

California Breast Cancer Research Program

B C R P

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**Advances in
Breast Cancer
Research**

Executive Summary

“I consider BCRP among the most innovative, well-conceived, and well-developed research funding programs in the country. BCRP has recognized the value of the team approach in breast cancer research, and has gone the next step in designing a review process that can select quality work spanning multiple disciplines. The review panel members from diverse institutions represent a broad range of clinical and scientific backgrounds. Added to this diversity are the patient advocates, who provide unique perspectives regarding clinical relevance and key patient issues. These review panels provide sophisticated, integrated reviews. BCRP also takes on the challenge of reviewing cutting edge, high risk/high return projects for funding”.

While breast cancer is as serious a threat to women in other states across the U.S. as it is to the women of California, California is unique in the effort and resources it invests to find an end to this disease. In 1993, the California legislature, guided by breast cancer advocates across the state, recognized the need to respond to the breast cancer epidemic. With the passage of the Breast Cancer Act (sponsored by then Assemblywoman Barbara Friedman), the tobacco tax was increased by two cents per pack to create an ongoing source of funds to support what remains the largest effort by a state to decrease the human and economic cost of breast cancer. Each year, this tax provides new dollars (\$16.7 million in 1999) devoted exclusively to research on the cause, prevention, detection, treatment and cure of breast cancer. Additional funds (\$726,000 in 1999) come from taxpayer donations selected on the state income tax return, and from private donations. These funds are directed to the California Breast Cancer Research Program, administered by the University of California. The Program supports research projects awarded through a competitive process to scientists across the state at a variety of universities, research centers and other settings.

1999 was the California Breast Cancer Research Program's fifth year of operation, and marked another year of important achievements and growth for the BCRP. With a budget of \$17,432,000, BCRP was able to award 62 new projects across the state. The projects include work in the areas of:

- ♦ the biology of the normal breast,
- ♦ factors that increase the risk of breast cancer,.
- ♦ ways to reduce the risk of breast cancer,
- ♦ understanding how breast cancer develops,.
- ♦ developing new treatments for breast cancer,
- ♦ detecting breast cancer earlier.
- ♦ exploring socio-cultural, behavioral, and psychological aspects of breast cancer,

Over the past five years, the Program has provided more than \$75 million dollars to research on breast cancer. 193 research projects have been completed and another 133 projects are in progress. This report presents the discoveries and findings of the projects completed this year, interim reports on research in progress, as well as descriptions of the new projects begun this year. It also describes BCRP's recent activities, goals, progress, and plans for the challenges that lie ahead on the road to decreasing the human and economic cost of breast cancer for the people of California.



Advances in Breast Cancer Research 1999

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Message from the Director



It is my pleasure to present the 1999 Advances in Breast Cancer Research from the California Breast Cancer Research Program. The report summarizes key accomplishments and discoveries from the wide range of research supported by the Program. Throughout this report, you will see evidence of our continued efforts to identify, solicit and support high quality, innovative research that will have a significant impact on breast cancer in California, as well as our commitment to ensure that this research is disseminated and translated in the health care and public health arenas.

It is with mixed emotions that I acknowledge the fifth anniversary of the Program. How can one celebrate when the people of California continue to be faced with alarming numbers of breast cancer diagnoses and with the devastation of nearly 5,000 deaths per year? If only we could see our efforts result in reduced incidence and lives saved overnight or even within weeks or months. But we are confronted with the reality that research rarely leads to overnight solutions, and that we can rarely predict which path will lead us to the most immediate breakthroughs. In our continuing battle against breast cancer, it is likely that our advances will come in fits and starts and incremental progress, and that reductions in incidence and deaths will require years, if not decades, to achieve and measure. But our commitment remains unwavering and our hopes high. And while we cannot celebrate the ongoing need for the Breast Cancer Research Program, we do have reasons to celebrate. We can celebrate the ongoing commitment that California has made to eradicate breast cancer by supporting the largest state research program in the nation. We can celebrate the research discoveries described here and in prior Annual Reports. And we can celebrate and harness the maturity that the Program is now achieving. This maturity gives us the opportunity to carefully evaluate the Program's achievements and to use this information to strategize for the future, ensuring that we accelerate our progress in eradicating breast cancer.

The people of California can be proud of how much the Program accomplished in 1999. Meeting our mission "to reduce the impact of breast cancer in California" is challenging, and requires us to be proactive in identifying and addressing emerging gaps and opportunities in the multitude of research areas that touch on breast cancer. It makes it essential for us to partner with others in the medical, scientific,

“The BCRP is an important and unique resource to the breast cancer research community in California because of the high priority given to innovative research projects that forge into new experimental areas. As a direct result of the types of research endeavors funded by BCRP, there is no doubt that new perspectives in the biology, etiology and control of breast cancer have been and will continue to be developed”.

and lay communities. Our goal is to develop a multidisciplinary research agenda that brings together the expertise and knowledge from different areas of basic biological sciences, translational and clinical research health care delivery, behavioral science, and epidemiology that will stimulate a changing landscape of breast cancer research as an increasing collaboration among scientists, advocacy groups and policy-makers.

In 1999, as in previous years, we set new priorities for research funding, adding new award types to stimulate and support creative new ideas by bringing in people and research areas that have not before been used in breast cancer research. We continued our support of key areas (such as studying the normal breast and pursuing new ideas on what causes breast cancer) that we believe are underemphasized by other research funding agencies. And our second biannual symposium brought together more than 500 scientists, health care providers, survivors, and interested lay people to discuss the latest research findings and develop future directions.

While developing crucial new initiatives, however, the Program must also confront declining revenues. The Program is funded by a portion of the revenue from a two cent per pack tax on cigarettes. Several factors are playing a part in decreasing the consumption of cigarettes in California, a trend that we hope will continue. Eliminating tobacco use is a critical public health objective that we wholeheartedly support, and that will greatly reduce funding for many important public health programs. Declining funds from tobacco taxes are being faced by numerous health care, health education and research agencies. At BCRP, we are undertaking a number of efforts to sustain funding for breast cancer research, such as increasing awareness of the voluntary state income tax check-off and soliciting private donations. We encourage you to take advantage of the opportunity to support breast cancer research when submitting your California state income tax return.

I invite you to critically examine this Report - to learn from the research described, to question, to follow up areas that interest you on our website, where all of this research is presented in more detail. The work presented here reflects the efforts of hundreds of people - dedicated scientists, concerned advocates, and partner organizations. My continued thanks to the Breast Cancer Research Council for their hard work, commitment, leadership, and vision. Working together, we will continue to move towards a future in which breast cancer deaths are a rare occurrence.



Breast Cancer

We will measure the success of the Breast Cancer Research Program by its ultimate impact on breast cancer in California. But while we wait to reap these benefits, the feedback we receive from the medical, scientific, and lay communities indicate that the Program has other, more immediate impacts as well.

Kathryn Ely, Ph.D.

Director, Molecular Anatomy
of the Cell Program
The Burnham Institute, La Jolla

Perhaps this is one of the most important contributions of BCRP...to fund projects at a very early stage to promote innovation and to permit breakthroughs from the established or faltering current protocols. The breast cancer field will benefit greatly from this Program.

Gary Firestone, Ph.D.

