert Oshima, Ph.D.,** of **The Burnham Institute,** La Jolla will investigate the influence of pregnancy on the normal organization of breast blood vessels. He will also investigate how that blood vessel organization is influenced when breasts produce milk and when breasts go through the changes that come when they stop producing milk. He will also determine whether altered levels of the blood vessel growth factors (proteins from

outside cells that trigger division, maturing or other growth processes) can make mammary gland tumors more or less likely to develop or grow.

- **Genetic Changes in Normal Epithelium of the Cancerous Breast. Shanaz Dairkee, Ph.D.,** of the **California Pacific Medical Center Research Institute,** San Francisco will investigate genetic changes that occur in normal-appearing breast cells to identify changes that indicate a propensity to become cancer.
- **Method for Measuring Breast Epithelial Turnover in Humans.** A reliable measure of the rate of epithelial cell division is important to understanding how cancer develops and to test how cancer preventive agents work. **Marc Hellerstein, Ph.D.,** of the **University of California, Berkeley** will use a technique his laboratory recently developed for measuring the rate at which T cells in AIDS patients divide. He will attempt to measure breast epithelial cell division in animals and people accurately, without using radioactivity or toxic metabolites. A second goal in this project is to use the test to determine how genistein affects breast cell division. Genistein is found in soybeans and is a potent cancer preventative agent in rats. In addition, Dr. Hellerstein will establish normal rates of breast cell division in humans and see how these rates are affected by factors that are associated with higher or lower levels of breast cancer risk among women, such as age, weight, ethnicity and diet.

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Earlier Detection: Improving the Chances for a Cure

As more California women have regular mammograms, examine their own breasts and receive breast exams from their physicians, breast cancer is being detected at earlier stages more often. Earlier detection combined with improvements in treatment has led to a 25% drop in the rate of death from breast cancer in the state. However there's still room for improvement. Women need detection methods that can find smaller tumors and distinguish harmless breast abnormalities from cancer. Mammograms don't provide information about how aggressive a tumor is, or other diagnostic information. Areas of research BCRP funds include:

- **Developing and Improving Imaging Technologies**: Technologies such as Magnetic Resonance Imaging (MRI) or optical detection hold promise for finding tumors faster and more easily. We have also funded projects to improve the accuracy of the x-ray technology used for mammograms.

- **Improving Women's Access to Screening**: California women don't all have equal access to mammograms now, so we fund research on how to make present detection methods available to all.

- **Novel Screening Approaches**: Finding a substance in the body that indicates the presence of breast cancer could lead to a blood or urine test as a detection method.

Research Conclusions

Developing and Improving ImagingTechnologies

Hybrid Grid-Detector to Improve Early Detection Imaging

John Boone Ph.D., of the **University of California, Davis** studied a hybrid grid detector system (HGDS) that might be suitable for digital mammography. He attempted to improve the screen that converts X-rays to visible light (which produces the image) and to reduce the X-rays that "scatter" out of the breast and degrade the film image. While he successfully designed and acquired the screen material and a leaded-glass matrix to hold it, he couldn't combine the two components to realize the design goals. However, the components were superior to current mammogram devices. He developed several important tools, including accurate x-ray spectral models and other mathematical techniques for measuring the radiation dose to breast gland tissue during a mammogram. Computer simulations also demonstrated that the HGDS may be capable of producing twice the light output for the same amount of x-rays. This would improve accuracy of the image. Numerous publications resulted from this project, including *Physics in Medicine and Biology* 43:2569-82 (1998).

Digital Mammography
Several studies in this section discuss digital mammography. Digital mammography uses x-rays to create an electronic computer image of the inside of the breast, instead of the traditional x-ray film.

Research Conclusions

Early Breast Cancer Detection with Fiberoptic-CMOS Detector

J. Anthony Seibert, Ph.D., at the **University of California, Davis** completed a project to improve digital mammography. He evaluated the use of a new, potentially very low-cost, digital (CMOS) X-ray detector, and combined it with devices called fiberoptic scintillators that could detect x-rays with high efficiency. The fiberoptic scintillators were too inefficient at converting x-rays to light. He substituted an alternative (CsI) scintillator , but because of electronic problems with the CMOS detector, the image quality wasn't good enough to recommend its use in digital mammography. However, he developed several important tools, including a novel method to increase the accuracy of the electronic image of the breast. Published results from this study included *Medical Physics* 24:279-85 (1997).

Harnessing Technology to Improve Mammography Effectiveness

Laura Esserman, M.D., M.B.A., of the **University of California, San Francisco- Mt. Zion Breast Care Center** investigated ways to achieve high-quality mammogram screening in California for the least possible cost. When a mammogram shows something abnormal in the breast, the next step is a biopsy, where a tissue sample is taken with a needle or surgery. In the U.S., biopsies reveal cancer at a lower rate than in Europe. Dr. Esserman found this was not because physicians inter-

preting the mammograms in Europe were missing more cancers, but because physicians there were better at identifying cancers. The more mammograms a physician interpreted, the more likely she or he was to find the cancers that were present and less likely to falsely identify a feature as cancer. Therefore, centralizing mammogram screening so that physicians interpret a high volume of mammograms would improve detection services. Digital mammography could play a major role in this, because computer images of breasts could be transmitted like e-mails from a wide range of locations to a central site where they could be interpreted. Unfortunately, the technology to transmit electronic breast images has not progressed to the extent anticipated at the study's outset. However, Dr. Esserman and her team created a cost model for mammogram screening in the US. They identified the variables that most affect cost and efficiency, along with organizational changes that might save hundreds of millions of dollars, increase cancer detection, and decrease biopsy rates.

Sentinel Node Detection via Targeted Fluorescence

Each breast tumor at first drains its lymph through a single lymph node, the sentinel node. But dozens of armpit nodes serve the breast. At present, they are often all removed to find out if cancer is likely to have spread. However, by finding and removing just the sentinel node, women may be spared the pain and side-effects of having a large portion of the lymph nodes under their arm removed. The challenge is to find the sentinel node. To make this easier**, David Vera, Ph.D.,** of the **University of California, San Diego** synthesized a molecule that consisted of (1) a glucose chain, (2) a molecule called DTPA radioactively labeled with technetium-99, (3) another chemical, mannose, that binds avidly to lymph nodes and (4) a fluorescent agent, fluorescein. Attaching a radioactive label allows the molecule to be detected in the body with a specialized camera; attaching the fluorescent agent allows it to be detected with light. Having two ways to detect the compound increases the probability of being able to find it in the body. Mannose should make the lymph nodes take up more of the molecule than other surrounding tissues. Dr. Vera is now ready to test the molecule by injecting it into animal tumors to see if it can be used to find a tumor's sentinel lymph node.

Improving Women's Access to Screening

Benign Breast Disease, Biopsy & Cancer Preventive Self-Care

Jacqueline O'Connor, Ph.D., of the **University of California, Davis** investigated psychological characteristics that motivate women to get mammograms, examine their own breasts and get breast exams from health care practitioners. She also studied variables that predict whether a woman is likely to stop these early detection practices after a breast cancer scare, such as a mammogram that looks like possible cancer followed by a biopsy that reveals no cancer. She found that younger women consider routine breast cancer screening and diagnostic experiences to be more stressful, on average, than do older women. Perhaps this is due to heightened awareness about the issue. Even among study participants with no history of breast problems, younger women reported feeling more at risk and vulnerable to developing breast cancer, on average, than did older women. This was true even though they knew that breast cancer risk increases with age. Women who have experienced a false-positive mammogram or have had a breast biopsy report greater anxiety about breast cancer and heightened perceptions of personal vulnerability than women who have had only routine screenings with normal outcomes. These feelings may last for more than a year. Finally, even though they feel more vulnerable and anxious, women who have had a breast cancer scare generally don't stop performing breast self exams, or stop obtaining mammograms or clinical breast exams. Results from this funding were published in the *American Journal of Roentgenology* 171:55-8 (1998).

Research Conclusions

Improving Access to Mammography in an Urban Underserved Area

Bruce Allen, Jr., Dr. P.H., of the **Charles R. Drew University of Medicine and Science,** Los Angeles collaborated with researchers at the **UCLA-Jonsson Comprehensive Cancer Center**. They investigated how to increase the use of screening mammography among African-American and Latino women in a low-income area of Los Angeles. African American and Latino women are diagnosed more frequently with advanced stages of breast cancer. Detecting the disease earlier by raising the rate at which they get mammograms is considered to be an achievable way to reduce their death rate. A baseline survey found that 61% of these African-American and Latino women had had a screening mammogram in the last 24 months, which is lower than the estimate for the general population (71.3%). The survey found that inconvenience, cost, and difficulty in getting to a clinic or office are still barriers to screening. The survey also found that health practitioners can influence whether a woman has a mammogram by providing accurate information in a sensitive manner. Women who had never had a mammogram were more likely to fear breast cancer and radiation exposure, and to be concerned about inconvenience of screening. A short telephone interview resulted in an 8.3% increase in the number of women getting a mammogram, but this was not statistically significant.

Breast Cancer Screening Among Hmong In California

Marjorie Kagawa-Singer, Ph.D., of the **University of California, Los Angeles** and **Mary Ann Foo, MPH,** of the **Orange County Asian and Pacific Islander Health Alliance,** Garden Grove conducted a pilot study in preparation for a larger intervention study. They found that 51% of Hmong women they surveyed had ever performed a breast self-examination, and 54% had ever had a clinical breast exam. Only 27% had ever had a mammogram. These results underscored the need to increase screening in the 60% of the U.S. Hmong population who live in California. The team is now developing and testing an intervention to increase screening in this population with a new BCRP grant.

Novel Screening Approaches

TIMP-3, an Early Indicator of Breast Cancer?

TIMP-3 (Tissue inhibitor of metalloproteinases-3) is a protein that helps to prevent enzymes from destroying tissues. **Susan Hawkes, Ph.D.,** of the **University of California, San Francisco** developed an antibody that specifically identified TIMP-3. She tested whether the presence of TIMP-3 was associated with more aggressive cancer cells in culture. She found that TIMP-3 was present at low levels in early stage cancer and undetectable in late stage cancer. In the body, it was not detectable in normal or benign tissues, but it was detectable in all pre-cancers (DCIS) and half of the invasive cancers tested. The study provides preliminary evidence that TIMP-3 is an early indicator of breast cancer.

Galectin-4 as a New Marker for Breast Cancer

Galectin-4 is a protein found at high levels in pre-cancerous and invasive breast cancer cells, but not in normal cells. **Margaret Huflejt, Ph.D.,** of the **La Jolla Institute for Allergy and Immunology** examined over 200 breast cancer tissues and tissues from 70 benign disease cases for the presence of galectin-4. She found that 100% of the early cancers (*in situ* carcinomas) and 97% of the invasive cancer showed an abundance of galectin-4. In ten of the cases of benign disease, the patients developed invasive cancers within 1-4 years. All ten had "hot spots" of galectin-4 in their benign disease tissues. Dr. Huflejt plans to extend this observation using a larger sample size. Galectin-4 is a promising early biomarker for breast cancer, and it also could help to identify patients at high risk of developing the disease. Dr. Huflejt used this support to contribute as a co-author to a publication in *Cancer Research* 60:2584-8 (2000).

Research Conclusions

Identification of Novel Secreted Proteins of Breast Cancer

H. Phillip Koeffler, M.D., from **Cedars-Sinai Medical Center**, Los Angeles identified a breast cancer gene, called Cyr61. This gene produces a Cyr61 protein that breast cancer cells secrete. Once secreted, the Cyr61 protein helps the cells attach to nearby cells, migrate and form blood vessels that nourish the tumor. Dr. Koeffler showed that estrogen induced the Cry61 protein into two breast cancer cell lines, and that treatment with the drug tamoxifen kept it out. When he introduced the Cyr61 gene into cells, they grew and stimulated blood vessel growth in a manner like that of more aggressive cancers. This research topic is of high interest, because finding proteins that breast cancer cells secrete could lead to a blood test to detect the disease. It could also lead to a treatment that blocks only the specific protein and would not affect normal cells, so it would possibly have fewer side effects. A publication describing these findings was recently accepted by *The Journal of Biological Chemistry*.

New Imaging Modality for Early Detection of Breast Cancer

Monoclonal antibodies (MAbs) that bond with a single protein found on breast cancer cells can be made in the laboratory. They could be tagged with radioactivity and used for early detection using standard scanning techniques, if only they could reach the tumor in sufficient quantity. **William Pardridge, M.D.,** at the **University of California, Los Angeles- School of Medicine** attempted to increase the ability of MAbs to cross the blood-tumor barrier, the tiny capillary vessels supplying blood to the breast tumor. He first altered the surface electrical charge of the antibody ("cationization") to determine if this would enable it to cross the blood tumor barrier, and then set out to "tag" the cationized antibody with radioactivity and see if it could still cross. Since human breast cancers often have high levels of a protein called the epidermal growth factor receptor (EGFR), Dr. Pardridge mass-produced a highly promising MAb that binds with the EGFR, cationized it, and tested it to show that the altered MAb retained its structural integrity. He showed that the cationized MAb maintained its active binding to the human EGFR. He also established a method for attaching radioactive 111-

Indium to the cationized Mab using a binding molecule called DTPA. He used these approaches to produce images of experimental breast cancers in animals. Results have been published in the *Journal of Pharmacology and Experimental Therapeutics* 286:548-54 (1998).

Development of EGFR-based Imaging Agents for Breast Cancer

Henry VanBrocklin, Ph.D. of *the* **Lawrence Berkeley National Laboratory,** Berkeley is attempting to develop new, radioactively-labeled pharmaceuticals that can be used with nuclear medicine imaging methods to detect epidermal growth factor receptors (EGFR) in breast cancer. The EGFR are membrane proteins found at the surface of breast tumor cells which, when stimulated, initiate a cascade of cellular events that leads to tumor growth. Dr. VanBrocklin studied five new compounds. Three of them were found to target the EGFR and did not bind similar proteins. Thus, they are promising candidates for imaging breast cancer. He plans to continue to screen new compounds, using many of the techniques perfected in this project, to find an optimal radioactively-labeled pharmaceutical to detect the EGFR in breast cancer.

Research in Progress

Developing and Improving Imaging Technologies

- **Measurement of Breast Tissue Viscoelasticity Using MRI. Michael Buonocore, Ph.D.,** of the **University of California, Davis** is adapting Magnetic Resonance Imaging (MRI) to detect breast abnormalities based on differences in the elasticity and viscosity (thickness) of abnormal breast tissue as compared to normal breast tissue. These same mechanical properties enable a health care professional to detect a lump during a clinical examination. Dr. Buonocore needs to build a device to generate mechanical waves in breast tissue, and to develop advanced MRI techniques to measure the small tissue displacements these waves cause. He has built the wave generator and produced images that show that this approach is feasible. Next, he will test the adapted MRI in human subjects and develop methods for calculating tissue viscoelasticity from the images.
- **UCLA Biomedical Physics Graduate Training in Breast Cancer. Carolyn Kimme-Smith, Ph.D.,** of the **University of California, Los Angeles** is training graduate students to design and improve early detection and diagnostic imaging equipment, and to solve medically significant problems involving these technologies. The training emphasizes awareness of the needs of clinicians and patients. During the first year, three students have been enrolled: one is working on testing a prototype miniature gamma camera for the breast, another on a device to improve radiation treatment, and the third on reducing breast compression for digital mammography.

Improving Women's Access to Screening

- **Increasing Breast Health Access for Women with Disabilities. Mary Smith, M.S., CRC,** of the **Alta Bates Foundation**, Berkeley and **Carol D'Onofrio, Dr.P.H.,** of the **Northern California Cancer Center**, Union City are addressing problems facing women with disabilities in receiving timely and appropriate breast health-related services. They have begun analyzing the 1994 National Health Interview Survey (NHIS), and have conducted and begun analyzing their own supplemental health survey. They have also finished the first draft of a manual to encourage community organizations to do their own needs assessment and intervene to improve disabled women's access to breast cancer screening and other breast health services.

Novel Screening Approaches

Biomarkers are genes or proteins found in tumors. They can be used to predict how fast tumors will grow or determine what medication will work best against a particular tumor. Two research projects focused on new biomarkers and screening approaches for breast cancer.

- **Oncogenes, Progression and Biomarkers. Robert Cardiff, M.D., Ph.D.,** of the **University of California, Davis** improved the immunohistochemistry technologies used to determine the prognosis and treatment regimens of individual cancers. These technologies involve attaching a dye to an antibody that then binds to certain proteins in cells. He also developed a battery of the antibodies required for these technologies.

Research in Progress

- **Clinical Utility of Breast Cancer DNA Markers in Plasma. Dave Hoon, Ph.D.,** at the **John Wayne Cancer Institute**, Santa Monica, is attempting to detect breast cancer-specific DNA in the sentinel lymph nodes (the node a tumor drains lymph into first) or in the blood of breast cancer patients. This information could eventually be used as a tumor marker. Dr. Hoon reported that the same markers can be detected in both the breast tumor and the sentinel lymph node plasma. In the coming year, he will refine his techniques and try to detect the markers in a larger number of patients.

Novel Screening Approaches

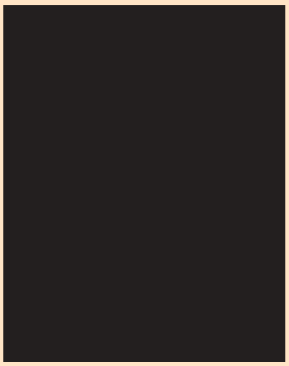
Two investigators will search for ways to detect cancer-related proteins in body fluids.