Department of Molecular
and Cell Biology
University of California, Berkeley

We have now started a collaboration with a local biotechnology company to develop indole-3-carbinol-based anti-cancer therapeutics. None of these exciting results would have been possible without the BCRP's goal of funding innovative research in the less developed areas of breast cancer research...As a direct result of the types of research endeavors funded by the BCRP, there is no doubt that new perspectives in the biology, etiology and control of breast cancer have been and will continue to be developed.

Hearing From You

Ben Anderson, M.D.
Medical Director, Bioclinical Breast Care
Program
University of Washington, Seattle

As a reviewer for BCRP, I have had the unique opportunity to observe the Program's development from the inside. I consider it among the most innovative, well-conceived, and well-developed research funding programs in the country...The BCRP has not only recognized the value of the team approach in breast cancer research, but has gone the next step in designing a process that can select quality work spanning multiple disciplines.

Donna Williams-Hill, Ph.D.
Assistant Professor
Department of Radiation Oncology
University of Southern California, Los
Angeles

The BCRP gave me a start in building a research program when other funding agencies were reluctant...My post-doctoral training was interrupted by the need to care for my mother as she entered the last stages of her battle with breast cancer...The BCRP funded my work when no other agency would take the chance...This is a very unique program in that the women who have this illness and their caretakers are actively involved with researchers...I cherish the opportunity to share my story with those who really understand the need for this fight and I salute the BCRP for giving me and others like me the chance to contribute to this fight.

Pierre-Yves Desprez
Staff Scientist
California Pacific Medical Center, San
Francisco

The criteria used by BCRP to fund projects are strictly based on the scientific merit of the project, and not based on the reputation and fame of the laboratory, which is not the case for every funding agency.

Breast Health Access for Women with
Disabilities (BHAWD), Berkeley
Nova Award Finalist

With your help, Breast Health Access for Women with Disabilities has been breaking through the barriers to early breast cancer detection for Bay Area women with disabilities and is stimulating interest and action by many health care providers throughout the nation.

**An anonymous advocate
reviewer**

The review process used by the California Breast Cancer Research Program is very impressive, very honoring of cancer survivors and very passionate about the cause.

Sandra Blank
President, Florida Breast Cancer
Resource Network

"Clearly California is setting the standard for the rest of the country to follow. Having participated in the Program as a peer-review advocate and as an Advocate Guide at the 1999 BCRP Symposium, I have learned first-hand about the unparalleled approach taken to funding breast cancer research. In the frustrating and all too political world of breast cancer research, it is encouraging that California is on the right track in trying to get the better of this disease.

Breast Cancer

California Breast Cancer Research Program: History and New Awards

While breast cancer is as serious a threat to women in other states across the U.S. as it is to the women of California, California is unique in the effort and resources it invests to find an end to this disease. In 1993, the California legislature, guided by breast cancer advocates across the state, recognized the need to respond to the breast cancer epidemic. With the passage of the Breast Cancer Act (sponsored by then Assemblywoman Barbara Friedman), the tobacco tax was increased by two cents per pack to create an ongoing source of funds to support what remains the largest effort by a state to decrease the human and economic cost of breast

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The California Breast Cancer Research Program was established at the University of California, Office of the President to spearhead efforts to stimulate innovative and creative breast cancer research that complements, but does not duplicate, research funded by other agencies. Program staff are responsible for implementing Program policies and managing all aspects of the solicitation, review, award and oversight of research grants.

The Breast Cancer Research Council determines the vision, priorities and strategies of the BCRP. The Council is composed of scientists, clinicians, representatives of industry and non-profit health organizations, and advocates, each serving a term of three years. As an advisory body, the Council determines the Program focus and investment strategy, assists in policy development, and provides the Program staff with input at critical decision points. The Council also carries out the programmatic review of applications - evaluating proposals for relevance to programmatic goals.

From its conception, the Program has been a partnership between all Californians concerned about breast cancer. Legislators, breast cancer advocates, academic and biotechnology scientists, clinicians, and University of California officials worked together to draft the enabling legislation. Representatives of these same constituencies advise the Program on research priorities and grant funding; similarly diverse groups are convened to review grant applications.

BCRP carries out its mission through four broad strategies: (1) by supporting the best, most innovative research; (2) funding the training of new researchers; (3) fostering the collaboration of new teams of researchers; and (4) fostering dissemination of research results to



scientists, health care professionals and the public. Through investing in these strategies, California is investing in the future of Californians. By encouraging and identifying innovative research on breast cancer, attracting and training some of the most talented scientists into this endeavor, and influencing the way scientists interact with each other and the lay public, California is making an investment that will pay vital dividends in years to come.


1999 marked another year of important achievements and growth for the BCRP. With a budget of \$17,432,000, BCRP was able to award 62 new single- and multiple-year grants at 26 institutions. The projects include:

- ⦿ 7 grants to expand our knowledge of the biology of the normal breast, including searching for, and understanding, the role of genes involved in the development of the normal breast, and examining the role of cellular products in the transition to breast cancer.
- ⦿ 6 grants to investigate factors that increase the risk of breast cancer, including exploration of hormones other than estrogen (i.e., leptin and growth hormones) and exploration of adolescent experiences and exposures that may bring about breast cancer later in life.
- ⦿ 3 grants to explore ways to reduce the risk of breast cancer, including exploring the mechanism by which exercise may reduce risk and investigating the combined effects of genes and soy consumption.
- ⦿ 19 grants to further understand how breast cancer develops, including how new blood vessels form to feed tumors, and how this process can be interrupted, different pathways in which tumor cells are instructed to grow, and how this can be interrupted, and investigation of newly discovered genes involved in breast cancer progression.
- ⦿ 11 grants to develop new treatments for breast cancer, including exploration of the effects of herbs used in Chinese medicine, development of vaccines, and the role of tumor markers in predicting response to therapy.
- ⦿ 5 grants exploring ways to detect breast cancer earlier by using biomarkers and detection of proteins and tumor cells in the blood.
- ⦿ 12 grants exploring socio-cultural, behavioral, and psychological aspects of breast cancer, including the role of support groups, partners and making meaning of the disease in quality of life, acceptability of genetic testing and chemoprevention, and communication of risk.
- ⦿ 4 grants to teams of community members/organizations and research scientists focused on issues identified by, and important to, communities in the state, including Asian and Pacific Islander populations, isolated women and working women.
- ⦿ 1 grant to a cross-disciplinary team of research scientists focused on bringing results of scientific research into practical application, by exploring the relationship between tumor markers and response to therapy in a community setting.
- ⦿ 18 grants to new investigators in breast cancer to establish their careers in areas that will make an impact in breast cancer.
- ⦿ 6 fully developed research grants in areas that have been identified as relatively under-funded, but important to advance our knowledge of breast cancer; namely biology of the normal breast, prevention and risk reduction, and socio-cultural, behavioral, and psychological issues.
- ⦿ 34 grants to explore innovative concepts that may open new avenues for breast cancer research and new options for prevention, detection and treatment of breast cancer.

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

Breast Cancer

Status of Breast Cancer in California

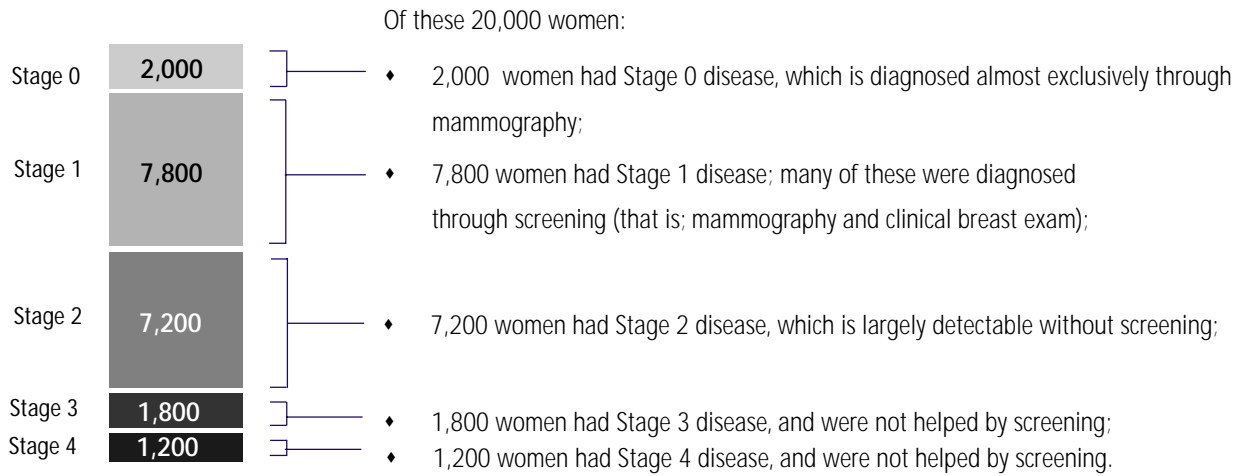


Breast cancer continues to rob women of their health, their productivity, and their very lives. It robs families of mothers, daughters, grandmothers, sisters, aunts, wives, and partners. In 1999 alone, an estimated 180,000 women in the U.S. were diagnosed with invasive breast cancer, and more than 44,000 women were lost to this disease. In 1999 in California, approximately 20,000 women were diagnosed with breast cancer and nearly 4,500 women died of breast cancer.

What will happen to those 20,000 women who were diagnosed with breast cancer this year?

While we do not yet have the data to answer this question, we can use what we know about patterns of breast cancer from recent years to make estimates.

20,000 Women Diagnosed in 1999



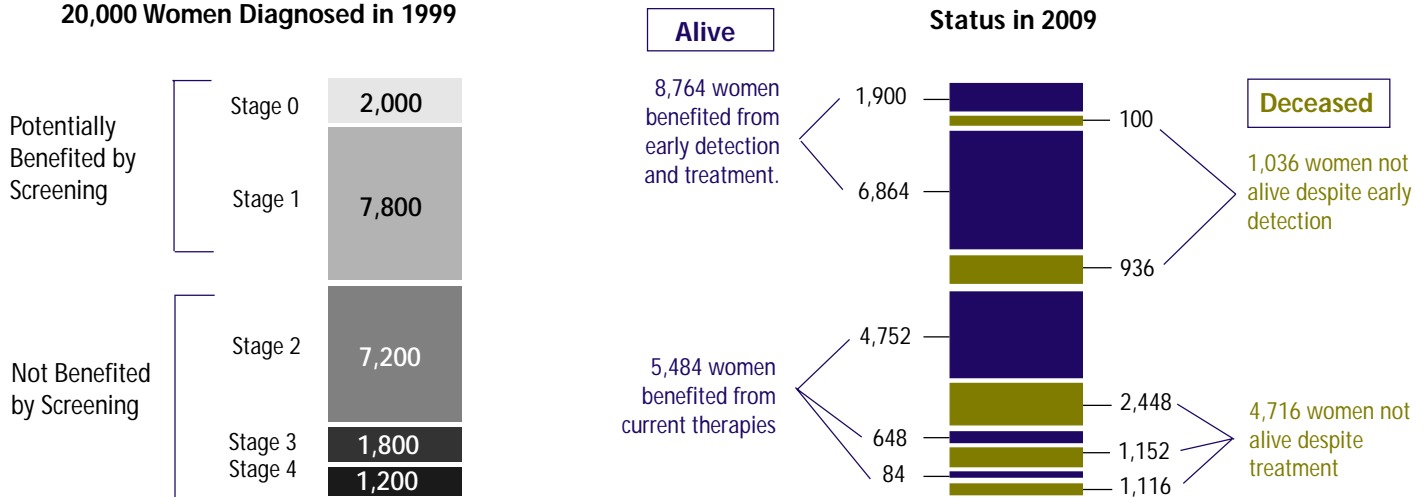
Thus, screening resulted in the diagnosis of 9,800 cases of breast cancer (nearly half of all breast cancer) at an early stage. The women with early stage cancer have a much better chance of surviving than women with more advanced cancer. But not all women with early stage cancer survive.

Of the 9,800 with early stage disease:

- ♦ 95% of the 2,000 women (1,900 women) diagnosed with Stage 0 breast cancer will be alive in 2009, but 100 women will have died of breast cancer during this 10-year period.
- ♦ 88% of the 7,800 women (6864 women) diagnosed with Stage 1 breast cancer will be alive in 2009, but 936 women will have died of breast cancer during this 10-year period.

Thus, if screening were responsible for all catching all of these cancers at an early stage, screening for one year in California would have saved 8,764 lives. But 1,036 women would have died of breast cancer despite the advantages of early detection.

20,000 Women Diagnosed in 1999



Screening can be said to have not benefited more than 50% of women diagnosed with breast cancer in 1999, screening cannot be said to have benefited them, either because they did not receive screening, or because screening was not effective in detecting their disease at an early stage.

For these 10,200 women:

- ♦ 66% of the 7,200 women (4,752) diagnosed with Stage 2 breast cancer will be alive in 2009, but 2,448 women will have died of breast cancer during this 10-year period.
- ♦ 36% of the 1,800 women (648 women) diagnosed with Stage 3 breast cancer will be alive in 2009, but 1,152 women will have died of breast cancer during this 10-year period.
- ♦ 7% of the 1,200 women (84 women) diagnosed with Stage 4 breast cancer will be alive in 2009, but 1,116 women will have died of breast cancer during this 10-year period.

Thus, early detection (screening) failed to help more than 50% of the women diagnosed with breast cancer in 1999, either because they did not receive screening services or because their cancer had advanced beyond the earliest stages despite early detection. Of these 10,200, more than half (5,484) will still be alive in 2009 due to treatments that have been developed through research. But nearly half of these women (4716 women) will die in the next ten years, despite our best available treatments.

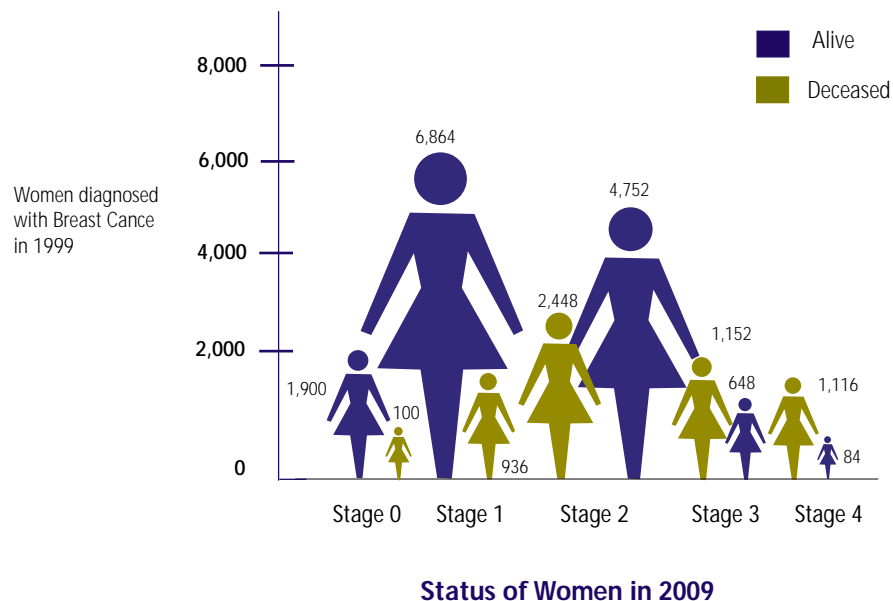
Overall, early detection coupled with early treatment saved the lives of 8,764 women in California in 1999, and treatment alone saved the lives of another 5,484 women. But despite the advances in early detection and treatment of breast cancer, 5,752 California women diagnosed with breast cancer in 1999 are destined to die in the next ten years.