- **Protein Markers in Nipple Aspirates for Breast Cancer. Helena Chang, M.D., Ph.D.,** at the **University of California, Los Angeles** will use protein chip technology to compare the proteins in fluid from the nipples of women who have had breast cancer with those from women who haven't. Protein chip technology (Surface-Enhanced Laser Desorption/Ionization, SELDI) is a method for rapidly detecting many molecules present in a substance. The advantage of using this technology is that it can detect changes in many proteins at once, whereas conventional technology had restricted researchers to examining a few proteins at a time.
- **Discovery and Study of Breast Cancer Secreted Proteins. Elizabeth Williamson, Ph.D.,** of the **Cedars-Sinai Medical Center**, Los Angeles will explore a yeast-based method to identify proteins found in cancer tissue, but not in normal tissue. She has already identified a protein called mammoglobin that is found primarily in breast cancer and secreted from the cells into the blood. In addition to finding new potential markers in serum (a part of the blood), Dr. Williamson will develop a test that will detect mammoglobin in blood.
- **Molecular Staging of Breast Cancer Progression. Cheng-Ming Chuong, M.D., Ph.D.,** of the **University of Southern California,** Los Angeles will look for ways to optimize clinical analysis of breast tissue. Dr. Chuong will compare genetic changes in a small number of normal cells to a small number of cells from different stages of pre-cancer or cancer. Dr. Chuong will use a method called, single-cell cDNA library amplification (SCLA). It could potentially be used to identify a small number of cancer cells within a population of normal cells. It could also help to refine our understanding of the correlation between genetic changes and stage or prognosis of breast cancer disease.

Research Initiated in 2000

- **Profiling of Tyrosine Phosphatases in Breast Cancer.** The second study examines a different set of changes. If a woman's breast tumor has mutations in certain genes that produce enzymes called tyrosine phosphatases, her prognosis is likely to be poor. However, it has been difficult to determine which of these enzymes are associated with poor prognosis. This is because these tyrosine phosphatases often react with each other, and most studies examine them independently. **Clifford Tepper, Ph.D.**, of the **University of California, Davis - Medical Center** will employ a method that will allow him to obtain a snapshot of all of the tyrosine phosphatases in a tumor and associate the enzyme patterns with breast tumor characteristics.
- **Non-Invasive Optical Characterization of Breast Physiology. Bruce Tromberg, Ph.D.** and **John Butler, M.D.** (co-PIs) from the **University of California, Irvine** will explore "breast diaphanography," a simple, low-cost, non-invasive method that uses light to create an image of the breast. Unlike mammography, diaphanography does not use ionizing radiation or breast compression. Dr. Tromberg and Dr. Butler will take advantage of recent developments in a new optical technique called Frequency Domain Photon Migration (FDPM). FDPM is sensitive to subtle physiological changes that occur in breast tissue throughout life, caused by processes such as aging, hormonal fluctuations, and menopause. This information could provide clinicians with immediate insight into the nature and severity of a potential breast tumor and the effectiveness of various treatments.
- **MRI for High Risk Breast Cancer Screening and Surveillance. Nola Hylton, Ph.D.** and **John Ziegler, M.D.,** (co-PIs) from the **University of California, San Francisco** will screen women at high risk for breast cancer using Magnetic Resonance Imaging (MRI). They plan to recruit 30 women per year who meet three different sets of criteria for being high risk. The first group will have lifetime risk levels higher than 30% based on such factors as the age they began menstruating, the age they had their first baby, and the number of relatives who have had breast cancer. The second group will carry mutations in BRCA1 or BRCA2 genes, which makes them susceptible to breast cancer. The third will have a greater than 10% probability of carrying BRCA mutations, based on family history. Dr. Hylton and Dr. Ziegler hope to increase the diagnostic performance of breast MRI, validate that breast cancer can be detected earlier with MRI than with other techniques, and stimulate more widespread use of this method. Women at high risk for breast cancer may experience profound anxiety that can reduce their quality of life even in the absence of disease. To address this issue, Drs. Ziegler and Hylton will conduct a survey to determine whether MRI screening reduces this anxiety.

Etiology: Finding the Causes



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Etiology: Finding the Causes

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

Environment and Gene/Environment Interactions: Nature vs. Nurture

Bovine Leukemia Virus and Human Breast Cancer Risk

Tumor viruses such as Mouse Mammary Tumor Virus can cause breast cancer in mice. Gertrude Buehring, Ph.D., of the University of California, Berkeley investigated whether a similar phenomenon occurs in humans. Bovine leukemia virus (BLV) is found in cow's milk. Humans who drink cow's milk are exposed to the virus, but will only be affected if BLV can infect human cells. Dr. Buehring investigated whether human cells can be infected with BLV, by looking for the BLV genome in human cells and for an immune reaction to BLV. She developed a test to identify whether a person has been exposed to BLV and which cells are infected by it. The results indicate that BLV can indeed infect human cells. In future studies, she will determine whether there is a correlation between BLV infection and breast cancer development.

Hormones and Nutrition: Understanding the Modern Woman's Lifestyle

Estrogen Formation (Biosynthesis) and Breast Cancer Risk

A higher breast cancer risk is associated with a higher lifetime exposure to estrogen. An important class of genes produces enzymes and proteins that control the formation and action of estrogen. The more active the enzyme or protein, the more estrogen action, and the higher the risk. Gerhard A. Coetzee, Ph.D., of the University of Southern California Norris Cancer Center, Los Angeles focused on a gene called CYP17, which produces the enzyme that controls the ultimate formation of all the body's estrogen. Strong epidemiological evidence exists that this gene is involved in breast cancer risk. Dr. Coetzee identified several variants of this gene and tested them to better understand how these genetic variations could cause differences in the level of the enzyme or its activity. Although he failed to detect a molecular mechanism that underlies the epidemiologic association, he was able to exclude some obvious candidate mechanisms. He concluded that the differences must be too subtle to detect with today's technologies. Further studies are therefore needed to improve methods that would allow for a better understanding of how enzymes produced by the CYP17 gene relate to breast cancer risk.

Physical Activity, Diet and Menarche in a Multi-Ethnic Cohort

Women who have their first menstrual period at an early age appear to have an increased chance of developing breast cancer. So do women who have a larger lifetime number of menstrual cycles in which they ovulate (release an egg). Carol Koprowski, Ph.D., R.D., of the University of Southern California, Los Angeles studied the relationship between physical activity, diet, when a woman has her first menstrual period (menarche), and whether or not ovulation occurs during early menstrual cycles. The results indicated that girls who spent 13 or more hours per week in physical activity were more likely to have their first menstrual periods at later ages, compared to girls who spent less than

five hours per week. The amount of calories the girl consumed did not appear to be an important factor in when a girl had her first menstrual period. However, girls with higher caloric intake were more likely to ovulate during their menstrual cycles. Girls who spent more hours in physical activity were less likely to ovulate. The results suggest that diet and physical activity during childhood and adolescence can affect breast cancer risk.

Role of Estrogen in the Origin of Breast Cancer

The estrogen receptor (ER) is a protein in breast cells that binds with the hormone estrogen. This binding triggers changes in the genes and other processes within the cell. The estrogen receptor can turn on genes through two different regulating sequences on the genes' structure, called ERE and AP1. Peter Kushner, Ph.D., of the University of California, San Francisco designed an estrogen receptor that turned on only the ERE or AP1 and examined how turning genes on at each location affected the development of the mammary gland and tumors in mice. His team made mammary gland cells with genes carrying extra AP1, and these cells divided at an abnormally fast rate in response to estrogen. After this study began, a second estrogen receptor beta (ERβ) was discovered independently by other investigators. In an unplanned bonus to this study, Dr. Kushner found that ERβ often activates the AP1 sites 10 times more efficiently than ER (now called ERα) in the presence of anti-estrogens. This may explain at least in part why cells develop resistance to the anti-estrogen chemotherapy drug tamoxifen. This function of ERβ will be an important consideration when designing anti-estrogen drugs in the future. Dr. Kushner also found that a cancer gene, src, can strengthen the effects of estrogen on breast cancer cells. Breast cancer cells often have higher levels of src activity, indicating that src could provide a new target for anti-estrogen therapy. More on this work can be found in *Science* 277:1508-1510 (1997) and *Clinical Cancer Research* 5:251-256 (1999).

Research Conclusions

Radiation, Reproductive & Menstrual Factors & Breast Cancer

Women diagnosed with breast cancer at an age younger than 40 may be different from those diagnosed at an older age. Deirdre Hill, Ph.D., at the University of Southern California, Los Angeles is exploring reasons that may help explain cancer that develops before 40. These include having a close family member with breast cancer, having cysts or lumps in the breast (benign breast disease) and possible exposure to cancer-causing events or substances in childhood. Women who get X-rays at today's levels probably do not have a higher risk of breast cancer. However, Dr. Hill wanted to find out whether women who got X-rays in childhood (before age 20) in the past (when dose levels were higher), might have an increased risk, especially if they also have benign breast disease or a close family member with breast cancer. Overall, breast cancer risk was only slightly increased among women who received childhood radiation. However, among women with benign breast disease, breast cancer risk was 2.4 times higher in those who received radiation during childhood than those who had not. Among women without benign breast disease, childhood radiation exposure was not related to breast cancer risk. Women with breast cancer in a family member did not have an increased breast cancer risk following childhood radiation, unless they also had benign breast disease. Among women with both benign breast disease and a family member with breast cancer, breast cancer risk was 3.4 times higher. Radiation exposure at age 20 or older was not related to breast cancer risk among women with benign breast disease, but it was possibly related to increased risk among women with breast cancer in a family member. The radiation doses that women received in this study are much higher than those received today, so the increases in risk do not apply to current exposures. These results may contribute to further understanding of the causes of breast cancer, and to prevention for women at high risk.

Other Searches for the Causes

Predictors of Recurrent Breast Tumors In Women With DCIS

Ductal carcinoma in situ (DCIS), is a pre-malignant breast lesion, usually found through a mammogram. Some cases of DCIS turn into invasive breast cancer, and some will recur as DCIS after surgery. Others do neither. Currently, there's no way to predict what will happen for an individual woman, so there's no consensus about treatment. Some women have a mastectomy, others a lumpectomy, and others lumpectomy with radiation. Karla Kerlikowske, M.D., of the University of California, San Francisco investigated better ways to define which DCIS will recur after lumpectomy. Working from data from medical records, Dr. Kerlikowske measured epidemiologic, clinical, tumor, and tumor function characteristics of 1060 women who had DCIS. A total of 208 (19.6%) women had developed recurrent disease in the same breast. Of these, 56% were DCIS and 44% were invasive cancer, 49 women (4.6%) developed recurrent disease in their other breast. The median time for recurrence was 73 months. Although BCRP funding for the study has ended, Dr. Kerlikowske will complete analysis next year on the epidemiology, pathology and genes or proteins that provide markers for cancer. This information will be essential for predicting the risk of recurrent breast tumors after lumpectomy. It will allow women at high risk of recurrence to consider radiation therapy and possibly mastectomy, and those at low risk to avoid receiving unnecessary treatment.

Research in Progress

Environment and Gene/ Enviroment Interactions: Nature vs. Nurture

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

- Mammographic Density, Cancer, Inheritance and Acquired Risk in Twins. Women whose breast tissue appears denser than average on a mammogram have a higher risk of breast cancer. Thomas M. Mack, M.D., of the University of Southern California, Los Angeles is trying to confirm whether this is true even within pairs of identical twins. He is also investigating the extent to which breast density is inherited. In addition, he is investigating whether certain adult exposures and experiences, known to be related to breast cancer risk, such as diet and taking hormone replacement therapy, modify breast density. He is obtaining risk factor information by interviewing both members of up to 2500 pairs of California twins, some of whom have had breast cancer. He is also using their mammograms to measure their breast density. He will then compare sets of identical and fraternal twins for breast density, past experiences, and the subsequent appearance of breast cancer. He has identified 3202 potentially eligible individuals from 1601 pairs, contacted 2133 of them, and obtained the cooperation of 1600 or 75% of those contacted.
- Oral Contraceptives, Hormonal Risk Factors and BRCA1. A large number of breast cancers diagnosed at an early age may be due to mutations in the breast cancer susceptibility gene, BRCA1. Recent evidence suggests, however, that not all women with one of these muta-

tions will develop breast cancer. Giske Ursin, M.D., Ph.D., at the University of Southern California, Los Angeles is conducting a large study to determine to what extent hormones, use of oral contraceptives, reproductive history, physical exercise and other non-genetic factors increase the risk of breast cancer in women with a BRCA1 mutation. She is using tissue samples from the women to sequence their BRCA1 genes, using the new ABI 3700 sequencer. She is investigating whether a certain type of mutation on the gene (non-truncating mutations) is important in causing breast cancer, and what role non-genetic factors may play in cancer development in women with this type of BRCA1 gene mutation.

- Breast Cancer Susceptibility Genes In Very High Risk Women. A woman with relatives who have had breast cancer has a higher risk of developing the disease than a woman whose relatives haven't had the disease. Moreover, a woman whose identical twin has breast cancer is at an even higher risk than other women with a family history of breast cancer. Ann S. Hamilton, Ph.D., at the University of Southern California, Los Angeles is testing the hypothesis that a structure on the CYP 17 gene may occur more often in twins where one or both of the women have had breast cancer than in twins who haven't had breast cancer. She is currently recruiting study participants.
- The Insulin-Like Growth Factor (IGF) System and Breast Cancer. The insulin-like growth factor (IGF) system consists of several proteins produced by many cells in the body and circulating in the blood. They can work together to increase or decrease cell division. The IGF system may contribute to breast cancer by causing breast cells to divide, either directly or by working along with estrogens. A recent study found a strong association between high blood levels of one protein in the IGF system, IGF-1, and increased breast cancer risk in pre-menopausal white women. Brian E. Henderson, M.D., also at University of Southern California, Los Angeles is investigating whether levels of IGF in the blood differ among women of varying ethnic groups. He is also investigating whether a repeat of a sequence [CA] in the structure of the IGF-1

gene leads to higher levels of IGF-1 in the blood. If so, he will investigate whether the sequence repeat is associated with postmenopausal breast cancer. In addition, IGFBP-3 is another protein in the system that binds with IGF-1. Dr. Henderson is investigating whether a single change in the structure of the gene that produces the IGFBP-3 protein is associated with postmenopausal breast cancer. Preliminary analyses found no differences in circulating IGF-1 levels in the blood samples from a multi-ethnic population (African American, Japanese, Latina) after controlling for age and weight. Preliminary analysis of blood from 460 healthy women did indicate racial and ethnic differences in mean blood levels of IGF-1 and IGFBP-3, with the highest values found among Japanese and African American women and the lowest values among Latina women. Identifying the gene structures that determine IGF system levels may provide greater understanding of individual variations in breast cancer risk, and potentially serve as indicators for women who would benefit most from screening or specific types of therapy.

- Unique Genes Expressed in Cancer Cells. Craig V. Byus, Ph.D., of the University of California, Riverside is trying to isolate the genes that are turned off or on by the enzyme ornithine decarboxylase (ODC) in cells. It appears that high levels of ODC turns on or off genes that allow a cell to become more like cancer. Dr. Byus engineered a breast cancer cell line that had high and stable levels of ODC activity, and identified a number of gene fragments that behaved differently in this high-ODC cell line, compared to a cell line that does not have high levels of ODC. However, he encountered difficulties in this approach. The procedure he used did not allow him to isolate entire genes, and the gene fragments appear to be due to the techniques he used in the experiment. He has engineered a new series of cell lines that do not have this problem, where the ODC can be artificially manipulated to any level. In the upcoming year, he will continue to analyze the genes turned on and off in response to high levels of ODC to provide a better understanding of the process by which normal breast tissue becomes cancerous.

Research in Progress

Hormones and Nutrition: Understanding the Modern Woman's Lifestyle

- Gene-Diet/Tobacco Interactions in Breast Cancer in Asians. Certain substances (heterocyclic aromatic amines or HAs; polycyclic aromatic hydrocarbons or PAHs; and arylamines such as 4-aminobiphenyls, or 4-ABP) are known to cause genetic changes and cancer in rodents. Humans are exposed to these substances through cooking, smoking, and working in some occupations. If these substances are involved in breast cancer, then variations in the structure of genes that produce the enzymes that metabolize these substances are likely to influence the risk for breast cancer. Anna H. Wu, Ph.D., of the University of Southern California, Los Angeles is investigating the roles of a series of these metabolism genes (NAT1, NAT2, CYP1A1, GSTM1, GSTT1, GSTP1) in a group of Chinese, Japanese, and Filipino-American women. Some of the women have had breast cancer and the control group has not. Dr. Wu is using a molecular biology based technique, polymerase chain reaction or PCR. Another year will be needed to complete collection of blood specimens, identification of the genes, and data analysis. This study will help to identify factors responsible for the increase in breast cancer in Asian-Americans and will also help to clarify the role of HAs, PAHs and arylamines in breast cancer.

Research in Progress

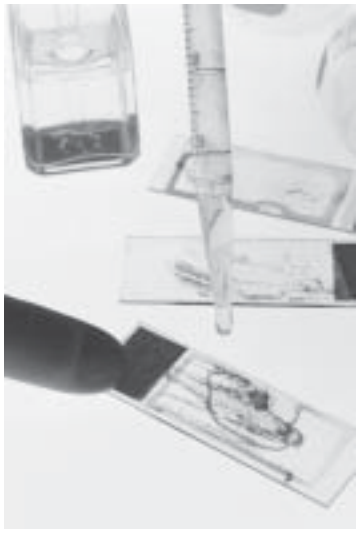
Other Searches for the Causes

- Breast Cancer Risk Factors: Lesbian and Heterosexual Women. Only a small amount of information is known about lesbians and breast cancer. However, scientists have proposed that lesbians' risk of getting the disease may be two to three times higher than that of heterosexual women. Suzanne L. Dibble, D.N.Sc., at the University of California, San Francisco and Stephanie Roberts. M.D., at Lyon Martin Women's Health Services, San Francisco clinic are trying to determine whether lesbians indeed have a higher risk. They are distributing surveys to lesbians age 40 and older throughout the state of California. They are also asking each lesbian participant to have a heterosexual female friend who lives in California fill out an identical survey, and if they have a sister, for the sister closest in age to fill one out, too. From questionnaires distributed, they have had a 33% response rate from lesbians (637 completed surveys), a 22% response rate from friends (434 surveys), and a 30% response rate from sisters (275 complete surveys and 301 with no sister). The typical lesbian responding to the survey is 50.4 years old, white (85.9%), educated (mean 17.1 years), employed (77%), and urban (53%). In the coming year, they will focus their efforts on reaching more lesbians of color; more elderly, less educated, and rural lesbians; and more lesbians with living sisters.
- USC/Norris Breast Cancer Research Training Program. An important goal of the BCRP is to encourage and support the training in breast cancer for new research scientists. Ronald K. Ross M.D., and Michael Press, M.D., maintain the multi-faceted Breast Cancer Research Training Program at the University of Southern California, Los Angeles. The program is now in its fifth year. Faculty include epidemiologists, prevention scientists, behavioral scientists,

tumor biologists and molecular geneticists, along with radiation, surgical and medical oncologists. The program encourages trainees to fully utilize the numerous patient and data resources available at the Norris Comprehensive Cancer Center. These include the SEER cancer registry; a large registry of breast cancer in twins; dietary and lifestyle data from large, racially and ethnically diverse groups of women; a large and diverse clinical population at affiliated hospitals; and several large tumor and other biological sample banks for tumor biology and molecular genetics studies. The trainees also participate in a variety of specialized activities related to breast cancer. This past year, five trainees were supported after being matched with an appropriate faculty mentor. Trainees are interdisciplinary in their interests, which include pathology, molecular and cell biology, and molecular epidemiology. Ongoing trainee research projects include: *Migratory and Metastatic Potential of HER-2/neu; Improving Retroviral Vectors for Gene Therapy of Breast Cancer;* and *Anti-angiogenic Gene Therapy for Breast Cancer,* among others.