Past research has helped us save the lives of 14,248 Californians in 1999. Our goal is to support research to save the lives of those with breast cancer in the future and to prevent the disease from occurring in future generations.

Sources:

California Cancer Facts and Figures, 1999

National Cancer Database



Breast Cancer



BCRP carries out its mission through four broad strategies: (1) by supporting the best, most innovative research; (2) funding the training of new researchers; (3) fostering the collaboration of new teams of researchers; and (4) fostering dissemination of research results to scientists, health care professionals and the public.

Although BCRP is the largest California-based funder of breast cancer research, it is part of a much larger research enterprise in which the federal government (the National Cancer Institute within the National Institutes of Health, and the Department of Defense Breast Cancer Research Program), the private non-profit sector (voluntary health organizations and foundations), and the private for-profit sector (pharmaceutical companies and biotechnology firms) spend more on breast cancer research. Within this larger system, NIH supports the basic research to gain fundamental knowledge about health and disease processes; the DOD Program invests in breast cancer-targeted research, emphasizing innovation, translation and minority communities; foundations target specific projects and the private sector focuses on applications such as new drugs, diagnostic tools, and medical devices that are likely to produce a profit.

The challenge for BCRP is two-fold:

1. to determine specific, critical areas that are not being cultivated by these other sectors that BCRP can impact, and that will feed into or be fed by the work of these other sectors; and
2. to narrow this list of specific, critical areas to fit its budget.

Research Priorities

Our role is not to support the full range of research activities necessary to confront cancer - this is the role of much larger, national and federal agencies. Our role, instead, is to:

- ⊙ identify the critical areas within the full range of research (behavior, epidemiology, cancer control, prevention, detection, diagnosis, treatment, quality of life, basic sciences) that are not being cultivated by other agencies;
- ⊙ identify the gaps in current knowledge and barriers to gaining that knowledge that we can reduce or eliminate;
- ⊙ stimulate new ideas that can be fed into the federal and for-profit research sectors.

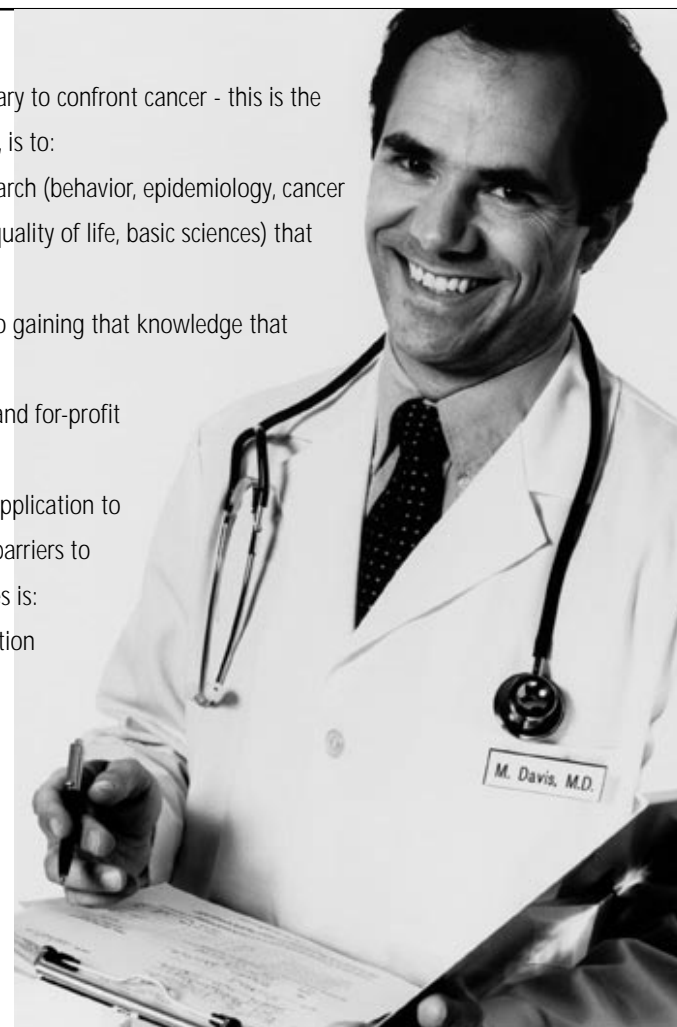
BCRP's goals are to foster innovation and discovery, facilitate their application to the care of people with breast cancer and those at risk, and topple barriers to progress. The central question in determining the Program's priorities is: "What critical elements can BCRP add to rapidly achieve the prevention and cure of breast cancer?"

In setting priorities and planning for the future, we rely on our diverse constituencies to help us identify new opportunities, gaps, and barriers to progress, as well as to help us create new programs and improve existing ones.

Vision, creativity, planning, meticulous and methodical work, and an occasional stroke of luck - all are needed to achieve progress in breast cancer research. Most critical, however, is recognizing and acting on promising research opportunities at key points in time, and ensuring that new opportunities are being generated.

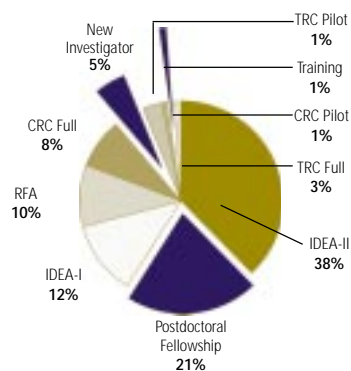
With these considerations in mind, the Breast Cancer Research Council established the following priorities for research funding in 1999:

- ⊙ Enhance understanding of the **etiology** (causes) of breast cancer
- ⊙ Increase understanding of the **biology of the normal breast**
- ⊙ Enhance understanding of the **pathogenesis** (development) of breast cancer
- ⊙ Develop new approaches to **prevent** breast cancer
- ⊙ Develop more effective techniques for the **earlier detection** of breast cancer
- ⊙ Develop **health care policy and health care delivery** strategies that will serve women more effectively
- ⊙ Explore **innovative treatment** modalities
- ⊙ Increase understanding of, and support for, the **socio-cultural, behavioral and psychological issues** of women with breast cancer or at high risk for the disease



Award Types

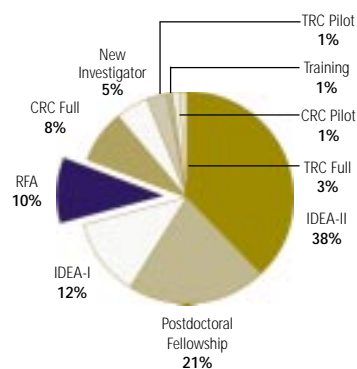
Research Training: Maintenance of Needed Human Resources



Distribution of 1999 Funds

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

Targeted Research Efforts



Distribution of 1999 Funds

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

Sociocultural, Behavioral and Psychological Aspects of Breast Cancer — This

Request for Applications encouraged qualitative and quantitative research into sociocultural, behavioral and psychological issues affecting women with respect to the risk or occurrence of breast cancer.