Environment and Gene/Environment Interactions: Nature vs. Nurture

- Influence of Localized DDT Exposure on Breast Cancer. DDT is not eliminated from the body after exposure. It remains stored in the fat surrounding the breast tissue where cancer originates, and can act like hormones. So the question of whether DDT might increase breast cancer risk is of concern. Vicki L. Davis, Ph.D., at the Center for Women's Health, Cedars-Sinai Medical Center, Los Angeles will try, by clever experiments in animal models, to isolate the effects of the two main compounds formed when DDT is metabolized in the body. One of these compounds may stimulate cell growth. The other may interfere with the hormone androgen. Androgen is normally present in the tissue surrounding the breast cells; it inhibits the growth of cells prone to becoming cancerous. The results could shed light on whether DDT accumulation in breast tissue can influence the cell division processes that lead to breast cancer.
- **DNA Polymorphisms and Breast Cancer in a Multi-Ethnic Cohort.** Naturally occurring variations in human genetic makeup not only



account for the visible differences between people, but also influence risk for certain diseases. Such variations include those in the BRCA1 and BCRA2 genes, which are responsible for a small portion of inherited breast cancer risk. However, variations in many other genes may interact with each other and the environment to affect the risk of breast cancer. Brian Henderson, M.D., of the University of Southern California, Los Angeles will use a new, accurate, rapid, reliable and inexpensive method (single base extension–SBE–combined with fluorescence resonance energy transfer, FRET) to categorize variations in 25 genes that affect key hormone levels in the body. He is testing genes from 800 women: 200 African-American, 200 Asian-American, 200 Latina and 200 white. Half of each group have had breast cancer and half have not. Next, he will use statistical methods to quantify the relationship between genetic variations and the risk of breast cancer.

Research Initiated in 2000

Hormones and Nutrition: Understanding the Modern Woman's Lifestyle

- Mammography Density and Sex Steroid Genes. *Sue Ingles, Ph.D.*, of the University of Southern California, Los Angeles will investigate whether some genetic variations could provide a measure of future risk of breast cancer. Women whose breasts appear to be more dense on their mammograms have a greater breast cancer risk. Since hormonal levels are known to influence breast density, variations in the genes that produce female sex hormones may be associated with breast density. If this is the case, it would help us better understand the role of these hormones in breast cancer. Dr. Ingles will also examine whether women with specific variations in their genes who also are on hormone replacement therapy have very dense breasts. This could provide preliminary evidence that might be used to identify women who are at higher breast cancer risk if they use hormone replacement therapy.
- Physical Activity and Diet in Adolescents with Disabilities. Carol Koprowski, Ph.D., and *K. Sarah Hall, Ph.D.,* at California State University, Northridge will develop assessment tools to measure physical activity and diet in adolescent girls with disabilities. The tools will be used in a future planned study of the relationship between physical activity, diet and serum hormone levels in this population. The information gathered would be useful for creating lifestyle intervention programs for this underserved group during a susceptible time in their physical development.
- Genes Determining Estrogen Susceptibility in Breast Cancer. Many breast tumors are initially estrogen dependent and can be treated with anti-estrogen drugs. However, some tumors eventually progress to an estrogen-independent form and become drug resistant. Wensheng Wei, Ph.D., at **S**tanford University, Palo Alto will investigate possible mechanisms that might explain why. He will employ a recently-developed procedure to identify, isolate and map the structure of estrogen susceptibility genes (ESGs) that are required for breast cells to respond to estrogen stimulation. Dr. Wei hopes to ultimately identify the changes in the ESGs that lead to breast tumors becoming estrogen independent.
- Tamoxifen-Induced Endometrial Cell Transformation. Zhimin Lu, Ph.D., of the Salk Institute for Biological Studies, La Jolla will try to understand the mechanism of the

chemotherapy drug tamoxifen's severe side effects. He will also seek approaches for developing more effective breast cancer therapies and prevention without these side effects. Tamoxifen blocks estrogen. It also inhibits a group of enzymes called Protein Kinase C. One of these enzymes, PKC δ, may suppress the development and growth of tumors, so inhibiting it may promote tumor formation. Dr. Lu will investigate whether tamoxifen, by inhibiting PKC δ, does have a tumor-promoting effect on rat or mouse cells. He will also examine how tamoxifen in human uterine cells causes PKC δ to fail to inhibit the cancer process. Finally, he will investigate which cancer-related genes are turned on and which tumor suppressor genes are turned off after tamoxifen treatment.

Other Searches for the Causes

- Breast Cancer in California Teachers–Regional Variations. Large differences in breast cancer rates from one geographic area to another have long puzzled the concerned public and have generated many hypotheses about what might cause breast cancer. Most studies investigating geographic breast cancer patterns have used population-level data, with no individual data on personal risk factors. Peggy Reynolds, Ph.D., of the Public Health Institute, Berkeley will use the personal information available on 133,000 active and retired female California school employees participating in the California Teachers Study (CTS). She will determine the degree to which established and suspected risk factors explain the geographic patterns of breast cancer incidence observed in this group of women.

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Health Care Delivery and Health Policy: Serving Women's Needs

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

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

Research Conclusions

The Breast Care Center: Innovative Care for the Underserved

Imperfections in the coordination of care and provider communication adversely affect the cancer care provided in many facilities. The problem is particularly severe for patients with advanced disease, as is often the case with indigent patients. **Jay K. Harness, M.D.,** at the **Northern California Cancer Center,** Union City conducted a study of the effectiveness of Breast Care Centers in bridging the gap between professionally-trained providers and indigent patients with breast cancer. The project's goal was to foster care for indigent women with breast cancer at the highest professional level, which makes it more likely that the women will follow appropriate recommendations. Dr. Harness evaluated the experience of women treated at the Highland Campus of the Alameda County Medical Center, which is working to develop a Breast Care Center. When he compared women treated at a Breast Care Center to those treated in a general hospital setting, he found differences in: family backgrounds; medical care histories; the short term effects of the care; the psychosocial effects of being evaluated for clinically suspicious findings; and satisfaction with different aspects of the care received. He found that disorganization and delays were major problems with the care. Many of the difficulties were linked more to institutional coordination problems than to the low income or cultural backgrounds of the patients. To address this, the project team developed, and implemented at Highland, a prospective computerized database. The database generates concise summaries of current patient status and clinical recommendations made by the Highland Tumor Board, and facilitates tracking the system's adherence to these recommendations. Steps have been made to extend this approach to cancer care in other facilities. The database techniques and a relatively inexpensive organizational model can improve coordination of care and communication among providers in different facilities. This will foster more consistent and timely provision of care.

Research Conclusions

Study of Inadequate Follow-up of Mammographic Abnormalities

Daramola Cabral Evins, Dr.P.H., P.A., of the **San Francisco Department of Public Health, Arthur H. Coleman, M.D.**, of the **Bay View Hunters Point Health Care Task Force,** and **Marion M. Lee, Ph.D.**, of the **University of California, San Francisco** investigated barriers to African American women getting timely follow-up care when they have abnormal mammograms. Working with breast cancer experts, they developed and pilot-tested a culturally specific questionnaire in community focus groups that included a total of 51 African American women with abnormal mammograms. The team found that factors in the personal and social environment of women, as well as in the health care delivery system, are associated with inadequate follow-up of abnormal mammograms. Barriers included lack of access to care, previous dissatisfaction with the health care system, competing family priorities, and inadequate physician communication. The need for information and social support were also important. The women in the study expressed fear most often, which they linked to the expectation of a painful mammogram procedure and the possibility that the results might reveal cancer. Fear was also linked to the loss of a breast or breasts. Fear was both a barrier and a promoter to follow-up of abnormal mammograms and was often the cause of denial. The investigators are planning a full-scale study of inadequate follow-up.

Research in Progress

- **Samoans and Breast Cancer: Evaluating a Theory-Based Program.** Samoan-American women have a high incidence of breast cancer, a low awareness of the disease, and a low rate of use of early detection services. **Shiraz I. Mishra, Ph.D.**, at the **University of California, Irvine** and **Pat H. Luce-Aoelua, M.S.,** in the **National Office of Samoan Affairs,** Carson are implementing and evaluating an innovative, theory-based, culturally sensitive and linguistically appropriate breast cancer control educational program for Samoan-American women. The goals are to enhance breast cancer awareness, increase screening and early detection rates, and over time, potentially lower breast cancer incidence and deaths in this marginalized community. The educational program consists of three components: specially developed English- and Samoan-language educational materials, skills building exercises, and interactive group discussions. The team has continued administering pre-test surveys, conducting education sessions, and started administering post-test surveys. During study year three, they will continue these activities and conduct focus groups with women who changed or did not change their behaviors.

Research Initiated in 2000

- **Does a Peer Navigator Improve Quality of Life at Diagnosis?** Peer navigator programs match newly-diagnosed breast cancer patients with breast cancer survivors to help the new patients deal with the many complex issues and decisions they face. However, well-designed research hasn't been done to test the effectiveness of peer navigator programs. This research could contribute to good training of peer navigators. **Caroline Bliss-Issberg, Ph.D.**, of the community group **WomenCARE,** Palo Alto and **David Spiegel, Ph.D.**, and **Janine Giese-Davis, Ph.D.**, at **Stanford University,** Palo Alto are conducting a pilot study to assess the peer navigator program run by WomenCARE. They are investigating the program's effect on various aspects of well-being among women who participate, including their mood, quality of life and how well the women function. The team is also assessing how well the program's referral system is working. Finally, they are investigating the feasibility of a Spanish-language based program. They will use the results from this study to prepare to expand and evaluate the peer navigator program in a three-county area.
- **Race/Ethnicity, Socioeconomic Status and Breast Cancer. William Wright, Ph.D.,** at the **Public Health Institute,** Berkeley is using innovative statistical methods to analyze data from California's statewide cancer registry and the Women's Health Survey, a 1998 survey of 4000 California women from various ethnic groups. He will investigate the relationship between race/ethnicity and socioeconomic status in the risk of developing breast cancer. He will also investigate whether the relationship between socioeconomic status and severity of the disease at diagnosis in California varies for different racial and ethnic groups. Finally, he will study the importance of including race and ethnicity when making projections of breast cancer incidence rates, which isn't currently done. The results could provide insights into the unequal burden of cancer among California's various racial and ethnic groups, and help inform policy decisions to reduce these inequities.

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Innovative Treatments: Search for a Cure

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

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

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

Research Conclusions

Immune Therapy: Mobilizing the Body's Defenses

Receptor Antibody-Enhanced Chemotherapy for Breast Cancer

In order to grow, tumor cells require a substance produced in the body, insulin-like growth factor. Insulin-like growth factor-I receptor (IGFIR) is a substance on tumor cells that allows them to take up insulin-like growth factor. **Yoko Fujita-Yamaguchi, Ph.D.,** of the **Beckman Research Institute – City of Hope,** Duarte designed a therapeutic approach that blocked tumors' IGFIR as a means of stopping tumor growth. She successfully constructed an anti-IGFIR antibody that blocked the receptor and inhibited the growth of human tumors that were transplanted into mice. She tested whether the inhibitory effects of the antibody could enhance the effects of the chemotherapy drugs doxorubicin and tamoxifen. Anti-IGFIR did not enhance doxorubicin, but therapy with anti-IGFIR and tamoxifen was more effective than either component alone. Results from this project were published in *Cancer Immunology and Immunotherapy* 49: 243-252 (2000).

Peptide-Pulsed Dendritic Cell Therapy for Breast Cancer

Dendritic cells are white blood cells that enable the immune system to identify foreign proteins more effectively. CEA (carcino-embryonic antigen) is a protein that is present on the surface of some tumor cells but is not generally found on normal cells. **Jeffrey Weber, M.D., Ph.D.,** of the **University of California, Los Angeles** completed an early clinical trial to determine (1) whether patients who had

tumors with CEA could be treated with their own dendritic cells that had been taught to recognize CEA, and (2) whether this treatment caused side effects. He found that, since the patients had been heavily pre-treated with chemotherapy, the function of the dendritic cells was impaired and the treatment did not stimulate the immune system or cause tumors to shrink. However, dendritic cell therapy has succeeded in melanoma patients whose cancer has spread to other parts of the body, but who have not had chemotherapy. So Dr. Weber believes breast cancer patients with minimal disease who have not had chemotherapy would be ideal for future dendritic cell therapy trials.

New Drug Design: Creative Science

A New System for Breast Cancer Drug Delivery

Daryl Drummond, Ph.D., from the **California Pacific Medical Center**, San Francisco finished a project to modify liposomes (microscopic fat particles) that contain a chemotherapy drug, to target them more specifically and effectively toward breast tumors. This should reduce the toxicity of the drug to the rest of the body. The critical need was to administer these liposomes in the blood, then have them 'home in' on breast tumors. Using human breast tumors grown in mice, they targeted the liposomes to the breast cells by placing an antibody (anti-Her2) on the liposome surface. Overcoming a major technical hurdle, they formulated liposomes that did not release the chemotherapy drug they contained, doxorubicin, until after the breast cancer cells took up the liposomes. The initial success in cells and animal models indicted that this approach could greatly reduce systemic toxicity associated with chemotherapy. Dr. Drummond published his results in *Pharmacological Reviews* 51: 691 (1999) and *Biochem. Biophys. Acta* 1463: 383 (2000).

Research Conclusions

Novel Drugs to Inhibit Breast Cancer Metastasis

Joseph Konopelski, Ph.D., from the **University of California, Santa Cruz** targeted for drug development (1) a protein (laminin), which is needed by both normal and tumor cells and found in their immediate micro-environment and (2) its molecular interaction with a surface receptor on breast cancer cells (Laminin Binding Protein-LBP). The drug design involved only a small region of laminin, called peptide 11, which is responsible for this process. Dr. Konopelski's collaborators at Montana State University determined the amino acid side-chain and backbone molecular structure of peptide 11. Then, his team developed a chemical synthesis for a potential inhibitor of the laminin peptide 11-LBP interaction. They were unable to complete the complex synthesis in the time frame of BCRP's funding. However, the National Institutes of Health and the Congressionally Directed Research Program at the Department of Defense are funding the continuation of this work.

Mechanism of Novel Anti-Angiogenic Therapy for Breast Cancer

Continuing research BCRP funded from 1995-98, **Francis Markland, Ph.D.,** from the **University of Southern California,** Los Angeles completed a project to develop the therapeutic potential of a protein from snake venom, called contortrostatin (CN). The net effect of CN is to block both blood vessel formation and the spread of breast cancer cells. Integrin adhesion receptors are found on all types of cells; they attach individual proteins found in the cells' micro-environment to the cells. Dr. Markland's team succeeded in identifying the specific breast cancer and blood vessel integrin adhesion receptors that CN blocks, and they moved towards defining how CN does this. In addition, Dr. Markland's group made important strides in developing a method for delivering CN to the body, and they studied small peptide compounds derived from CN. Several publications resulted from this support, including articles in *Biochemistry & Biophysics Research Communications* 267: 350 (2000), and *Breast Cancer Research & Treatment* 61: 249 (2000). BCRP is continuing to fund this project.

Research Conclusions

Novel Enzyme Inhibitors for Estrogen-Dependent Breast Cancer

Masato Tanabe, Ph.D., of **SRI International**, Menlo Park designed orally-administered drugs that inhibit estrone sulfatase, an enzyme responsible for producing estrogen. The drugs cut off the estrogen supply for estrogen-dependent breast tumors. He was able to develop three new estrone sulfatase inhibitors (ESIs) that have strong activity against human breast tumors grown in mice. An advantage of these ESIs over most estrogen inhibitors is that the ESIs do not themselves have estrogenic activity, and therefore cause fewer side effects. At least one of the new ESIs is effective enough to undergo further pre-clinical and clinical testing and may ultimately provide a viable, less toxic alternative to anti-estrogens currently in use.

Blocking Stromelysin-3 to Inhibit Breast Cancer Metastasis

Nurulain Zaveri, Ph.D., also at **SRI International,** Menlo Park investigated Stromelysin-3 (ST-3), one of a class of enzymes called proteases that tumor cells release to digest their immediate micro-environment and allow tumor cell movement. However, ST-3 does not actually act as a protease. Rather, it counteracts inhibitors of this process and permits other, more potent proteases to function. Dr. Zaveri synthesized inhibitors of ST-3. She first designed protein-like inhibitors, and then worked on synthetic, non-protein inhibitors. These were tested though a collaboration with Dr. Stephen Weiss at the University of Michigan. This research validated ST-3 as an attractive target for therapy to prevent the spread of breast cancer to other parts of the body. Dr. Zaveri's efforts advanced two approaches against ST-3 that are part of rational drug design: (1) using solid support, a quicker type of chemical synthesis useful with low yields; and (2) combinatorial chemistry, where the researcher produces and tests all types of a specific molecule.