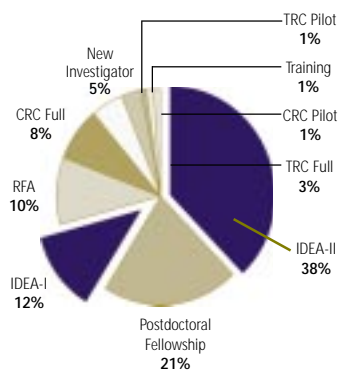
Basic Breast Biology Relevant to Development of Breast Cancer — This Request

for Applications encouraged studies aimed at achieving a greater knowledge of the normal breast, through all stages of development and change, in order to better understand anomalous changes that may lead to cancer.

Breast Cancer Prevention, Risk Identification and Risk Reduction — This Request

for Applications encouraged research that will enable more effective and appropriate prevention interventions by increasing our knowledge of modifiable breast cancer risk factors.

Innovation in Research



Distribution of 1999 Funds

The Council has encouraged researchers to develop and explore innovative and risky concepts in the specific priority areas that it judged important. Innovative Developmental and Exploratory Awards (IDEAs) allow researchers to take risks and explore new concepts in breast cancer etiology, pathogenesis, prevention, earlier detection, treatment, health policy, and delivery of health care that could lead to breakthroughs in these fields.

Through these efforts to explore new concepts and build on existing knowledge, the resulting improvements in prevention, detection and cure of breast cancer will advance the day when we can say with confidence that breast cancer is no longer a threat to the people of California.

Putting Research to Use - Initiatives in Collaboration, Translation and Dissemination

Research in and of itself does not save lives. It is only when the discoveries made through research are translated into new prevention, detection and treatment modalities that the research will have a positive impact.

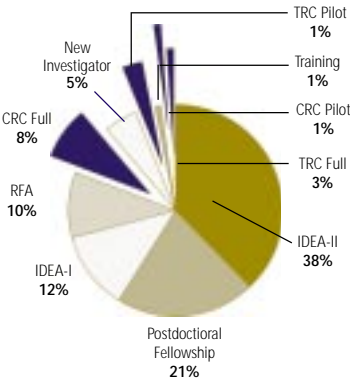
We know that progress has its roots in discovery. But we also know that a gap exists between discovery and application that will not be closed unless we set in place structures that will speed the engine of discovery, create bridges among all components of the breast cancer research enterprise, and encompass the care of those with cancer and those at risk into the research system.

There are many barriers to application and translation of research results. Perhaps the most significant barrier is that the same person who made the initial discovery can rarely carry out this work. In this age of information overload, it is a challenge for most of us to stay fully informed in one field. It is the rare individual who can be fully informed and expert in more than one. In addition, turning a new idea into a discovery requires intense focus on details, rather than on the "big picture." And yet, in the path from new idea, to discovery, to development, to practical application, multiple fields of expertise are required, and the same focus on detail that was required to make the discovery can prevent a scientist from seeing the potential uses of his or her discovery.

"The BCRP gave me a start in building a research program when other funding agencies were reluctant... The result is that I am building momentum in two areas of breast cancer research — the genetic basis of breast cancer susceptibility and cancer prevention".



To meet this challenge and overcome these barriers, BCRP is building a system of “bridges” among all aspects of research - between research and clinical practice, between research and industry, and between research and communities. Our activities in the following areas are helping to not just span the gap between discovery and application in the clinic and the community, but to transform the process by which we bring discoveries to the benefit of people.

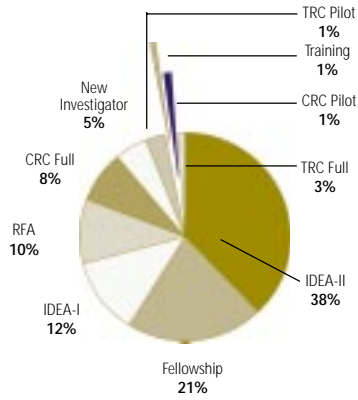


Distribution of 1999 Funds

We must nurture and strengthen the ties between diverse research areas, and between the research system and those whose lives breast cancer touches, to ensure that the benefits reaped by new ideas and new technology flow directly into the reduction of suffering from cancer.

Translational research is critical to develop fully the major advances made by basic scientists in areas such as molecular genetics, regulatory proteins, and cellular signaling into new detection technologies, targeted treatments, and prevention strategies.

Distribution of 1999 Funds



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



Dissemination of Research Results

The BCRP is committed to disseminating the results of the research that it funds, both to the scientific and medical communities (to advance the understanding of breast cancer and its treatment) and to the public (as stakeholders in the Program). To this end, funded research is widely publicized in a variety of ways:

- BCRP maintains a website accessible to the public, where abstracts of all of the projects and their progress are posted.
- A Newsletter reports on new awards, research results and other Program news.
- Publications are widely distributed and posted on the web site, with direct linkage to PubMed abstracts
- Descriptions of new awards are published in the Compendium of Awards
- The annual progress report for each project is posted yearly on the BCRP web site
- Final results of projects are described on BCRP's web site and in the annual report

Researchers also publish final results in peer reviewed scientific journals and present them at scientific conferences; these publications and presentations are tracked by BCRP.

The legislation that established BCRP included the following additional objectives for the Program:

"Provide for systematic dissemination of research results to the public and the health care community in order that these findings may be applied to the planning, implementation, and evaluation of breast cancer-related programs.

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

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

California Breast Cancer Research Symposium



BCRP held its second Symposium in September 1999, bringing together individuals with a wide variety of backgrounds, but a common interest in determining the cause of, and cure for, breast cancer. This symposium was distinct from most other scientific conferences in that it had a strong attendance by breast cancer advocates and the community at large, and presentations were geared toward the general public.

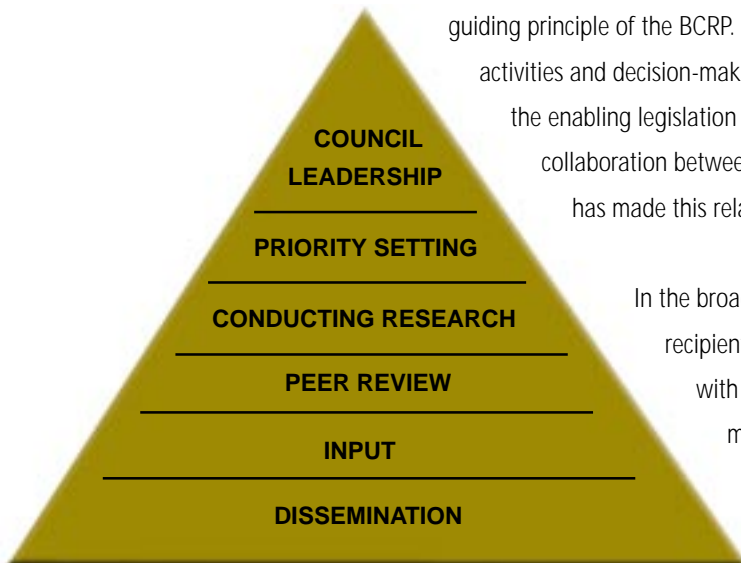
The content and the composition of the symposium reflected the goals of BCRP. Over half of the more than 500 attendees characterized themselves as lay people. The activities available to

the participants included: listening to Keynote Speaker Susan Love, M.D., attending the plenary session on Prevention of Breast Cancer, viewing artwork by and about people with breast cancer; visiting exhibits by non-profit breast cancer organizations; attending informational seminars about how to be funded to do breast cancer research; and attending talks and posters given by investigators who were funded by BCRP.