Hormone and Chemotherapy Targets: Improving Today's Arsenal

Enhancing Breast Cancer Sensitivity to Chemotherapy

Daniel Mercola, M.D., Ph.D, from the **Sidney Kimmel Cancer Center**, San Diego explored whether blocking a series of protein interactions inside cells (called the JNK pathway) will overcome cell resistance to chemotherapy. Dr. Mercola inhibited JNK by using special "antisense" molecules in order to make breast cancer cells and tumors sensitive to a chemotherapeutic drug, cisplatin. This approach had promise specifically in one type of breast tumor (Her-2/neu-positive), but did not appear effective in another type, estrogen-receptor-positive tumors. Dr. Mercola performed these experiments on human tumor cell lines grown in mice. Several publications resulted from this funding, including a report in *Cell Growth & Differentiation* 10:545-554 (1999). Matching appropriate therapies to subgroups of breast cancer patients whose tumors interact with specific hormones or other bodily substances is a topic of intense research interest. Also, new approaches are needed to tackle Her-2/neu-positive breast cancer, since the current drug, Herceptin, is successful in only about 30% of patients.

How Indole-3 Carbinol Inhibits Breast Cancer Cell Growth

Liqun Zhang, Ph.D., at the **University of California, Berkeley** investigated how indole-3-carbinol (I3C), a compound found in cruciferous vegetables such as cabbage and broccoli, inhibits growth in breast cancer cells. She exhaustively studied a series of protein interactions that take place inside cells, the MAPK (mitogen-activated protein kinase) pathway. In a variety of experiments, it appeared that MAPK is not connected with I3C, and her team plans to look at other protein interactions inside cells to understand I3C's growth-inhibiting effect on breast cancer.

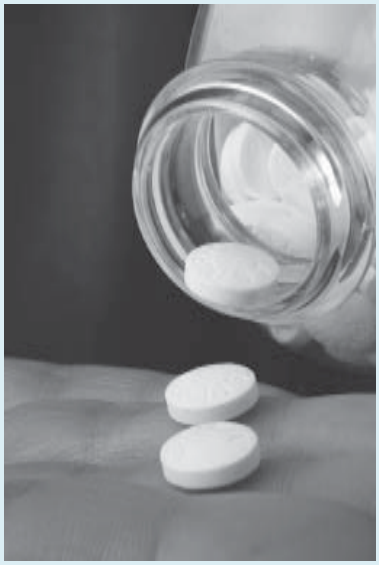
Gene Therapy and Other Treatments: New Frontiers

Outpatient Stem Cell Transplants for Breast Cancer

High-dose chemotherapy with bone marrow or stem cell transplant is a treatment option for breast cancer that has spread to other parts of the body or for high-risk breast cancer. Traditionally, it requires prolonged inpatient hospitalization. **Kathryn Hollenbach, Ph.D.,** of the **University of California, San Diego** compared two groups of women, one who had the treatment as inpatients, and another who had it as outpatients. She compared the groups for (1) cost , (2) the patient's psychological well being, (3) the psychological well being of the family member or friend who acted as caregiver, (4) toxicity associated with treatment, and (5) hospital re-admissions. There were no statistically significant differences between inpatient and outpatient groups on number of days from first date of high-dose chemotherapy to the date the patient returned to the referring oncologist. There were also no differences in toxicity, number of hospital re-admissions, or length of hospital readmission. Adjusting for age and symptom severity, on average, outpatient costs were 71% less than inpatient. No differences in well-being were seen in patients or caregivers at the beginning of treatment or 60 days after treatment. However, after adjusting for age, symptom severity and quality of well being at the beginning of treatment, outpatients had significantly poorer well-being during treatment. Similar differences were not seen for caregivers. There was no difference in well-being between the inpatient and outpatient groups at the end of treatment or at subsequent follow-up. Results demonstrate that this therapy, administered in an outpatient setting, was associated with significant cost savings and no permanent adverse effects. The significant cost savings support consideration of making this therapy widely available. Dr. Hollenbach was co-author of a publication reporting this research, *Bone Marrow Transplantation* 21:927-32 (1998).

Research Conclusions

Improved Delivery of Pharmaceuticals to Breast Cancer



Demetrios Papahadjopoulos, Ph.D., (deceased) and **Dmitri Kirpotin, Ph.D.,** at the **California Pacific Medical Center Research Institute**, San Francisco completed a project with the goal of designing a new way to deliver chemotherapeutic drugs directly to breast tumors. They encapsulated an anti-cancer drug inside liposomes (microscopic fat particles that can enter the cell wall), and targeted the liposomes to the tumor cells through the blood. They also heated the tumor slightly above normal to enlarge tumor blood vessels and maximize the efficiency of delivering anti-cancer drugs. Drs. Papahadjopoulos and Kirpotin found that when they heated a tumor, it took up three times more liposomes. They designed specialized liposomes they called "stealth" liposomes that work especially well with heating tumors. This study has resulted in a Phase I/II clinical trial, where the drug delivery method will be tested for safety and effectiveness in humans. Additional details were published in *Pharmacological Reviews* 51: 691-743 (1999).

Targeted Gene Therapy Using Anti-p185Her2 Immunoliposomes

John Park, M.D., of the **University of California, San Francisco** developed a way to use liposomes (microscopic fat particles) to deliver genes to breast tumors. The formulation he developed, called anti-Her2 immunoliposomes, contains liposomes, genes or DNA, and an antibody that targets the treatment to breast cancer cells. Dr. Park was able to deliver test genes to breast cancer cells in test tubes and to human breast tumors grown in mice. Most of the targeting systems developed for delivering gene therapy to breast tumors are based on technologies that use viruses. Dr. Park's study has shown the promise of using a non-viral system for delivering gene therapy to breast tumors. This study is discussed in numerous publications, including one in the *Annals of the New York Academy of Sciences* 886:293-6 (1999).

Research Conclusions

Mechanism of Radiosensitivity in Breast Cancer Cells

Xiaofei Wang, Ph.D., of **The Scripps Research Institute**, La Jolla investigated how cells become resistant to radiation and attempted to determine the best way to enhance radiation-induced cell killing. He found evidence that two macromolecules, ATM and Cds1, are required for establishing resistance to radiation in breast cancer. By designing inhibitors to these molecules, it may be possible to develop treatments that will increase the effectiveness of radiation therapy.

Liposomes

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

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

Research in Progress

Immune Therapy

- **Her-2/neu DNA Vaccines for Breast Cancer.** The Her-2/neu gene is found in invasive breast tumors, and also in about 50% of cases of DCIS, a precancerous condition of the breast that may turn into cancer. **Michael Campbell, Ph.D.,** from **University of California, San Francisco** is pursuing a vaccine approach that could prove a powerful preventive agent in women at risk for progressing to invasive disease. Dr. Campbell reports the potential for Her-2/neu DNA-based viral vaccines to elicit an immune response in mice.
- **Antibody-IL-2 Fusion Protein for Breast Cancer.** Fusion proteins are two separate proteins that have been combined to make a single new protein. **Joseph Lustgarten, Ph.D.,** of the **Sidney Kimmel Cancer Center,** San Diego has found that both heregulin-IL2 fusion proteins and Her-2/neu-IL2 fusion proteins are able to inhibit tumor cell growth in laboratory and experimental mouse models.

New Drug Design

- **Treating Breast Cancer with Chinese Herbs: A Pilot Study. Debasish Tripathy, M.D.,** of **University of California, San Francisco** is testing whether Chinese herbal extracts can keep cancer cells from growing or kill them. Dr. Tripathy is using cell lines and tumor-bearing mice with cloned genes transferred into their DNA to test the effect of the herbal extracts on cell growth. After testing 76 extracts, the team found several herbal combinations that inhibit cell growth. They will next try to isolate a cell growth-inhibiting compound from these extracts.

Her-2

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

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

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

Hormone and Chemotherapy Targets

- **Biologic Determinants of Response to Paclitaxel and Radiation.** **Silvia Formenti, M.D.,** and **Peter Danenberg, Ph.D.,** at the **University of Southern California,** Los Angeles are analyzing the effectiveness of treating patients with either the chemotherapy drug paclitaxel alone or paclitaxel plus radiation before surgery. They are also identifying the features of the breast tumors that predict the response to treatment. They found that 1/3 of the tumors responded to paclitaxel and radiation, but only 1/10 responded to paclitaxel alone. Early results indicate that tumors with a low level of the Her-2/neu protein respond to paclitaxel plus radiation.

Gene Therapy and Other Treatments

- **Can Molecular Markers Predict Response to Adjuvant Therapy.** Tumor-related markers are genes or proteins found in tumors that may provide information on the nature and severity of the disease. **Shelley Enger, Ph.D.,** of **Southern California Kaiser Permanente** and **Michael Press, M.D., Ph.D.,** at the **University of Southern California,** Los Angeles are investigating whether some of these markers, including Her-2/neu, p53 and Bcl-2, can be used to predict whether a patient is likely to respond to various therapeutic regimens. It is critical that physicians treating beast cancer patients have new information to better match therapeutics with individual patient tumor markers.

Research in Progress

- **Molecular Mapping of Surgical Margins. Shanaz Dairkee, Ph.D.,** at the **California Pacific Medical Center**, San Francisco is investigating genes in breast surgery specimens. She has found that the gene changes present in breast tumors were also detectable in nearby breast tissue that appears to be otherwise normal, and in abnormal non-cancerous lesions. By examining the "normal" cells at the genetic level, it may be possible to better assess a woman's risk of the cancer growing back at the same site after surgery.
- **Breast Cancer Gene Expression Using Amplified Core Biopsies. Stefanie Jeffrey, M.D.,** from **Stanford University,** Palo Alto successfully amplified small surgical samples of tumors from needle core biopsies to get a genetic profile previously thought possible only with larger tumor samples. Tumors are composed of cells with varying degrees of malignancy and genetic makeup. Dr. Jeffrey is pursuing amplification to see if it can be used to detect genetic differences between various cells in a single tumor.
- **Bispecific Antibodies for Radiotherapy of Breast Cancer. Michele Winthrop, Ph.D.,** from the **University of California, Davis** is developing antibodies that simultaneously carry a radiochemical (^{90}Y-DOTA), and a recognition site for tumor cells (Muc-1) to make the antibody interact with tumor cells, but not normal cells. This approach promises advances in both the detection and the treatment of breast tumors by delivering radiation through the blood, rather than external radiation focussed on the tumor site. Progress on this project was recently published in the *Quarterly Journal of Nuclear Medicine* 44:284-295 (2000).
- **New Radiation Therapy for Her-2-overexpressing Breast Cancer. Richard Pietras, M.D., Ph.D.,** of the **University of California, Los Angeles** is using a mouse model to determine the best schedule for combining the chemotherapy drug Herceptin (used with tumors containing a high level of the Her2/neu protein) and radiation treatments. They have found that close timing maximizes the effectiveness of these two therapies. Dr. Pietras is also investigating the underlying mechanism for this synergistic effect.

Immune Therapy

- **Cell-Based Immunotherapy for Breast Cancer. Nabila Jabrane-Ferrat, Ph.D.,** of the **University of California, San Francisco** will incorporate 'danger signals' (HER-2/neu with CIITA, CD80 or interferon gamma) into vaccines. These danger signals are proteins present in tumor cells at higher levels than in normal cells or with a structure slightly different from the protein in normal cells. The goal is to stimulate the immune system to produce a type of white blood cell that will recognize the danger signal and attack the tumor as a foreign body.

New Drug Design

- **Targeted Delivery of an Anti-breast Tumor Agent. Francis Markland, Ph.D.,** and **Fred Hall, Ph.D.,** from the **University of Southern California- Keck School of Medicine**, Los Angeles and **Gary Fujii, Ph.D.,** at **Molecular Express, Inc.,** Los Angeles are teaming up for a cross-disciplinary project. They are in the early stage of developing a novel drug to block tumor blood vessel formation (angiogenesis). The drug is based on contortrostatin (CN), a protein found in a snake venom. CN works in simple tests on tumor cells in culture, now they are working on a way to deliver CN to tumors via the blood following an injection, using animal model systems.
- **Novel Anti-Angiogenic Agents for Breast Cancer Therapy. Keith Laderoute, Ph.D.,** at **SRI International,** Menlo Park will investigate the mechanism of action of a novel selective estrogen receptor modulator (SERM). SERM blocks tumor cell growth, and also appears to selectively inhibit the growth of human tumor blood vessel cells and antagonize the formation of new tumor blood vessels.
- **Computer-Aided Discovery of Novel Breast Cancer Therapeutics. Gilda Loew, Ph.D.,** at the **Molecular Research Institute**, Menlo Park and **Marcia Dawson, Ph.D.,** from the **Molecular Medicine Research Institute**, Menlo Park, are teaming up from two complementary disciplines. The first is computer software design that generates 3-dimensional models of sections of proteins in cells that could potentially interact with drugs; the second is breast cancer biology. They will work on vitamin A compounds, called retinoids, that regulate cell differentiation and proliferation. The goal is to use retinoids as an anti-breast cancer chemotherapy that would be less toxic than current drugs.

Research Initiated in 2000

- **Arginine Deiminase as an Innovative Anti-Breast Cancer Agent. Wei-Chiang Shen, Ph.D.,** at the **University of Southern California,** Los Angeles will investigate an enzyme, arginine deiminase, which is found in certain microorganisms, and can inhibit new blood vessel growth. It works by interfering with the production of the amino acid arginine, thereby altering the regulatory balances within the cell. Dr. Shen will explore the feasibility of using this newly-discovered agent as a breast cancer therapy.

Hormone and Chemotherapy Targets

- **Novel Agents for Treatment of Advanced Breast Cancer. Ling Jong, Ph.D.,** at **SRI International,** Menlo Park will explore the therapeutic potential of a new class of compounds derived from indole-3-carbinol (I3C), a compound found in cruciferous vegetables such as broccoli and Brussels sprouts. I3C also interferes with estrogen action. Dr. Jong will optimize the effect of these drugs using cells in culture, and then evaluate their action on breast tumors grown in animals.
- **Identifying the Breast Cancer Target for Indole-3-Carbinol. Urmi Chatterji, Ph.D.,** at the **University of California, Berkeley** is also studying I3C. Because I3C appears to inhibit tumors that respond to estrogen (which can be treated with the drug tamoxifen) and tumors that don't respond to estrogen (which are resistant to tamoxifen), Dr. Chatterji is trying to discover the protein within cells that initially binds with I3C. If she succeeds, this information could lead to a common strategy to combat the two major variants of the disease.
- **A New Class of Drugs to Treat Breast Cancer.** Most anti-estrogen therapies involve blocking the binding of estrogen to its receptor (a protein inside the tumor cell). **Thomas Robertson, Ph.D.,** of the **University of California, San Francisco** will use computer modeling to design compounds that selectively block the estrogen receptor before it has a chance to turn on other genes in the cell.
- **Role of $p14^{ARF}$ in Metastatic Breast Cancer.** A protein found in both normal cells and tumor cells, p53, triggers death of tumor cells after they have been damaged by chemotherapy or radiation. Some breast tumors have defective p53, but many of those with normal p53 appear to be missing another protein, $p14^{ARF}$. The tumor cells without $p14^{ARF}$ appear to have lost the ability to initiate cell

death. **Ruth Gjerset, Ph.D.,** at the **Sidney Kimmel Cancer Center,** San Diego plans to use gene therapy to introduce $p14^{ARF}$ into breast tumors. She wants to see whether there is a 'bystander effect,' where altered cells kill neighboring tumor cells. Any success to validate the bystander process would be exciting, since gene therapy approaches are often limited by low efficiency.

- **Targeted Chemotherapy to Treat Breast Cancer.** Breast cancer cells frequently have a sugar-binding molecule on their surface, called CD44. Sugar containing molecules, called hyaluronans, will bind CD44 with poor affinity. However, when the hyaluronans are formulated into microscopic fat droplets, called liposomes, the cancer cell binding increases dramatically. **Francis Szoka, Ph.D.,** at the **University of California, San Francisco** will explore the potential for this novel technology by incorporating a chemotherapeutic drug, doxorubicin, into liposomes that contain hyaluronan.

Gene Therapy and Other Treatments

- **Wnt Signaling in Breast Cancer.** The large family of Wnt proteins are secreted by cells to control diverse aspects of development in organisms ranging from fruit flies to mammals. An extensive body of evidence suggests these proteins are essential for both normal development and tumor formation. **Randall Holcombe, M.D., Marian Waterman, Ph.D.,** and **Lawrence Marsh, Ph.D.,** (co-PIs) from the **University of California, Irvine** plan to measure the amounts of Wnt in tumor and normal cells, along with associated genes, using two technologies, differential display and analysis with gene microchip arrays. They also plan to study the role of Wnt and associated proteins from patients with known genetic predisposition to breast cancer, such as those with BRCA1 and BRCA2 mutations.
- **Stress Protein Induction and Drug Resistance in Human Breast Cancer.** In solid tumors, such as breast cancers, there are regions of low oxygen concentration. Low oxygen starves cell metabolism and leads to the production of special stress proteins. **Amy Lee, Ph.D.,** at the **University of Southern California,** Los Angeles will investigate stress pro-

teins in breast cancers, and the potential for blocking their function as a novel method of therapy to overcome drug resistance.

- **Thrombosis for Anti-angiogenic Therapy of Breast Cancer.** Tiny tumor blood vessels are leaky and prone to becoming plugged with blood clots. Tumors appear to overcome this by creating their own system to prevent blood from clotting and maintain the blood flow essential for cell survival. **Min-Ying (Lydia) Su, Ph.D.,** from the **University of California, Irvine** will explore the possibility of inhibiting this tumor-based anti-clotting system as a novel means to attack breast cancer that has spread to other parts of the body.
- **Chinese Herbal Therapy (CHT) for Symptom Management. Debasish Tripathy, M.D.,** of the **University of California, San Francisco** will conduct a Phase III clinical trial (the final trial before a medication can be approved for use) to investigate whether Chinese herbs will relieve the side effects caused by chemotherapy.

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Pathogenesis: Understanding the Disease

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

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

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

Research Conclusions

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

Balance of Growth Factors in Breast Cancer Growth and Metastasis

Daisy De Leon, Ph.D., of **Loma Linda University** examined the role of two proteins, IGF-II and Cathepsin D, in breast cancer spreading to other parts of the body. She found that when breast tumor cells are exposed to the precursor form of IGF-II, they move and divide more. IGF-II causes both hormone-dependent and hormone-independent breast cancer cells to release Cathepsin D. Dr. De Leon's theory is that the release of Cathepsin D correlates with the breast cancer moving to other body parts. Dr. De Leon found that of the 5 to 6 different forms of Cathepsin D, only one was elevated in breast cancer tissues. This investigation showed that Cathepsin D and IGF-II are good candidates to serve as markers for tumors that are likely to spread to other body parts. Results from this funding were reported in three publications, including *Hormone Metabolism Research* 31:142-7 (1999).

Novel Breast Cancer Epithelial Cell Metalloproteinase

Pierre-Yves Desprez, Ph.D., from the **California Pacific Medical Center**, San Francisco planned to clone and study an invasion protease, metalloproteinase. An invasion protease is a protein that digests a cell's immediate environment and allows the cell to move. Metalloproteinase is secreted from breast cells under the control of Id-1, a type of protein called a transcription factor. Using a polymerase chain reaction (PCR) cloning method, the research team identified an interesting zinc finger protein, a type of protein that regulates and binds to DNA. Although it was not a protease, this new protein did exist in gene/protein databases. When the novel zinc finger protein was re-introduced into breast cells, it induced processes associated with milk secretion, but not through any role as a transcription factor. Dr. Desprez is continuing this research to find the relationship of the novel protein with Id-1 and its function in breast cells.

Research Conclusions

Abnormal Regulation in Breast Cancer Development/Metastasis

Ulla Knaus, Ph.D., from **The Scripps Research Institute**, La Jolla investigated a signaling protein, PAK, that appears to be a key player in relaying growth messages inside breast cancer cells. Dr. Knaus found that PAK was associated with two other proteins, Rac and Cdc42. These three proteins are collectively involved with critical functions of cell movement and the cancer's spread in the body. Results from this research were published in the *Journal of Biological Chemistry* 273:8137 (1998) and the *Proceedings of the National Academy of Sciences, USA* 97:185 (2000). Dr. Knaus received additional funding from the BCRP in 2000 to continue this research.

Research on Metastasis: the Spread of Breast Cancer

Breast cancer spreads through the blood and lymph system to form tumors in other parts of the body. Medical science is least able to control this part of the disease. Early detection won't solve the problem, because by the time a breast tumor is only 2 millimeters in size, it has acquired a blood supply and has the potential to spread. The process of spreading is complex and has many components. Any component could hold the key to a breakthrough, so they provide many avenues for research.

Role of Gamma-catenin in a Breast Cancer Mouse Model

Normal breast epithelial cells have a recognition system that maintains their organization. This recognition system works, in part, through cell surface proteins called cadherins, which relay messages though "switchboard" proteins, called catenins. **John Reed, M.D., Ph.D.,** from **The Burnham Institute**, La Jolla highlighted the mechanism by which two signaling proteins, called APC (a tumor suppressing protein first found in colon cancers) and Siah (the human counterpart of a family of *Drosophiila* eye development genes) cooperate to degrade catenins and limit cell growth. This research indicates that colon and breast cancers have similarities in this type of cell regulation. A portion of this work was published in *The Journal of Biological Chemistry* 275:15578-15585 (2000). Dr. Reed's team plans to pursue these findings, using animals with cloned genes transferred into their DNA that contain defects in key elements of the cell death (apoptosis) process.

Too Much Cell Growth: Defective Messages and Internal Signaling

Degradation of Growth Factor Receptors and Breast Cancer

Epidermal growth factor receptor (EGFR) and Her-2/neu oncogene receptor are two proteins that are often present in abundant amounts in breast tumor cells. Cells constantly recycle their receptors, and in normal cells the balance of receptor production and degradation is tightly regulated. Although intensive research has been undertaken to understand how receptors are overproduced in cancers, few studies have been done on how receptors are degraded. **Gordon Gill, M.D.,** of the **University of California, San Diego** investigated the degradation side of the equation. The cell system that directs degradation of EGFR uses a protein, SNX1, which is a member of the sorting nexin family of proteins. SNX1 recognizes a part of EGFR molecule. Dr. Gill found a second, previously undiscovered, related protein called SNX2 and, since then, 16 additional members of this protein family have been discovered. Dr. Gill found that SNX1 and SNX2 work together to bring EGFR into the part of the cell where it can be degraded by the lysosomes. Dr. Gill examined the structure of the sorting nexins and found that one part (the COOH terminus) is responsible for directing EGFR into the lysosomes and another (the PX domain) is responsible for interactions between SNX proteins. Continuation of the study may open up new approaches for stabilizing the receptor levels in breast cancer. This could make the cancer cells behave more like normal cells. The results were reviewed in *Current Opinions in Cell Biology* 11:483-8 (1999).

Receptors

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

Research Conclusions

Role of Rb Protein and Cell Cycle Defects in Breast Cancer

The retinoblastoma gene (Rb) has been investigated in many cancer types. It serves as a regulatory switch, turning off and on numerous key genes that keep cells from multiplying. Mutations in Rb or defects in other proteins that regulate Rb release cells from normal controls and have been found in breast and other cancers. **Kathryn Ely, Ph.D.,** at **The Burnham Institute,** La Jolla studied a protein that binds with Rb called RIZ. She focussed on a part of RIZ called the PR domain. The Ely laboratory conducted crystallography, nuclear magnetic resonance, and mutational analysis of the PR domain. In other published work, it has been reported that breast cancer cells produce a modified RIZ protein that lacks the PR domain. Thus, understanding how PR works and its structure could be important to restoring normal cell functions in breast cancer.

The Role of a Novel Estrogen Receptor in Breast Cancer

Ruth Lupu, Ph.D., at the **Lawrence Berkeley National Laboratory,** Berkeley explored the function, in normal and tumor breast cells, of a newly discovered protein, an estrogen receptor called estrogen receptor beta (ER-β). She found that ER-β was detectable in 20% of 50 breast tissues examined. It inhibits cell growth when introduced into cells that don't have estrogen receptors. Dr. Lupu also identified a variant of ER-β in these studies called ER-β5 that appears to inhibit ER-β's action. Additional details of the study can be found in *Oncology Reports* 7: 157-167 (2000).

Hormonal Control of HER2neu and BRCA1 in Breast Cancer

Unraveling how two genes involved in breast cancer, Her-2/neu and BRCA1, are turned on and off would provide critical clues to how the disease develops. **Wanda Reynolds, Ph.D.,** at the **Sidney Kimmel Cancer Center,** San Diego investigated the possibility that the Her-2/neu and BRCA1 genetic sequences have parts called Alu elements (AluHRE) which bind to hormones. If this is so, steroid hormones would turn the genes on and off. Dr. Reynolds found that the hormone estrogen bound to the AluHRE and increased the levels of both genes, but retinoic acid (Vitamin A) and thyroid hormone decreased the levels. The results support the theory that AluHRE plays a role in these genes getting turned on and off. One step in cells turning into cancer is breakage in their DNA. Dr. Reynolds investigated whether AluHRE were likely sites of DNA breakage, but found that this was not the case.

Research Conclusions

Apoptosis

Apoptosis is the internal mechanism of programmed death in normal cells. For example, apoptosis is the process the body uses to remove old white blood cells so they can be replaced with new ones, and to dissolve the cells between developing fingers in the human embryo.

Cancer cells have defects in apoptosis. Researchers believe this is why they are resistant to immune attack and chemotherapy treatment.

The process of apoptosis involves many sets of complex interactions between proteins inside cells. Cancer cells develop genetic mutations that alter these protein interactions. Intense research is underway to discover just which protein interactions allow cancer cells to avoid apoptosis, and to discover ways to bypass them. In the future, a woman might be pre-treated with a drug that enhances apoptosis to prime her breast cancer cells to die in response to another therapy.

A Novel Drug Induces Apoptosis in Breast Cancer Cells

When chemotherapy fails for the treatment of advanced breast cancer, it is in part because the tumor cells have mechanisms to evade programmed cell death (apoptosis). **Glenn Rosen, M.D.,** at **Stanford University,** Palo Alto found that a compound called Triptolide, derived from a Chinese herb, greatly enhances the effect of chemotherapuetic drugs. Triptolide works by suppressing the action of a protein from white blood cells, tumor necrosis factor (TNF). TNF turns on a series of protein interactions that inhibit cell death. In addition, Triptolide sends confusing messages for cell division; the cell responds by initiating cell death. Dr. Rosen reported this research in two publications in the *Journal of Biological Chemistry* 274:12451-13455 (1999) and 276: 2221-2227(2001). He is continuing these studies to determine the molecular site of Triptolide's action in breast cancer cells, and has applied for a patent for this approach in chemotherapy.

Fate Mapping of Progesterone Receptor Positive Breast Cells

The hormone progesterone and its receptor (the protein that allows cells to take it up) are intricately involved in guiding the development of the breast. However, the mechanism is unclear. **G. Shyamala, Ph.D.,** at the **Lawrence Berkeley National Laboratory,** Berkeley attempted to determine how cells that have progesterone receptors become distributed during breast development. She made genetically engineered mice that carried a 'tagged' progesterone receptor in the mammary gland. Due to unexpected difficulties, Dr. Shyamala was unable to follow the distribution of the progesterone receptor-tagged cells. However, she did find that the mammary glands in these mice grew much more slowly than their normal counterparts. This indicates that a part of the progesterone receptor can impede normal breast development.

Research Conclusions

p53 and the p53 Pathway

Several projects in this section deal with p53. The tumor suppressor p53 is a protein produced by both breast cancer cells and normal cells. When radiation or chemotherapy damages a cell's DNA, p53 springs into action and starts a complex process in the cell. This process, known as the p53 pathway, ultimately kills the cell. In breast cancer, p53 can become mutated so the cells no longer die after radiation or chemotherapy. BCRP funds research into p53 and proteins that could affect p53's action, to discover how to restore p53's cell-killing role and make breast cancer treatment more effective.

Regulation of Wnt: Clues for Breast Cancer Pathogenesis

Heidi Theisen, Ph.D., of the **University of California, Irvine** resigned for medical reasons before this study was completed . The goal of the project was to determine the series of genes that get turned on and off in cell growth, beginning with a protein made by a gene called Wnt. Dr. Theisen was examining the interaction between Wnt and a protein called TGF-β during cell division in the simpler developmental system of flies. She was attempting to pinpoint genes that behave similarly in human breast cancer development. She was able to develop the DNA she needed to insert into the flies before she had to resign.

The Regulation of p53 Activity in Breast Cancer

Yang Xu, Ph.D., from the **University of California, San Diego** resigned before this study was completed. Proteins in cells can be activated or de-activated when a molecule of phosphorus is added to them (phosphorylation). Dr. Xu planned to study the parts of a protein, tumor suppressor p53, where the phosphorus molecules can be added. Processes that lead to cell death could be influenced by changes in p53 phosphorylation specific to breast cancer. Even though most breast cancers appear to have normal p53, their p53 could have defects that keep them from attaching to the phosphorus molecule that would lead to cell death and other responses. Research begun with BCRP funding was published in the *EMBO Journal* 15:19 (2000).

Mistakes on the Master Blueprint: Molecular Genetics and Gene Regulation

Molecular Analysis of BRCA1

Mark Chapman, Ph.D., at the **Salk Institute for Biological Studies**, La Jolla investigated the ways in which the BRCA1 gene is involved in regulating other genes in the cell. When a woman has mutations in the BRCA1 gene, she runs a higher risk of breast cancer. Dr. Chapman studied the normal BRCA1 genes, which do not have the mutations that make breast cancer more likely. His hypothesis was that normal BRCA1 genes inhibit cell growth by turning on the p53 pathway, a complex process that eventually causes cell death. However, he found that BRCA1 is triggering additional processes that are more important than any action it causes by turning on p53. Dr. Chapman found a previously unidentified protein that interacts with both BRCA1 and BRCA2 genes and appears to amplify the effects of the genes.

Biochemical and Functional Characterization of BRCA1

The key hereditary breast cancer gene 1 (BRCA1) was cloned in 1994, but researchers haven't yet learned what the gene does or how it is regulated. **Heinz Ruffner, Ph.D.,** also from the **Salk Institute for Biological Studies,** La Jolla published a key study (*Molecular and Cellular Biology*, 19:4843, 1999) that demonstrated an interaction of a protein that regulates the normal process of cell growth and division, CDK2, with the BRCA1 protein. Apparently, CDK2 adds a molecule of phosphorus to the BRCA1 protein at a location on the protein structure known as serine residue 1497. Adding a molecule of phosphorus generally turns off or on a protein's function. Dr. Ruffner is continuing to investigate the function of CDK2's modification of BRCA1.

Research Conclusions

Siah-family Genes: Effectors of p53 in Breast Cancer

Simple organisms, such as fruit flies, yeast, and nematodes, have yielded clues to important cell regulatory genes that might be relevant to cancer biology. *Drosophila* (fruit fly) and *Caenorhabditis* (nematode worm) are animals that have strong regulatory mechanisms to control cell division. These mechanisms could be used to halt breast cancer growth. **Shu-ichi Matsuzawa, Ph.D.,** at **The Burnham Institute,** La Jolla explored the role of Siah genes, which are human counterparts of a family of *Drosophila* eye development genes. Dr. Matsuzawa found that Siah and proteins that interact with Siah work through a group of proteins that control the stability of an important protein, called β-catenin. β-catenin maintains the integrity of the normal epithelial cell layer. Most breast cancer develops in the breast's epithelial cells. Degradation of β-catenin allows tumor cells to escape control of the structure around them and to grow as cell masses. This process is better understood for colorectal cancer, but is also important for most breast cancers. Part of this research was published in the *EMBO Journal* 17:2736-2747 (1998).

Genes Involved in Multistep Mammary Tumorigenesis

Gregory Shackleford, Ph.D., of the **Children's Hospital, Los Angeles** took steps toward creating a mouse model that would identify genes involved in breast cancer development and serve as a tool to dissect the ways in which the genes interact. Dr. Shackleford genetically engineered mice to carry an inhibitor of a protein produced by breast cells, a growth factor called FGF (fibroblast growth factor). He mated these animals with a different line of genetically engineered mice carrying a gene, Wnt10b. Genetic pathways are combinations of genes that initiate some process in cells when they are turned on or off. Through future experiments, the team will determine whether the genetic pathways associated with FGF and Wnt10b work together to affect the growth of breast tumors and ultimately identify other genes involved in this process. Dr. Shackleford was co-author in a study reporting key findings from this funding, *Oncogene* 17:2711-2717 (1998).

Alteration of Developmental Genes in Breast Cancer

Fumiichiro Yamamoto, Ph.D., of **The Burnham Institute,** La Jolla investigated ways that genes can be turned on or off by a process called methylation. He also investigated developmental genes, called homeotic genes, that perform functions that are remarkably similar to those involved in tumor development. The goal was to determine whether developmental genes that are regulated by methylation play a role in tumor development. Dr. Yamamoto found that methylation is different in some homeotic genes, such as Hox B13 and IPF-I, in most breast cancer cases, when compared to normal tissue. However, these differences did not translate into mutations on the genes or changes in the levels of proteins the genes produced. Methylation inhibitors were able to decrease Hox B13 levels, and had varying effects on the levels of other homeotic genes. These results indicate that DNA methylation inhibitors may be poor candidates for use in breast cancer therapy.

Searching the Unknown: Novel Breast Cancer Genes

Identification of New Candidate Breast Cancer Genes

Breast cancer cells undergo dramatic deletions, duplications, and rearrangements of their chromosomal DNA, and these account for some of the increases and decreases in the amounts of gene-produced proteins measured in tissue samples from tumors. **Donna Albertson, Ph.D.,** first at **Lawrence Berkeley National Laboratory,** then at **University of California, San Francisco,** used a microscopic, direct visualization technique called fluorescence *in situ* hybridization (FISH) to examine breast cancers and identify novel genes and chromosomal regions. This search led to the discovery of a gene called ZNF217 that appears to be a key player in the immortilization of breast cancer cells, the

process that allows tumor cells to keep dividing after they have completed the normal number of divisions for breast cells (about 100). A gene physically associated with ZNF217, called CYP24, also appears to be important in breast cancer. Three publications were supported by this funding with the most recent in *Nature Genetics* 25:144-146 (2000). Dr. Albertson and colleagues are continuing to analyze the gene sequence of breast cancer using another technique, gene expression microarrays, which yields more information in a smaller amount of time.

Breast Carcinoma Associated MAR-binding Proteins p90 and p70

Sanjeev Galande, Ph.D., from the **Lawrence Berkeley National Laboratory,** Berkeley investigated how the attachment of chromosomal DNA to proteins in the nucleus of breast cancer cells differs from normal cells. Differences in the attachment of DNA on the chromosome could underlie larger differences in gene structure seen in breast cancer. Working with his mentor, **Dr. Terumi Kohwi-Shigematsu**, Dr. Galande unexpectedly identified a protein complex, previously associated with DNA repair, that seems to play a role in making the DNA in cancer cells different from that of normal cells. This complex is composed of two proteins, called PARP and DNA-dependent-protein kinase (DNA-PK), and is seen in increased amounts in breast cancer cells. Results from this research were published in the *Journal of Biological Chemistry* 274:20251 (1999) and *Critical Reviews of Eukaryotic Gene Expression* 10:63 (2000). Dr. Kohwi-Shigematsu is receiving further funding from BCRP to pursue this work.

Unraveling the Path to Breast Cancer: Tumor Progression

Does Cell Aging Cause Breast Cancer?

Breast epithelial cells are the cells where most breast cancer begins. They co-exist in the mammary gland with other cells called fibroblasts, which form the connective tissue framework of the gland. As the body ages, the supporting fibroblasts become less functional, senescent (elderly) cells.

Research Conclusions

Judith Campisi, Ph.D., from the **Lawrence Berkeley National Laboratory,** Berkeley showed that epithelial cells engineered to represent the early stages of breast cancer were stimulated by senescent fibroblasts, but not by normal fibroblasts. This shows that younger women have breast tissue barriers to prevent epithelial cells from developing into cancer. In contrast, older women have less functional control systems, which allows early cancers to emerge, divide, and go on to develop into more aggressive cancers. Dr. Campisi is continuing this work to identify the specific changes in aging fibroblasts that allow breast cancer, and to find the breast epithelial genes that normal fibroblasts most highly regulate.