The next California Breast Cancer Research Symposium is now being planned for September 2001 in Oakland.

Collaboration with Communities

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



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

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

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

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

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

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



Program Evaluation



The mission of the BCRP is to reduce the impact of breast cancer in California by supporting research on breast cancer and facilitating the dissemination of research findings and their translation into public health practice. Are we fulfilling this mission? We believe we are, but we also believe that our future work should be informed by evaluation of past efforts. Thus, in 1999, a Council committee was formed to develop a formal evaluation of the past five years of research funding. This Committee is currently developing processes to answer such questions as:

- ♦ Has BCRP fostered innovation in breast cancer research?
- ♦ Has BCRP funding drawn new people into breast cancer research?
- ♦ Have the research findings enhanced our understanding of breast cancer?
- ♦ Has BCRP research resulted in new methods of early detection or treatment of breast cancer?
- ♦ What can we determine about the impact of the BCRP on the health, social, economic and psychological status of Californians?

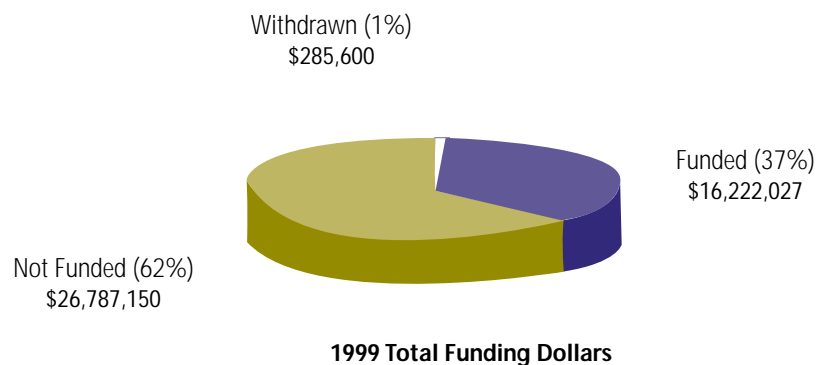
Evaluation activities are planned to take place in 2000 and 2001.

Breast Cancer

Unmet Need

Although many areas of need have been identified in setting BCRP's research priorities, only a few of these areas have been funded to date. Other areas that BCRP has not had the funds to support include:

- ♦ clinical trials to test the effectiveness of new therapies;
- ♦ the development of promising new agents into drugs ready for clinical testing;
- ♦ long-term prospective studies of California girls/women and the risk factors that lead to breast cancer in our population;
- ♦ tissue banks with samples of tumors from California women, together with their clinical information, that could provide the basis for answering numerous questions now and in the future;
- ♦ services provided by community-based organizations that are developed or tested through BCRP research
- ♦ increased involvement by Program staff scientists in developing networks of California researchers and forging new collaborations
- ♦ the more than 100 grant applications that were not funded by BCRP in 1999.



The decline in tobacco tax revenue, which is BCRP's primary source of funding, makes it unlikely that BCRP will ever be able to address these gaps without additional funding from other sources.

Breast Cancer

In 1999, a number of research projects funded in 1995 through 1998 were completed. The results of these projects are summarized in this section. Other projects funded in 1995 through 1998 are still underway. The emerging findings based on the annual progress reports submitted to BCRP are also reviewed in this section. Finally, a new portfolio of grants was awarded in these same areas in 1999. These new projects are also summarized in this section.

BCRP staff monitor the progress of each grant through contact with the investigators throughout the year; investigators also describe their research progress in an annual report to BCRP. Summaries of these reports are rapidly posted to BCRP's web site to allow others to learn of results quickly, rather than to wait the 1-2 years it often takes to reach publication in scientific journals. Once results are published in journals, these citations are placed on the web site, along with links to the abstracts of these articles.

Breast Cancer



the starting point

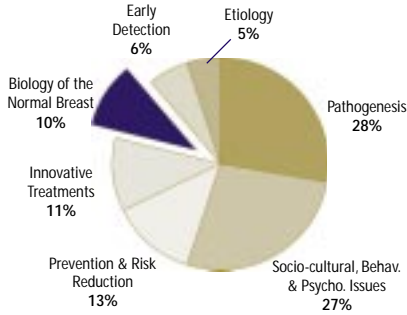
Although much research has been done on the biology of breast tumors; we still know very little about the structure and biochemistry of the normal breast. BCRP has made studying normal breast biology a priority in hopes that we will be able to sort out early steps that occur before actual tumors form.

Research Conclusions

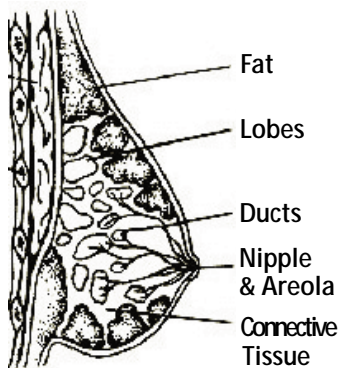
All grants in this priority issue are still underway.

Research In Progress

Distribution of 1999 Funds



All of the projects investigating normal breast biology were underway this year, and several have made significant progress. One group of studies is investigating the influence of hormones and growth factors on breast development. **Mary Helen Barcellos-Hoff, Ph.D.** of **Lawrence Berkeley National Laboratories** has begun studies to determine how the activity of a particular protein called TGF-beta (Transforming Growth Factor-beta) is regulated in different parts of the breast during the different stages of development. The growth and development of particular parts of the breast ductal system (endbuds and lobulo-alveolar structures) are controlled by the hormones estrogen and progesterone. She found that TGF-beta was activated during the growth of these parts of the breast ductal system. Through studies in which mice were treated with hormones, she was able to provide the first evidence that TGF-beta produced in the breast inhibits certain aspects of breast development and that TGF-beta biological activity is under hormone regulation through its precursor. **Satyabrata Nandi, Ph.D.** from the **University of California, Berkeley** is continuing a project to find breast cancer-related genes associated with pregnancy. It is recognized that full-term pregnancy in young women offers a lifetime protective effect of about 30% for later developing breast cancer. Dr. Nandi uses a rat model system and has identified a novel gene, called RMT1, that appears to be present in high amounts in the breast cells of virgin rats. The virgin rats are more susceptible than parous (already having completed pregnancy and birth) rats to chemical carcinogens. The rationale and background for this project were recently published in the *Proceedings of the National Academy of Sciences, USA* (Mar 2, 1999; 96(5): 2520-5).