Progesterone Receptor and Remodeling of Basement Membrane

The maintenance of mammary gland structure is important for the normal functioning of the epithelial cells (the cells both responsible for milk production and the origin of more than 95% of breast tumors). In the breast, epithelial cells lie on a complex structure called the basement membrane, which is composed partly of collagen. Factors that affect the integrity of the basement membrane can have a significant effect on the development of breast tumors. **G. Shyamala, Ph.D.,** at the **Lawrence Berkeley National Laboratory,** Berkeley created genetically-engineered mice to test the hypothesis that the steroid hormone progesterone is involved in the integrity of the basement membrane. She found that mice with excess progesterone receptor-A lacked appropriate amounts of basement membrane components. This caused the epithelial cells to form abnormal structures. This study emphasizes the necessity for considering the effects of progesterone when devising hormonal therapies.

Proteolysis of Cyclin E in Normal and Malignant Breast Cells

Heimo Strohmaier, Ph.D., from **The Scripps Research Institute,** La Jolla studied the underlying molecular mechanism that allows breast cancer cells to have elevated amounts of a protein that promotes cell division, cyclin E. Using yeast cells as a model system, the team identified a protein called Cdc4, which appears to be a key factor that regulates the cell quantities of cyclin E. Next, they plan to identify the proteins and groups of interacting proteins that control cyclin E production in human breast cancer cells.

Research in Progress

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

- **Breast Cancer Cell Binding to the Endothelium. Brunhilde Felding-Habermann, Ph.D.,** from **The Scripps Research Institute,** La Jolla is finding that in the final stage of spreading to another part body, breast cancer cells appear to interact with cells in the blood called the platelets. Integrin receptors are substances found in both normal breast cells and cancer cells; in normal cells integrin receptors help keep the cell in place, but they play a role in the spread of breast cancer cells. Dr. Felding-Habermann found that the integrin receptor on breast cancer cells, called $\alpha_v\beta_3$, can exist in both an activated and de-actived state. Only the activated form of $\alpha_v\beta_3$ will support the interaction of breast cancer cells with the endothelial cells that line blood vessels, which is one step in cancer's spread. If ways of blocking this process were discovered, then breast cancer would be less capable of spreading.
- **Spatial Control of Matrix Proteolysis in Breast Cancer. Alex Strongin, Ph.D.,** at **The Burnham Institute**, La Jolla found that the integrin receptor $\alpha_v\beta_3$ appears to bind directly with a protein, the matrix metalloproteinase MMP-2, which is found in the structural framework that surrounds breast cells. This binding is one of the interactions that makes it possible for tumor cells to move from the breast into the blood and to other parts of the body. These results were published in the *International Journal of Cancer* 86:15-23 (2000).
- **How Does Endostatin Inhibit Breast Cancer Angiogenesis?** Endostatin is an anti-angiogenic protein (a protein that inhibits the formation of blood vessels). A large amount of research is being done on it, because it eliminates cancer in mice without side effects or creating tumors resis-

tant to it. However, researchers don't understand very clearly how it works. **Kristiina Vuori, M.D., Ph.D.,** at **The Burnham Institute,** La Jolla reports that endostatin binds with two integrin adhesion receptors found on the surface of cells that line blood vessels. It appears that the endostatin-integrin binding is involved in some as-yet-undiscovered function of integrin receptors. The results of these studies are in press in the *Proceedings National Academy Sciences, USA*.

Too Much Cell Growth: Defective Messages and Internal Signaling

- **Role of the EphB4 Receptor Tyrosine Kinase in Breast Cancer. Elena Pasquale, Ph.D.,** at **The Burnham Institute,** La Jolla is investigating whether a protein called EphB4 makes tumors more aggressive. EphB4 regulates the normal developmental processes of cell adhesion and movement in human and animal embryos. It is also present in human breast cancer cell lines and in aggressive mouse tumors, as well as mouse tumors that are spreading to other parts of the body. Dr. Pasquale has made cells with decreased EphB4 activity. Because these cells are engineered to appear green, their location and movement can be directly visualized. Dr. Pasquale has also made the unexpected observation that increased EphB4 can stop cell growth.
- **GATA-3 Expression in Hormone Responsive Breast Cancer.** The protein GATA-3 is elevated in tumors that grow faster when the hormones estrogen and progesterone are present. The chemotherapy drug tamoxifen works by blocking estrogen; apparently, GATA-3 is involved in tumors developing resistance to tamoxifen therapy. **Ronald Weigel, M.D., Ph.D.,** at **Stanford University,** Palo Alto is investigating whether GATA-3 binds

with the estrogen receptor (a protein that allows a cell to take up estrogen), if the binding decreases cell levels of GATA-3, and if lower levels of GATA-3 allow the cell to evade the effect of tamoxifen. He found that GATA-3 and the estrogen receptor do not bind directly, but they may interact through an intermediary protein. Loss of GATA-3 function does not appear to explain tamoxifen resistance, but Dr. Weigel is pursuing the idea that there may still be another breakdown in the GATA-3 mechanism of action.

Searching the Unknown: Novel Breast Cancer Genes

- **Role of DNA Damage Response Gene in Breast Cancer. Eric Brown, Ph.D.,** at the **California Institute of Technology,** Pasadena is studying a gene, called ATR, that may regulate how efficiently cells can repair DNA damage. Cells with DNA damage tend to turn into cancer. If ATR regulates cell repair of DNA damage, the gene could be critical for restraining the growth of cancer and pre-cancer cells.

Unraveling the Path to Breast Cancer: Tumor Progression

- **TGF-β Receptor Signaling and Breast Cancer.** Signaling proteins turn on changes inside the cell after a receptor protein has bound to a substance from outside the cell. **Kunxin Luo, Ph.D.,** at the **Lawrence Berkeley National Laboratory,** Berkeley discovered two new signaling proteins

called SnoN and Ski. These proteins are able to block the cell growth inhibition caused by a protein called TGF-β. Dr. Luo is continuing to investigate how these proteins exert their control over TGF-β and their influence on normal and tumor breast cell development.

- **Role of a DNA Damage Response Gene in Breast Cancer.** One step normal cells go through on the way to becoming cancer cells is immortalization, where they escape from the fixed number of divisions that limit the life of most cells. **Martha Stampfer, Ph.D.,** at the **Lawrence Berkeley National Laboratory,** Berkeley originally set out to identify new genes that were activated or deactivated during the process of cell immortalization. However, during the course of the investigation, Dr. Stampfer noticed that the activation of a cancer gene called raf1 stops growth in mortal cells, but it pushes immortal cells further on the path toward becoming cancer. Her team is continuing to investigate why raf1 has these differing effects.

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

- **Analysis of Genes Predictive of Breast Cancer Metastasis. Jeffrey Gregg, M.D.,** from the **University of California, Davis** is following up on an observation about experimental mouse tumors with an enzyme called phosphoinositol kinase 3 (PI-3 kinase). When PI-3-kinase is turned on, the tumors will spread more often to the lung than to other parts of the body. PI-3 kinase works by activating a series of other enzymes and proteins. Dr. Gregg is using several screening techniques to determine which of these other proteins are directly involved in the spread of cancer.
- **Profiling Serine Protease Activities in Breast Cancer** and **Identifying Breast Cancer Targets for Protease Inhibitors.** Proteases are proteins that digest other proteins and allow cells to move. **Benjamin Cravatt, Ph.D.,** and **Yongsheng Liu, Ph.D.,** at **The Scripps Research Institute,** La Jolla are identifying and studying proteases specific to breast cancer. They are using a novel chemical strategy developed in Dr. Cravatt's laboratory, termed Activity-Based Protein Profiling (ABPP). This technique allows them to monitor not just the amount, but the activity of many proteases simultaneously in samples of whole cells, the experimental media surrounding the cells, and tissues. Dr. Cravatt and Dr. Liu will also try to understand why lower levels of estrogen receptor proteins make cancer cells less likely to spread.
- **Role of Matrix Metalloproteinases in Breast Tumor Initiation and Aggressiveness. Jimmie Fata, Ph.D.,** at the **Lawrence Berkeley National Laboratory,** Berkeley will also study how the type of protein called proteases plows a path for cancer cells to migrate. Dr. Fata will investigate a process called epithelio-mesenchymal transdifferentiation (EMT), which is associated with aggressive breast cancer. In this process, epithelial cells (the cell type responsible for more than 90% of breast cancers) become more like another type of cells called fibroblasts. In contrast to epithelial cells, fibroblasts are very mobile and less tightly associated with other cells. Thus, as epithelial cells become more like fibroblasts, they gain the ability to move and spread.
- **TGF-β3 and small GTPases in Invasive Breast Cancer. Vesa Kaartinen, Ph.D.,** of the **Children's Hospital, Los Angeles** is also investigating the EMT process where breast epi-

thelial cells become more like fibroblasts, and become more able to move. Dr. Kaartinen is investigating the role in the EMT process of three types of protein: transforming growth factors (TGF-β3), adhesion molecules (integrins), and signaling molecules (GTPases).

- **Analysis of Angiogenic Pathways in Metastatic Breast Cancer. Elizabeth Hindmarsh, Ph.D.,** at **The Burnham Institute,** La Jolla plans to use gene chip microarrays, a technique that allows her to measure proteins produced by 10,000 genes at a time. She'll compare the proteins produced by genes–from normal tissues, breast tumors and breast cancer that has spread to various organs–to determine which genes are involved with the growth of blood vessels.
- **The Role of IL-8 and Its Receptors in Angiogenesis.** Interleukin-8 (IL-8) is a substance produced in the human body known for its role in inflammatory diseases, where it attracts white blood cells into an area of tissue injury. Interestingly, IL-8 is produced by breast cancer cells. **Ingrid Schraufstatter, M.D.,** from the **La Jolla Institute for Experimental Medicine,** will investigate whether IL-8 stimulates cells that line nearby blood vessels to promote the growth of blood vessels that nourish tumors.
- **Cell Adhesion and Drug Resistance in Breast Cancer.** Breast cancer cells can sometimes avoid being killed by chemotherapy, but researchers don't know how. **Kristiina Vuori, M.D., Ph.D.,** at **The Burnham Institute,** La Jolla will attempt to address this issue. She will examine whether the local micro-environment of breast cancer cells could provide a protein that either allows cancer cells to survive chemotherapy, or blocks the cell death process after chemotherapy.

Too Much Cell Growth: Defective Messages and Internal Signaling

- **The Control of Breast Cancer Cell Death. Daria Mochly-Rosen, Ph.D.,** from **Stanford University,** Palo Alto will study the protein kinase C (PKC) family of enzymes. She will identify the member or members of the PKC family that allow breast cancer cells to live and form tumors. Then, her lab will test compounds to inhibit these specific PKC enzymes, looking for potential new breast cancer drugs.

Research Initiated in 2000

- **A Novel Signal Transduction Pathway in Breast Cancer.** Previous research has identified a unique response mechanism breast cancer cells use to evade the body's immune system. A series of interactions between proteins and genes, called NF-κB appears to be involved. **Yixue Cao, M.D., Ph.D.,** at the **University of California, San Diego** will use yeast as a model system to determine how NF-κB can become dysfunctional in breast cancer.
- **Anti-E-Cadherin Apoptosis of Inflammatory Breast Carcinoma. Mary Alpaugh, Ph.D.,** at the **University of California, Los Angeles- School of Medicine** will use a unique mouse model to study inflammatory breast cancer, an unusual type of the disease that invades many nearby blood and lymphatic vessels.
- **Novel Mechanisms of ErbB-2-Mediated Breast Cancer Metastasis.** Her-2/neu is a gene involved in cell growth in some types of breast cancer. **Richard Klemke, Ph.D.,** at **The Scripps Research Institute,** La Jolla will investigate how specific segments of the protein produced by the Her-2/neu gene activate interactions between other proteins inside breast cancer cells. He will also see if the interactions are the same in breast cancer cells that migrate to other body parts.
- **The Role of the BMK1-MEKK3 Pathway in Breast Cancer. Ta-Hsiang Chao, Ph.D.,** also from **The Scripps Research Institute,** La Jolla is investigating cell growth related to the Her-2/neu cancer gene. Dr. Chao will use a yeast system to identify and isolate a key protein that turns on a series of interactions between genes and proteins that makes cells grow. The goals are to design compounds that inhibit breast cancer cells, but not normal cells, and to better understand the molecular nature of these gene-protein interactions that may be involved with breast cancer spreading.
- **Studies on the Role of the ER-β in Breast Cancer.** ER-α and ER-β are two estrogen receptors, proteins that allow cells to take up the hormone estrogen, triggering a process involved in cell growth. **Eli Gilad, Ph.D.,** from the **Lawrence Berkeley National Laboratory,** Berkeley will explore situations where both ER-α and ER-β are present in the same cell, and see how they stimulate cell growth responses.
- **Cell Growth Control of Breast Epithelial Cells. Ulla Knaus, Ph.D.,** at **The Scripps Research Institute,** La Jolla will investigate the observation that a protein that is consistently active in human breast cancer cells, called Rac3, is required for tumor cells to grow and spread, while a related protein, Rac1, is not. In normal breast cells, Rac3 and Rac1 are turned on by hormones and by proteins called growth factors that come from outside the

cells. However, since Rac3 is consistently turned on in tumors, it may be tricking cells into growing at inappropriate times. Rac3 does not have mutations, so Dr. Knaus is looking at alternative ways that Rac3's normal function can be altered. The possibilities include Rac3 changing location within the cell and Rac3 interacting with other proteins to stimulate cells to grow and spread.

Searching the Unknown: Novel Breast Cancer Genes

- **DNA Packaging Defects in Breast Cancer. Terumi Kohwi-Shigematsu, Ph.D.,** from the **Lawrence Berkeley National Laboratory,** Berkeley is continuing research developed with prior BCRP funding to study how chromosomal DNA is attached to proteins in the cell nucleus. This attachment provides structure to the long, looping DNA molecule. Dr. Kohwi-Shigematsu will explore the role of a protein complex, previously thought to be involved in DNA repair, as a key player in changes in DNA function in breast cancer.
- **Metastasis Suppressor Genes for Breast Cancer. Stanley Cohen, M.D.,** at **Stanford University-School of Medicine,** Palo Alto will attempt to discover novel tumor suppressor genes, which might be a means to inhibit breast cancer growth and progression. He is looking for a gene that, when de-activated, turns on the genetic changes that lead to breast cancer spread. He will use a novel cloning method and DNA microarrays, a technique that allows testing a tissue sample for many genes at once. When he finds a possible suppressor gene, he will check to see if it is missing in breast cancer cells, then test to see if inserting it in breast cancer cells makes them behave more like normal cells.
- **Suppressor Genes of Breast Cancer. Shi Huang, Ph.D.,** at **The Burnham Institute,** La Jolla will test whether three genes, and the proteins they produce that regulate the activity of genes, PFM4, PFM7, and PFM11, are suppressors of breast cancer.
- **A Novel Antigen Associated with Breast Cancer Metastasis.** Monoclonal antibodies can be made in the laboratory; they bond with a single protein on breast cancer cells. The proteins antibodies bond with are called antigens. **Jacqueline Testa, Ph.D.,** from the **Sidney Kimmel Cancer Center**, San Diego has made a monoclonal antibody called mAb 41-2 that recognizes a breast cancer antigen and blocks the spread of cancer cells. Dr. Testa is planning to characterize the structure and precise function of this newly discovered antigen in

the hopes that it will eventually serve either as a biomarker (a substance present in tumors that helps physicians determine the most effective treatment) or as a therapeutic target.

- **Tumor Suppression by Dystroglycan in Breast Epithelial Cells.** Dystroglycan is a protein found on the surface of breast epithelial cells that allows the cells to attach to a protein called laminin outside the cells. It appears that dystroglycan is either absent or not working in breast cancer cells. **John Muschler, Ph.D.,** from the **Lawrence Berkeley National Laboratory,** Berkeley will study whether introducing dystroglycan into breast cancer cells changes them into more normal cells. He also plans to test variant forms of dystroglycan to discover which parts of dystroglycan's chemical structure are responsible for this action.
- **Analysis of a New Human Caspase in Breast Cancer.** Caspases are proteins that split other proteins, causing the normal process of cell death (apoptosis). Each caspase may link a particular cell death stimulus—such as radiation, chemotherapy, or the body's immune system—to a specific series of chemical changes in the cell death process. **Sug Hyung Lee, M.D., Ph.D.,** at **The Burnham Institute,** La Jolla will clone and study a new human caspase that was initially discovered in mice.

Unraveling the Path to Breast Cancer: Tumor Progression

- **Role of p53 in Irradiated Stroma and Mammary Carcinogenesis.** By the time a breast tumor can be detected, it has developed for up to 10 years and its genes have changed to allow it to escape normal control processes. The slow progression from normal cell through the pre-cancerous and early cancerous stages is not well understood. **Mary Helen Barcellos-Hoff, Ph.D.,** at the **Lawrence Berkeley National Laboratory,** Berkeley focuses on this topic, as do the two studies discussed immediately below. Ionizing radiation such as x-rays can cause cancerous changes in breast cells. Most studies concentrate on the genetic changes in epithelial cells, but radiation may change other cell types in the breast. The p53 gene tends to be mutated by radiation and is also mutated in many breast tumors. Dr. Barcellos-Hoff is investigating whether radiation causes p53 mutations in the stromal cells that are part of the framework that supports breast epithelial cells.

Research Initiated in 2000

- **A Study of the Molecular Heterogeneity of LCIS.** Women who have the breast disease lobular carcinoma *in situ* (LCIS) have an increased breast cancer risk. However LCIS may actually be several diseases, and only a subset of them may lead to a high risk for breast cancer. **Sanford Barsky, M.D.,** from the **University of California, Los Angeles** will use molecular analysis and statistical analyses to correlate breast cancer risk with the different types of LCIS.
- **Immortalization of Human Mammary Epithelial Cells by ZNF217.** The ZNF217 gene is present at higher than normal levels in many breast tumor cells, and it allows cells to continue dividing past their normal limits. **Paul Yaswen, Ph.D.,** at the **Lawrence Berkeley National Laboratory,** Berkeley will investigate how ZNF217 affects proteins that suppress tumors, cell growth control processes, cell genes, and the internal skeleton of cells.

Gene-Chips

Recently, researchers completed the initial mapping of the human genome; we possess about 30,000 genes. But which genes cause breast cancer? And how genetically different are individual cases of breast cancer? We know there must be a large number of breast cancer subtypes, because women differ dramatically in their response to various therapies. Gene differences in breast tumors are likely to be subtle. A given gene may be present in amounts only slightly different from normal cells.

A new technique called gene-chips, also known as DNA microarray, is helping answer these questions. Thousands of fragments of DNA from known genes are placed as tiny dots on a glass slide (or other surface) with a grid pattern. The researcher adds a sample prepared from a tumor. If the tumor sample has DNA or RNA material identical to a spot on the gene-chip, it will bind to it and be detected by special fluorescent dyes. In minutes to a few hours, the gene-chip will display a complex pattern of small spots in varied colors that represent the amount of each gene in the tumor sample. Comparing the tumor pattern to a sample of normal breast tissue provides a complete catalog of genetic changes in cancer cells.

Within a few years, refinement of gene chips may allow cancer specialists to more accurately classify breast cancer, make critical treatment decisions, and follow a tumor's response to treatment.

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Prevention: Ending the Danger

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

- **Diet and Other Active Lifestyle Modification: What Women Can Do Now.** Because our diet is something we can change, many of the studies we fund explore the components of the diet that increase or decrease the risk of breast cancer.
- **Safer Preventive Drugs: Investigating Naturally Occurring Compounds.** The chemotherapy drugs currently available for prevention do not have ideal risk/benefit ratios. BCRP studies investigate compounds from food that show potential for preventing breast cancer.
- **Hormones or Environmental Contamination Interacting with Known Risk Factors.** The connection between environmental contaminants and breast cancer is difficult to prove, because the interactions between cancer-causing substances in the environment and breast tissue are complex. Our studies are designed to investigate those complex interactions, identify those most susceptible to cancer-causing environmental substances and devise prevention methods.

Diet and Other Active Lifestyle Modification: What Women Can Do Now

Alteration of Dietary Fat to Reduce Breast Cancer Metastasis

Previous studies with human cell lines have indicated that some types of dietary fat can decrease the ability of breast tumors to grow or spread to other parts of the body. **Kent L. Erickson, Ph.D.,** of the **University of California, Davis** looked for the mechanism behind this effect. He asked, does fish oil with n-3 fatty acid (found in most fish, with higher levels in salmon, tuna and lake trout) decrease breast tumors' ability to stimulate blood vessel growth? And does it decrease the level of specific proteins tumors need to grow and spread? The answer is yes to both questions. Dr. Erickson's results indicated that fish oils may decrease tumor cells' ability to lodge in the lung. Fish oil decreases the number of macrophages, a type of white blood cell, in breast tumors. Macrophages produce a specific protein that tumors appear to need to make their blood vessels grow. Decreasing a tumor's ability to grow blood vessels appears to limit the tumor's ability to grow and spread. Dr. Erickson also found that tumors produce a unique enzyme necessary for blood vessel growth. The enzyme increases in animals fed safflower diets and is inhibited in animals fed fish oil diets. This research strengthens the theory that altering dietary fat can be used as an additional therapy at any stage of breast cancer.

Safer Preventive Drugs: Investigating Naturally Occurring Compounds

Analogs of Tea Polyphenols for Breast Cancer Chemoprevention

Previous reserach has suggested that a compound in green tea, epigallocatechin-3-gallate (EGCG), could potentially be used to prevent or treat cancer. However, to get a therapeutic effect, a woman would need to drink 8-10 cups of green tea per day. **Nurulain Zaveri, Ph.D.**, of **SRI International,** Menlo Park modified the complex chemical structure of EGCG to derive similar, more potent compounds. The lead compound, SR 13197, attacks tumors by killing the inner cells of tumor blood vessels, thus decreasing the tumor's blood supply. BCRP is funding Dr. Zaveri over the coming year to further develop compounds derived from EGCG.

Safer Preventive Drugs: Investigating Naturally Occurring Compounds

- **Breast Cancer Prevention with Phytoestrogens in Grape Juice. Shiuan Chen, Ph.D.,** at the **Beckman Research Institute, City of Hope,** Duarte is testing compounds isolated from red grape juice for their ability to prevent tumor formation in animal cell lines. He is also investigating whether these red grape juice-derived compounds inhibit aromatase, an enzyme that generates estrogen. His work is aimed toward discovering whether the most potent grape juice-derived compounds will either prevent cancer cells from forming, or eradicate them once they form, or both. The goals include a possible preventive medication for post-menopausal women.
- **Dietary Indole Analogs for Breast Cancer Prevention.** Indole-3-carbinol–found in cruciferous vegetables, such as cabbage, broccoli, and brussels sprouts–is a promising breast cancer preventive. **Ling Jong, Ph.D.,** at **SRI International,** Menlo Park has varied the structure of one of the major forms of Indole-3-carbinol that is active in the digestive tract. She tested the resulting compounds in a breast cancer cell line for anti-tumor activity. Two compounds showed the highest anti-tumor activity. Dr. Jong will test them in animal models over the coming year.

Research in Progress

Diet and Other Active Lifestyle Modification: What Women Can Do Now

- **Diet & Breast Cancer in the California Teachers Study Cohort. Pamela Horn-Ross, Ph.D.,** of the **Northern California Cancer Center,** Union City is analyzing data on the diets of women who are part of the California Teachers Study. This statewide study is following a large group of teachers over time, tracking which women develop cancer, and gathering other information about the women's lives. Preliminary analysis suggests that the diet over the previous year may not influence the development of breast cancer. However, Dr. Horn-Ross needs to complete substantial additional analyses of the data during 2001.

Diet and Other Active Lifestyle Modification: What Women Can Do Now

- **Bovine Leukemia Virus Infection and Human Breast Cancer Risk. Gertrude Buehring, Ph.D.,** at the **University of California, Berkeley** has previously shown that a majority of women have antibodies to bovine leukemia virus. This virus is found in beef and milk and can be transmitted to humans. It causes mammary tumors in animals. The antibodies in women may be a response to a live virus, or to a harmless, de-activated part of the virus, and it isn't possible to determine which through laboratory testing. Therefore, Dr. Buehring will begin to test the speculative hypothesis that bovine leukemia virus is associated with an increased risk of breast cancer. She is using a case-control study of 338 women to see if women with breast cancer are more likely to have the virus in their breast tissue than women with no history of breast cancer.

Safer Preventive Drugs: Investigating Naturally Occurring Compounds

- **Mechanisms of Reduced Metastasis by Conjugated Linoleic Acid.** Conjugated linoleic acid is a naturally-occurring compound found in some sources of dietary fat, including beef and dairy products. In small amounts, it has been shown to reduce the spread of mammary cancer in mice. **Kent L. Erickson, Ph.D.,** of the **University of California, Davis** is investigating how conjugated linoleic acid can reduce a tumor's ability to form blood vessels it needs in order to grow. He is also investigating how conjugated linoleic acid reduces a tumor's ability to make compounds that enable tumor cells to travel and take root in other parts of the body.
- **Breast Cancer Prevention by Analogs of EGCG from Green Tea. Nurulain Zaveri, Ph.D.,** at **SRI International,** Menlo Park is building on previous successful BCRP-funded research to improve the breast cancer preventive action of a compound found in green tea, epigallocatechin-3-gallate (EGCG). She will test individual components of EGCG for their

ability to inhibit cell growth in a breast cancer cell line. Next, she will modify the most active components to make them more potent or to introduce characteristics that make the modified components easier for the body to absorb and use. The eventual goal is a medication that will be more effective, and have fewer side effects, than the current breast cancer prevention drug, tamoxifen.

How Hormones or Enviromental Contaminants Interact with Known Risk Factors

- **Upregulation of BRCA1 as a Cancer Preventive Strategy.** Abnormal BRCA1 genes predispose women to breast cancer. In theory, the normal BRCA1 gene produces a protein that makes cells resistant to cancer. **Donna Williams-Hill, Ph.D.,** of the **University of Southern California,** Los Angeles is investigating how altering the levels of hormones surrounding the normal BRCA1 gene affects the gene's ability to produce this protein. She is altering hormone levels in female rats, measuring the level of protein produced by the BRCA1 gene, then determining how much mammary cancer the cells develop under the varying hormonal conditions. She will also analyze normal and cancerous human breast tissue (obtained under another BCRP-funded study) for levels of BRCA1-produced protein.
- **Genetic and Environmental Modifiers of Breast Cancer Risk. Argyrios Ziogas, Ph.D.,** of the **University of California, Irvine**, will investigate how two types of genes interact to raise or lower breast cancer risk. The first type of genes are BRCA1 and BRCA2, on which abnormalities are already known to increase a woman's risk of breast cancer. The second type of gene interacts with cancer-causing chemicals in the environment and may elevate breast cancer risk. Dr. Ziogas will use data from the unique resource of a breast and ovarian cancer registry of 1,176 families, a questionnaire providing environmental exposure and lifestyle information, and analysis of the families' genes. Results should add to our understanding of the BRCA genes' role in breast cancer, and of interactions between BRCA genes and genes that interact with environmental contaminants. This could lead to improved individualized risk prediction, and targeted preventive strategies.

Research Initiated in 2000

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

Socio-Cultural, Behavioral and Psychological Issues: The Human Side

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Socio-Cultural, Behavioral and Psychological Issues: The Human Side

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

Research in Progress

- **Do Community Cancer Groups Enhance Well-Being? Matthew J. Cordova, Ph.D.,** at **Stanford University,** Palo Alto is examining how past traumas and current social support influence how women with breast cancer think and feel about the disease. He is also investigating whether support groups are helpful, and, if so, what aspects are most helpful. At the half-way point in the study, he has found that cancer patients who write about their cancer experience using more cognitive words and fewer emotional words report greater emotional distress. He has also found that patients who have higher confidence in managing their feelings about cancer are more likely to use a fighting spirit to decrease their emotional distress.
- **Effectiveness of Electronic Support Groups for Breast Cancer. Morton Lieberman, Ph.D.,** of the **University of California, San Francisco** is engaged in a pilot study to determine whether support can be provided at a therapeutically effective level over the Internet. If it can, he is also investigating how Internet support differs from traditional face-to-face support. Preliminary findings suggest that on-line groups can, over time, develop in the direction of providing therapeutically effective support. One important factor seems to be the behavior of the on-line group leader. When leaders express inclusiveness and positive emotions, and also limit tentativeness, it leads to a more cohesive group. Members' expression of positive emotions are maximized by leader expression of positive emotions and low rates of anxiety and sadness. Dr. Lieberman will use the results of this pilot study to design a larger and more definitive study.
- **Alternative Support for Rural and Isolated Women in an HMO. Cheryl Koopman, Ph.D., Stanford University,** Palo Alto and **Mary Anne Kreshka, M.A., Sierra Nevada Memorial Hospital Cancer Center**, Nevada City are investigating a support alternative for women with breast cancer who are psychologically, socially or geographically isolated. The team is adapting a workbook-journal developed in a pilot BCRP study. They have revised the workbook-journal based on three focus group meetings, a

literature review, and feedback from the pilot study. The revision added two new sections: "Feeling Alone," and "Spirituality." They are ready for the major data collection phase of the study, to determine whether women who receive the workbook-journal will show reduced distress and improved coping, as compared to a control group. The team will also examine characteristics of women who benefit most from the workbook-journal.

- **Breast Cancer Survivorship: Partner's Role in Recovery.** The transition from being a breast cancer patient on active treatment to being a survivor on long-term follow-up can be upsetting and disruptive. This is especially true for women who don't get support from their intimate partners. **Beth E. Meyerowitz, Ph.D.,** of the **University of Southern California,** Los Angeles is investigating how partners' reactions during this transition relate to patients' quality of life, relationship adjustment, personal growth, and coping. During the project's first year, she developed, designed and printed questionnaires. She has begun recruiting women with breast cancer and their partners. Understanding the role that partners play in patient adjustment will enable medical teams to provide couples with information to enhance quality of life and communication.
- **Beliefs and Risks of Breast Cancer Among African Immigrants.** Cultural beliefs affect women's health care behavior. Understanding cultural beliefs can help shed light on why some groups of women don't get early detection services and tend to consult a doctor when their disease has progressed to later stages. **Yewoubdar Beyene, Ph.D.**, of the **University of California, San Francisco** is undertaking a qualitative anthropological study. She will identify culturally-specific factors that influence how African immigrant women in California understand breast cancer symptoms and perceive their risks, as well as how these beliefs create barriers to early detection. Initial findings, based on focus group interviews, indicate that immigrant African women do not generally feel comfortable with breast self-examination, because touching the breast is considered sexual. They often associate breast cancer with death. African immi-

Quality of Life

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

grant women generally have little knowledge about treatments available when a diagnosis is made early. The most common consequence of breast cancer they mention and fear is mastectomy. Many Africans believe in reincarnation and that a person who has body parts removed will return with those body parts missing. As the study continues, it will provide information vital for developing culturally-appropriate education guidelines for early detection of breast cancer in African immigrant communities.

- **Tamoxifen Prevention: Is it Acceptable to Women at Risk?** The chemotherapy drug tamoxifen has been shown to reduce the incidence of breast cancer in women at high risk for the disease who have been enrolled in clinical trials. However, numerous concerns remain about tamoxifen's potential adverse effects and the drug's benefits for high-risk women in the general population. **Joy Melnikow, M.D., M.P.H.,** of the **University of California, Davis** is developing a deeper understanding of how women at high risk of breast cancer weigh the risks and benefits of tamoxifen. In the first year of a three-year project, she has begun to determine the degree to which breast cancer risk, calculated with a risk-screening tool developed by the National Cancer Institute, is correlated with self-perceived risk of breast cancer. She has also started to develop an educational script, which includes a flip chart and color-coded beads to represent probability of risk, to be used to educate women at high risk for breast cancer about the potential benefits and risks of tamoxifen. In addition, she has started to assess how women's underlying attitudes towards tamoxifen-related outcomes may influence their decisions about taking tamoxifen to reduce their breast cancer risk. Over the next year, she will interview a diverse group of approximately 450 women in English or Spanish.

Research Initiated in 2000

- **A Patient Decision Support Framework for Breast Cancer.** It's difficult for physicians to pinpoint the best treatment for breast cancer today. For example, chemotherapy only benefits approximately 10% of patients, and physicians are searching for ways to identify those women. **C. Anthony Hunt, Ph.D.,** from the **University of California, San Francisco** is attempting to demonstrate the feasibility of a computerized process to aid physicians and women with breast cancer in making decisions about treatment. The process allows the physician to input personal information about a patient (such as age, ethnic group, family history of breast cancer) and information about her tumor, including the tumor's size, stage, and a large amount of information about the tumor's genes and proteins. The computer process then predicts the possible risks and benefits of various treatments, using available information about outcomes for patients with similar personal and tumor characteristics. The information about possible treatment outcomes is presented in computer graphics that can be understood by both patient and physician. This research is designed to allow physicians in the future to optimize breast tumor treatments for individual patients, reduce errors, and improve outcomes, with considerable cost savings for women affected by breast cancer and society.

- **Mechanisms of Radiation-Induced Fatigue in Breast Cancer.** Breast-conserving surgery followed by radiation is a treatment option selected by more than half of breast cancer patients. One of the most common side effects of radiation therapy is fatigue. Fatigue is not typically debilitating. However, it can interfere with daily activities, and significantly impair quality of life, mood, and social relations. This all comes at a time when women are trying to cope with the demands of diagnosis and treatment. **Julienne Bower, Ph.D.,** at the **University of California, Los Angeles** will study factors that may contribute to fatigue. She will investigate how psychological and behavioral responses to breast cancer may impact fatigue. She will also consider biological factors, such as radiation-induced changes in the immune system, that may also contribute to fatigue. The goals are to advance understanding of radiation-induced fatigue, and point toward interventions to reduce this symptom. Another goal is to develop ways to identify women at risk for long-term fatigue, who could benefit from intervention at an earlier stage.
- **Cognitive Changes After Adjuvant Therapy for Breast Cancer.** Many breast cancer patients who receive chemotherapy say that they suffer memory and concentration problems, even years after therapy. Some recent publications also suggest that cognitive deficits may

occur in women treated with high-dose or standard post-operative chemotherapy. **Rebecca Rausch, Ph.D.,** also at the **University of California, Los Angeles** will evaluate possible cognitive changes in four groups: 1) breast cancer patients receiving standard-dose adjuvant chemotherapy after surgery; 2) breast cancer patients treated with anti-estrogen (tamoxifen) therapy after surgery; 3) breast cancer patients not treated with chemotherapy or hormonal therapy; and 4) healthy women with no history of cancer. Dr. Rausch will also investigate the relationship of any cognitive impairments to hormone changes induced by therapy, and assess the role of factors such as menstrual history, age, educational level and tumor stage.

- **Communicating Breast Cancer Risk in Ethnically Diverse Women.** Women can now take the chemotherapy drug tamoxifen to reduce their risk of breast cancer. Other preventive medications are likely to become available. **Linda Lillington, R.N., D.N.Sc.,** at **Harbor-UCLA Research & Education Institute** will investigate how best to communicate complex issues about breast cancer risk reduction. Patients need education to make informed decisions about risk-reduction therapy with their health care providers. Careful consideration must be given to individual risk factors and the potential risks and benefits of prescribed treatments. There are currently no educational materials that health care providers can use to effectively present quantitative information about recent breast cancer prevention results to ethnic minority women. Dr. Lillington will develop, and begin evaluating, educational materials written at a 6th grade level and designed to give English-speaking and Spanish-speaking women at a public hospital a clear understanding of the risks and benefits of taking tamoxifen to reduce their risk of breast cancer.
- **Breast Cancer Prevention: The Views of Women and Physicians. Celia Kaplan, Ph.D.,** of the **University of California, San Francisco** will investigate how doctors advise their patients about breast cancer risk, and the knowledge, attitudes and practices of women and physicians with regard to breast cancer prevention. She will conduct a telephone survey of 1200 women ages 40-75, from four ethnic groups, who have recently had mammograms. Women at high and low risk of breast cancer from each ethnic group will be included in the survey. Dr. Kaplan will also survey 1000 randomly selected Bay Area physicians about their views on obstacles to breast cancer prevention.