Some investigations are looking into factors that influence whether cells behave like cancer cells. **Gary Bokoch, Ph.D.** of **The Scripps Research Institute** is continuing his investigation into the connection between growth factors and cell death. He has found that certain enzymes called PAKs have the ability to suppress the cell death that normally occurs when certain growth factors are removed. This is a new mechanism that may explain one way that breast cancer cells avoid dying. Dr. Bokoch has also found that PAK acts on a molecule that regulates the ability of cells to

tamoxifen

contract, a function critical to cell movement and tumor metastasis. He is investigating how this PAK target, as well as others, contribute to cell motility. **Vito Quaranta, M.D.**, also of **The Scripps Research Institute**, is finding that cell motility can be regulated when a particular component of the cellular matrix, Laminin-5, is cut by a specific enzyme, MMP-2. This discovery could ultimately lead to a new therapeutic target for treating breast cancer metastasis. Other researchers are investigating factors that have ultimate chemopreventative implications for breast cancer. **Xiao-kun Zhang, Ph.D.** of **The Burnham Institute** is continuing to characterize the biological effects of different types of retinoids (Vitamin A) on breast cancer cells. His findings have uncovered a molecular basis for the ability of a retinoid acid receptor (RAR-beta) to induce cell death in breast cancer cells. **Nicholas Rampino, Ph.D.**, also of **The Burnham Institute**, is investigating the influence of different estrogen-blocking agents (anti-estrogens) on protecting breast and endometrial cells from damage caused by oxygen. He is finding that after exposure to oxygen, estrogen-sensitive cells treated with raloxifene show lower mutation rates, less DNA damage and less interference with the cell cycle, as compared to those treated with tamoxifen or the pure anti-estrogen ICI 182,780. This finding could provide a basis for optimizing chemoprevention of breast cancer.

Recently Initiated Research

In previous years the Normal Breast Biology Priority Issue could only be addressed by large projects run by established investigators. In 1999 (Cycle V), we offered postdoctoral, new investigator and IDEA awards in this priority issue and awarded seven grants.

mutations

Two postdoctoral fellows are searching for as yet unidentified genes involved in normal cell behavior that could prove to be critical sites for mutations in cancer cells. **Jarnail Singh, Ph.D.** of **The California Pacific Medical Research Institute** is searching for genes that act as intermediates for the Id-1 gene in influencing cell movement and **Hong Zhang, Ph.D.** of **Stanford University** is searching for genes responsible for causing cells to stop dividing (senesce).

Two investigators are determining whether genes that regulate the growth and physiology of normal cells in non-human species, or tissues other than breast, are functional in the breast. **Peter Jackson, Ph.D.** at **Stanford University** is studying POP genes, which when mutated cause yeast to make abnormal amounts of DNA. He is determining whether the POP genes are playing a similar role in the breast. If they are, mutations in these genes could be the basis for oncogene amplification (an early step in the development of cancer) in breast tumors. **Carmen Hagios, Ph.D.** of **Lawrence Berkeley National Laboratory** is undertaking a postdoctoral

fellowship to investigate the role of two embryonic genes, HOXA-1 and HOXB-7, in normal breast. She will determine whether they are factors in breast development and whether deregulation of these genes leads to tumor formation.

Two investigators are defining the role in the normal breast of cellular factors that have already been correlated with tumor formation, with the ultimate goal of determining whether the factors can be exploited for breast cancer treatment, detection, or prevention. **Wen Xie, M.D., Ph.D.** of **The Salk Institute for Biological Studies** is using transgenic mice in her postdoctoral fellowship to characterize the effect of extra ACTR/AIB1, a mediator of estrogen action, on normal breast development and susceptibility to cancer. Nitric oxide stimulates breast tumor development, but there are several conflicting theories about how it is achieving its effect. **Carol MacLeod, Ph.D.** of the **University of California, San Diego** is using transgenic mouse models to investigate the effect of removing nitric oxide on the normal breast, the immune system and tumor development.

Finally, **Sheldon Miller, Ph.D.** of the **University of California, Berkeley** will study the secretory process of the breast. The basic function of the breast is to produce milk, which involves the transport of water across the epithelial cells and into the breast ducts. This essential process of breast biology is poorly understood. Moreover, there is a condition called gross cystic disease, which involves the abnormal accumulation of water in the breast ducts. Women with this condition have an increased risk of developing breast cancer when compared to the general population. Dr. Miller's investigation will provide insight into this condition.

tumor



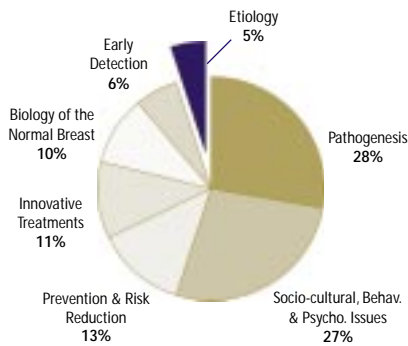
Breast Cancer

Finding the Causes

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

Research Conclusions

Environment and gene/ environment interactions: nature vs. nurture



Distribution of 1999 Funds

Peggy Reynolds, Ph.D. of the **Public Health Institute** investigated whether California flight crews on American airline carriers might have an elevated breast cancer risk as a result of their possible increased exposure to chemicals, cosmic radiation, electric and magnetic fields. This collaborative project between the Association of Flight Attendants (AFA) and the California Department of Health Services' environmental and occupational health programs, found that the two most common invasive cancer types in this group, female breast cancer and malignant melanoma of the skin, occurred substantially more frequently among flight attendants than would be expected from the rate of the general population. Breast cancer incidence was over 30% higher than expected, and melanoma incidence was roughly twice that expected. These findings were consistent with the results from a much smaller European study of cabin crews, and suggest that follow-up investigations should focus on the potential relative contribution of workplace exposures and lifestyle characteristics to the higher rates of disease for these two cancers.

Margaret Wrensch, Ph.D. of the **University of California, San Francisco** and **Mary Gould**, of the **Marin Breast Cancer Watch (MBCW)**, a grass-roots organization of approximately 350 members, were funded to do a pilot study regarding the high incidence of breast cancer in Marin County. They are investigating the question: did adolescent and pre-adolescent experiences differ between women with and without breast cancer in Marin County? They completed comprehensive literature reviews into the role of pre-adolescent and adolescent factors in breast cancer development; the effects of recall bias (differential and non-differential) on interpretation of results of case-control studies; and on mechanisms for enhancing recall and minimizing effects of recall bias. Focus groups were conducted, one aim being to develop methods to help women remember accurately their pre-adolescent and adolescent experiences and exposures, with the aim of using these methods in a population-based research project. The success of this pilot enabled the collaborative team to obtain a full BCRP research grant to pursue these questions further.

virus

Linda Kingsbury, Ph.D. of the **University of California, Berkeley** completed a two-year postdoctoral fellowship entitled "Bovine Leukemia Virus and Mammary Cell Infection" that investigated whether bovine leukemia virus (BLV) was able to infect human breast cells. The theory that BLV infection can lead to breast cancer in humans is based on the observation that infection by a virus (MMTV) can lead to breast cancer in mice. BLV, a virus similar to MMTV, has been found in milk from cows but can only cause breast cancer if it has the ability to get inside human cells. Viruses enter cells through specialized proteins called receptors. Dr. Kingsbury performed studies to determine whether these receptors exist in human breast cells. She employed five different methods to detect BLV receptors. She was able to identify BLV receptors in several human breast cancer cell lines as well as in human fibroblasts. This

supports the idea that the BLV will be able to enter human breast cells and infect them – the first step toward the development of cancer.