BCRP Staff

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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 to be funded. In each Grant Cycle, BCRP awards grants based on the Council's recommendations, which are based on peer reviewers' evaluations, Council members' assessment of responsiveness to program priorities, and available funds.

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

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

Breast Cancer Research Council

List of Council Members:
Column 1: Chair / Vice Chair 2001 - 2002: Mary Ann Jordan, Barbara Brenner
Column 2: Chair / Vice Chair 2000 - 2001: Anne Wallace, Floretta Chisom
Column 3: Advocates: Vicki Boriak, Akua Jitahadi, Michele Rakoff








From Left to Right:
Row 1: **Advocate:** Sandra Walsh; **Ex-Officio member:** Georjean Stoodt; **Industry Represenatives:** Teresa Burgess, I. Craig Henderson, Kevin Scanlon; ***Row 2:*** **Medical Specialist:** Robert W, Carlson, Bobbie Head; **Non-Profit Organizations:** Felicia Hodge, Irene Linayao-Putman, Judith Luce,
Row 3: **Non-Profit Organizations:** M. Ellen Mahoney, **Scientist/Clinicians:** Hoda Anton-Culver, Susan Blalock, Tammy Tengs and Anna Wu.

Chair and Vice Chair

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

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

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

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

Chair and Vice Chair

ANNE WALLACE
(8/27/97 - 6/30/00)

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 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.

FLORETTA CHISOM
(8/27/97 - 6/30/00)

Floretta Chisom brings her many years of experience in committee work and team building to the BCRC. She is recently retired from her position as 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. Chisom with her strong motivation for eradicating breast cancer.

Advocates

VICKI BORIAK
(10/15/99 - 3/1/01)

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

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

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

Advocates

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

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

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

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

Ex-Officio Member

GEORJEAN STOODT
(10/25/00 — Ongoing)

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

Industry Representatives

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

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

KEVIN SCANLON
(2/10/98 - 1/0/00)

Kevin Scanlon, Ph.D. 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.

Industry Representative

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

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

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

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

Dr. Henderson has delivered innumerable presentations at medical conferences, and conducted grand rounds at medical schools throughout the United States and Europe. He is a Fellow of the American College of Physicians, a Fellow of the Royal College of Physicians (Edinburgh), and a Member of both the American Association for Cancer Research and the American Society of Clinical Oncology.

Medical Specialist

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

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

BOBBIE HEAD
(1/15/97 - 6/30/00)

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 complementary 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, and is Medical Director of Hospice of Marin. She is active in clinical research and teaching and participates in national and pharmaceutical company trials that utilize new cancer therapies.

Non-Profit Health Organization

FELICIA HODGE
(7/1/99 - 6/30/00)

Felicia Schanche Hodge, Dr.P.H., is the founder and director of the Center for American Indian Research and Education (CAIRE). Dr. Hodge, a Wailaki Indian from Northern California, has been the recipient of several R01 research awards from the NCI and the NINR. Her research is in the area of cancer prevention and control, as well as behavioral modification. Dr. Hodge is currently the Director of Research at the California Rural Indian Health Board (CRIHB) an advocacy agency representing California Indians, and is an adjunct Professor at UCSF.

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

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

Non-Profit Health Organization

JUDITH LUCE
(8/12/97 - 6/30/00)

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."

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

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

Scientist/Clinicians

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

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

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

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

Scientist/Clinicians

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

Tammy O. Tengs, Sc.D., is the Director of the Health Priorities Research Group and an Assistant Professor in the School of Social Ecology at the University of California, Irvine. Previously she was a member of the research faculty in the Center for Health Policy Research and Education at Duke University. She completed her doctorate in Health Policy and Management at the Harvard School of Public Health in 1994. Before coming to Harvard, she earned a master's degree in Industrial Engineering and Operations Research at the University of Massachusetts, Amherst, and studied in the Engineering-Economic Systems Department at Stanford. Dr. Tengs directed the 1990-94 Lifesaving Priorities Project at the Harvard Center for Risk Analysis, supervising a team of 20 that amassed cost-effectiveness data for hundreds of public health and medical interventions. She is the principal author of the papers "Five-hundred life-saving interventions and their cost-effectiveness" and "The opportunity costs of haphazard societal investments in life saving." Following considerable media coverage, she has received approximately 1500 requests for these publications. Dr. Tengs is a "decision scientist." Broadly, her research interests include the economic efficiency of societal investments in health and science. With $2.7 million in grants, she is collecting information on the cost-effectiveness of different interventions aimed at cancer and developing a computer simulation model to predict the long-term economic and public health consequences of any change in federal tobacco policy.

Scientist/Clinicians

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

Anna M. Wu, Ph.D. is an Associate Professor of Molecular Biology at the Beckman Research Institute of the City of Hope, in Duarte, CA, and an adjunct Associate Professor in the Dept. of Molecular and Medical Pharmacology, UCLA School of Medicine. She graduated from Radcliffe College, Harvard University, with an A.B. in Biochemistry, and obtained her Ph.D. in the Dept. of Molecular Biophysics and Biochemistry, Yale University. Postdoctoral studies were conducted at Yale University and at the University of California, San Francisco. In 1984 Dr. Wu joined the research staff at the City of Hope, where her work has focused on applications of molecular biology to the diagnosis and treatment of cancer. Current research interests include development of genetically engineered antibodies for imaging, radiommunotherapy, and biological approaches to cancer theraphy. Dr. Wu has been active with local cancer support groups, and for several years has taught basic science with project LEAD of the National Breast Cancer Coalition.

Summary of Awards

	Duration	Direct Cost	Indirect Cost	Total
California Pacific Medical Center Research Institute				
Shanaz H. Dairkee Ph.D.				
Genetic Changes in Normal Epithelium of the Cancerous Breast	3	$403,650	$212,692	$616,342
California State University, Northridge				
Carol M. Koprowski Ph.D., R.D. / Kathryn S. Hall Ph.D.				
Physical Activity and Diet in Adolescents with Disabilities	1	$99,988	$25,217	$125,205
Cedars-Sinai Medical Center				
Elizabeth Williamson Ph.D.				
Discovery and Study of Breast Cancer Secreted Proteins	2	$80,000	$6,400	$86,400
Vicki L. Davis Ph.D.				
Influence of Localized DDT Exposure on Breast Cancer	2	$199,993	$105,996	$305,989
Subtotal		$279,993	$112,396	$392,389
Childrens Hospital, Los Angeles				
Vesa Kaartinen Ph.D.				
TGF-B3 and small GTPases in Invasive Breast Cancer	3	$217,269	$106,678	$323,947
Harbor-UCLA Research & Education Institute				
Linda Lillington R.N., M.N., DNSc.				
Communicating Breast Cancer Risk in Ethnically Diverse Women	2	$176,099	$71,260	$247,359
La Jolla Institute for Molecular Medicine				
Ingrid Schraufstatter M.D.				
The Role of IL-8 and its Receptors in Angiogenesis	1	$73,562	$78,932	$152,494

	Duration	Direct Cost	Indirect Cost	Total
Lawrence Berkeley National Laboratory				
Jimmie E. Fata B.Sc.				
Role of MMPs in Breast Tumor Initiation and Aggressiveness	2	$75,501	$0	$75,501
Eli Gilad Ph.D.				
Studies on the Role of the ER-beta in Breast Cancer	2	$80,000	$0	$80,000
Mary Helen Barcellos-Hoff Ph.D.				
Role of p53 in Irradiated Stroma and Mammary Carcinogenesis	2	$200,000	$136,866	$336,866
Paul Yaswen Ph.D.				
Immortalization of Human Mammary Epithelial Cells by ZNF217	2	$150,000	$99,792	$249,792
Terumi Kohwi-Shigematsu Ph.D.				
DNA Packaging Defects in Breast Cancer	2	$200,000	$133,335	$333,335
John L. Muschler Ph.D.				
Tumor Suppression by Dystrogylcan in Breast Epithelial Cells	2	$112,501	$76,203	$188,704
Mary Helen Barcellos-Hoff Ph.D. / Mina J. Bissell Ph.D. / G. Shyamala Ph.D				
Cancer and Complexity: Questions for a New Millenium	1	$14,160	$0	$14,160
Subtotal		$832,162	$446,196	$1,278,358
Molecular Research Institute				
Marcia I. Dawson Ph.D. / Gilda Loew Ph.D.				
Computer-Aided Discovery of Novel Breast Cancer Therapeutics	1	$100,000	$47,001	$147,001
Molecular Express, Inc.				
Gary Fujii Ph.D.				
Targeted Delivery of an Anti-breast Tumor Agent	2	$0	$0	$0
(Sub-contract to University of Southern California)				
Public Health Institute				
William E. Wright Ph.D.				
Race/Ethnicity, Socioeconomic Status and Breast Cancer	1	$33,778	$6,013	$39,791
Peggy Reynolds Ph.D.				
Breast Cancer in California Teachers- Regional Variations	2	$150,000	$15,578	$165,578
Subtotal		$183,778	$21,591	$203,369
Salk Institute for Biological Studies				
Zhimin Lu M.D., Ph.D.				
Tamoxifen-Induced Endometrial Cell Transformation	2	$80,000	$6,400	$86,400

	Duration	Direct Cost	Indirect Cost	Total
Scripps Research Institute				
Ta-Hsiang Chao Ph.D.				
The Role of the BMK1-MEKK3 Pathway in Breast Cancer	2	$80,000	$6,400	$86,400
Yongsheng Liu Ph.D.				
Identifying Breast Cancer Targets for Protease Inhibitors	2	$80,000	$6,400	$86,400
Ulla G. Knaus Ph.D.				
Cell Growth Control of Breast Epithelial Cells	2	$150,000	$115,950	$265,950
Benjamin Cravatt Ph.D.				
Profiling Serine Protease Activities in Breast Cancer	2	$150,000	$115,950	$265,950
Richard Klemke Ph.D.				
Novel Mechanisms of ErbB-2-Mediated Breast Cancer Metastasis	2	$150,000	$113,863	$263,863
Subtotal		$610,000	$358,563	$968,563
Sidney Kimmel Cancer Center				
Jacqueline E. Testa Ph.D.				
A Novel Antigen Associated with Breast Cancer Metastasis	1	$75,000	$61,875	$136,875
Ruth A. Gjerset Ph.D.				
Role of p14ARF in Metastatic Breast Cancer	2	$200,000	$165,000	$365,000
Subtotal		$275,000	$226,875	$501,875
SRI International				
Nurulain T. Zaveri Ph.D.				
Breast Cancer Prevention by Analogs of EGCG from Green Tea	2	$149,994	$146,201	$296,195
Ling Jong Ph.D.				
Novel Agents for Treatment of Advanced Breast Cancer	2	$199,989	$192,483	$392,472
Keith R. Laderoute Ph.D.				
Novel Anti-Angiogenic Agents for Breast Cancer Therapy	2	$199,999	$173,790	$373,789
Subtotal		$549,982	$512,474	$1,062,456
Stanford University				
David Spiegel M.D. / Caroline Bliss-Isberg Ph.D.				
Does a Peer Navigator Improve Quality of Life at Diagnosis?	1	$109,455	$52,143	$161,598
Wensheng Wei Ph.D.				
Genes Determining Estrogen Susceptibility in Breast Cancer	2	$80,000	$6,400	$86,400
Stanley N. Cohen M.D.				
Metastasis Suppressor Genes for Breast Cancer	2	$200,000	$112,937	$312,937
Daria Mochly-Rosen Ph.D.				
The Control of Breast Cancer Cell Death	2	$200,000	$106,447	$306,447
Subtotal		$589,455	$277,927	$867,382

	Duration	Direct Cost	Indirect Cost	Total
The Burnham Institute				
Elizabeth Hindmarsh Ph.D. / Sug Hyung Lee M.D., Ph.D.				
Analysis of Angiogenic Pathways in Metastatic Breast Cancer	2	$80,000	$6,400	$86,400
Shi Huang Ph.D.				
Suppressor Genes of Breast Cancer	1	$100,000	$95,000	$195,000
Sug Hyung Lee, M.D.				
Analysis of a New Human Caspase in Breast Cancer	2	$80,000	$6,400	$86,400
Robert G. Oshima Ph.D.				
A Vascular Restriction of Mammary Tumor Progression	2	$199,598	$184,868	$384,466
Kristiina Vuori M.D., Ph.D.				
Cell Adhesion and Drug Resistance in Breast Cancer	1	$100,268	$90,505	$190,773
Subtotal		$639,866	$389,573	$1,029,439
University of California, Berkeley				
Urmi Chatterji Ph.D.				
Identifying the Breast Cancer Target for Indole-3-Carbinol	2	$80,000	$0	$80,000
Marc K. Hellerstein M.D., Ph.D.				
Method for Measuring Breast Epithelial Turnover in Humans	2	$197,000	$0	$197,000
Gertrude C. Buehring Ph.D.				
Bovine Leukemia Virus Infection and Human Breast Cancer Risk	2	$189,387	$0	$189,387
Subtotal		$466,387	$0	$466,387
University of California, Davis				
Clifford G. Tepper Ph.D.				
Profiling of Tyrosine Phosphatases in Breast Cancer	2	$147,250	$0	$147,250
Jeffrey P. Gregg M.D.				
Analysis of Genes Predictive of Breast Cancer Metastasis	3	$221,925	$0	$221,925
Kent L. Erickson Ph.D.				
Mechanisms of Reduced Metastasis by Conjugated Linoleic Acid	3	$314,988	$0	$314,988
Subtotal		$684,163	$0	$684,163

	Duration	Direct Cost	Indirect Cost	Total
University of California, Irvine				
Randall F. Holcombe M.D. / John A. Butler M.D. / Bruce J. Tromberg Ph.D.				
Non-Invasive Optical Characterization of Breast Physiology	3	$499,915	$0	$499,915
Randall F. Holcombe M.D. / Marian L. Waterman Ph.D. / J. Lawrence Marsh				
Wnt Signaling in Breast Cancer: Translational Studies	2	$328,129	$0	$328,129
Min-Ying L. Su Ph.D.				
Thrombosis for Anti-angiogenic Therapy of Breast Cancer	2	$200,000	$0	$200,000
Argyrios Ziogas Ph.D.				
Genetic and Environmental Modifiers of Breast Cancer Risk	2	$287,987	$0	$287,987
Subtotal		$1,316,031	$0	$1,316,031
University of California, Los Angeles				
Mary L. Alpaugh Ph.D.				
Anti-E-Cadherin Apoptosis of Inflammatory Breast Carcinoma	2	$80,000	$0	$80,000
Sanford H. Barsky M.D.				
A Study of the Molecular Heterogeneity of LCIS	2	$150,000	$0	$150,000
Julienne E. Bower Ph.D.				
Mechanisms of Radiation-Induced Fatigue in Breast Cancer	3	$225,000	$0	$225,000
Helena Chang M.D., Ph.D.				
Protein Markers in Nipple Aspirates for Breast Cancer	2	$200,000	$0	$200,000
Helen Rebecca Rausch Ph.D.				
Cognitive Changes After Adjuvant Therapy for Breast Cancer	2	$199,997	$0	$199,997
Subtotal		$854,997	$0	$854,997
University of California, San Diego				
Sung Hee Baek Ph.D.				
The Role of NCo-R During Normal Mammary Gland Development	2	$80,000	$0	$80,000
Yixue Cao Ph.D., M.D.				
A Novel Signal Transduction Pathway in Breast Cancer	2	$80,000	$0	$80,000
Subtotal		$160,000	$0	$160,000

	Duration	Direct Cost	Indirect Cost	Total
University of California, San Francisco				
Nola M. Hylton Ph.D. / John Ziegler				
MRI for High Risk Breast Cancer Screening and Surveillance	3	$499,630	$0	$499,630
Thomas Robertson Ph.D.				
A New Class of Drugs to Treat Breast Cancer	2	$80,000	$0	$80,000
Michael J. Campbell Ph.D.				
Pregnancy and Breast Cancer: an Immunological Connection?	1	$75,000	$0	$75,000
C. Anthony Hunt Ph.D.				
A Patient Decision Support Framework for Breast Cancer	2	$150,000	$0	$150,000
Debasish Tripathy M.D.				
Chinese Herbal Therapy (CHT) for Symptom Management	2	$200,000	$0	$200,000
Francis C. Szoka Ph.D.				
Targeted Chemotherapy to Treat Breast Cancer	2	$200,000	$0	$200,000
Nabila Jabrane-Ferrat Ph.D.				
Cell-Based Immunotherapy for Breast Cancer	2	$125,371	$0	$125,371
Celia P. Kaplan Dr.P.H.				
Breast Cancer Prevention: The Views of Women and Physicians	3	$434,559	$0	$434,559
Subtotal		$1,764,560	$0	$1,764,560
University of Southern California				
Fred L. Hall Ph.D. / Francis S. Markland Ph.D.				
Targeted Delivery of an Anti-breast Tumor Agent	2	$420,669	$264,327	$684,996
Wei-Chiang Shen Ph.D.				
Arginine Deiminase as an Innovative Anti-Breast Cancer Agent	1	$50,000	$31,750	$81,750
Brian E. Henderson M.D.				
DNA Polymorphisms and Breast Cancer in a Multi-ethnic Cohort	1	$49,747	$31,589	$81,336
Sue Ann Ingles Dr. P.H.				
Mammography Density and Sex Steroid Genes	1	$62,842	$39,905	$102,747
Amy S. Lee Ph.D.				
Stress Protein and Drug Resistance in Human Breast Cancer	2	$200,000	$126,000	$326,000
Cheng-Ming Chuong M.D., Ph.D.				
Molecular Staging of Breast Cancer Progression	2	$150,000	$94,500	$244,500
Thomas M. Mack M.D., M.P.H.				
Mammographic Density, HRT and Hormonal Activity Genes	2	$435,688	$274,426	$710,114
Donna M. Williams-Hill Ph.D.				
Upregulation of BRCA1 as a Cancer Preventive Strategy	3	$375,543	$235,915	$611,458
Subtotal		$1,744,489	$1,098,412	$2,842,901
Women Care				
Caroline Bliss-Isberg				
Does a Peer Navigator Improve Quality of Life at Diagnosis? (Sub-contract to Stanford University)	1	$0	$0	$0