Donna Williams-Hill, Ph.D. of the **University of Southern California** completed a 3-year New Investigator award entitled “BRCA1 Regulation in Breast Cancer: A Rat Mammary Model”. Dr. Williams-Hill examined the role of the breast cancer gene, BRCA-1 in the development of the rat mammary gland. She found that BRCA1 is present in the breast tissues of adult rats proportional to their genetic susceptibility to induced breast cancer. Levels of BRCA1 increase as the rat matures. BRCA1 levels are lowest in the mammary gland of 3-week old rats and increases gradually as the rat ages to 5 weeks (pre-puberty) and 8 weeks (puberty). As BRCA1 increases, the susceptibility to breast cancer decreases. These observations are consistent with the reported role of BRCA1 in DNA repair. With this information, we could learn about what BRCA1 is doing in normal human breast cells and extrapolate what could be going wrong in cancer cells with the BRCA1 mutation.

Vitamin D

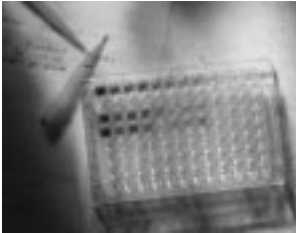
Sue Ingles, Dr.P.H. of the **University of Southern California** was funded to investigate the possibility that vitamin D may reduce the risk of breast cancer by interacting with vitamin D receptors (which occur in at least two different genetic “types”) in the breast and other tissues. Specifically, her goal was to develop genetic “markers” that could be used to measure vitamin D receptor types, and to determine whether women with specific vitamin D receptor types are relatively protected against breast cancer. Results indicate that nearly a quarter of women in California may be at increased risk of breast cancer, either because they have inherited two copies of a non-protective-type vitamin D receptor gene or because they have vitamin D deficiency. Therefore, development of effective interventions targeted to these at-risk women could significantly impact breast cancer incidence or mortality in California. Furthermore, she found a third vitamin D receptor genetic type and found that women who inherited this third type from both parents appear to have the highest levels of vitamin D in the blood. These results, however, need to be confirmed in larger studies.

Hormones and Nutrition: Understanding the Modern Woman’s Lifestyle



Anna H. Wu, Ph.D. at the **University of Southern California** was funded to investigate the causes of Asian-American’s increased breast cancer rates as compared to the rates of breast cancer in Asia, by testing the hypothesis that a diet rich in soy products reduces the risk of breast cancer. Preliminary analysis shows that the mean intake of soy (in milligrams of isoflavones per day) among Asian-American women without breast cancer in Los Angeles was one-fifth to one-half of that reported in recent Asian studies, with the highest intake of soy among the Chinese. In case-control comparisons, her findings showed a 30% reduction in risk in association with the highest level of isoflavone intake after adjustment for other factors that might also affect risk. When risk patterns in relation to intake of individual soy foods were examined, statistically significant reductions in risk were observed in association with the highest intake level of fresh tofu, eaten alone or in mixed dishes.

metabolites



Breast cancer risk has been hypothesized to increase with exposure to carcinogens formed when meat is cooked at high temperature. **Ralph Delfino, M.D., Ph.D.** at the **University of California, Irvine** examined the role of certain of these compounds (HAAs, heterocyclic aromatic amines). HAAs require an enzyme produced by the body to become potentially cancer causing. The rate of this enzyme's activity is determined by a gene called *NAT2*. Dr. Delfino and his group examined the effect of variations of the *NAT2* gene on breast cancer risk from exposure to meat comparing cooking method, doneness, and estimated intake of three important HAAs. There were no significant associations of breast cancer with red meat for any doneness category. However, white meat seemed to be significantly protective. Women eating over 67 grams per day had half the risk of breast cancer as compared with women eating less than 26 grams per day. The results were also similar for well-done pan-fried or barbecued chicken, which is known to have higher concentrations of HAAs. Therefore, these findings do not support a role for HAAs from meat or *NAT2* in the etiology of breast cancer. Results are still preliminary, and further research is needed to explain the apparent protective effect of white meat intake.

PhIP is a cancer-causing agent that can be generated by cooked meats and has been shown to cause breast cancer in rats. **James Felton, Ph.D.** of **Lawrence Livermore National Laboratory** completed a study investigating this compound entitled "Linking a Dietary Carcinogen to Breast Cancer Susceptibility". PhIP is broken down by the body into different chemicals (metabolites), which have different abilities to cause breast cancer. The ultimate goal of this project was to determine the PhIP metabolite profile that is associated with breast cancer susceptibility, and thereby generate a measure for determining a woman's relative risk of developing breast cancer. Dr. Felton developed a method to detect PhIP metabolites in human urine. Although he was unable to identify a specific profile for susceptibility, Dr. Felton was able to establish that individual metabolism can affect the amounts and rates of carcinogen excretion and that other dietary components (such as fruits and vegetables) can modulate it.

Heather Feigelson, Ph.D., M.P.H. of the **University of Southern California** expanded her earlier work on two genes, *CYP17* and *HSD17B1*, involved in the synthesis of estrogens and plasma levels of hormones in healthy, postmenopausal women. (Estrogens and other hormones play an important role in breast cancer.) This work indicated that a certain form of *CYP17* is associated with a 2.5 times increased risk for advanced breast cancer. Preliminary evidence suggested that both *CYP17* and *HSD17B1* influence body hormone levels. On average, levels of androstenedione and estrone are 5-9% higher in women with the "higher risk" type of either of these two genes (results did not reach statistical significance due to small number of samples). *CYP17* also influences a modifiable breast cancer risk factor: depending on *CYP17* genotype, some women were twice as likely to be current users of hormone replacement therapy (HRT), suggesting that *CYP17* genotype may be an important piece of information for women seeking advice on HRT use, and that the actual risk of breast

cancer associated with HRT use may be higher than previously reported. These results were consistent across all four ethnic groups (African-American, Japanese, Latina and White) included in the study.

Ann M. Geiger, Ph.D. of the **Kaiser Foundation Research Institute** investigated the possible relationships between commonly understood breast cancer risk factors and the presence of structures (receptors) in breast tumors that bind to the hormones estrogen and progesterone. These hormones can enter a tumor and influence the tumor's growth. She looked at the records of 2,441 women with breast cancer in a large HMO whose tumors had positive test results for estrogen and/or progesterone receptors. She then obtained information from the women on their risk factors for breast cancer. Analysis to date is focussing on postmenopausal women and has found that, for women with breast cancer, the presence of estrogen receptors on the tumor is less common in blacks and Hispanics than in white women; and more common in women whose mothers had breast cancer than in women whose mothers did not. Another preliminary analysis suggests that women who have used hormone replacement therapy are diagnosed with cancers at an earlier stage.

Other Searches for the Causes



Thomas Balon, Ph.D. of **City of Hope National Medical Center** completed his IDEA grant entitled "Nitric Oxide's Role in Breast Cancer Metabolism and Growth". Dr. Balon's goal was to determine whether chemicals that regulate the cell's ability to take up and metabolize fuel behave differently in normal and tumor breast cells and whether any differential regulation is influenced by estrogen. Nitric oxide (NO) is a chemical that is intimately involved in the transport of sugars (the source of energy) into the cell. Breast cells are able to produce nitric oxide, but when this production is inhibited, there is no effect on the growth of normal breast cells, hormone-responsive breast cancer cells or non-hormone responsive breast cells. However, Dr. Balon found that if he exposed the different cell lines to compounds that caused the cells to release nitrous oxide into the cell's surrounding environment, there was a differential effect. The normal breast cells and hormone responsive breast cancer cells did not respond, whereas the growth of the non-hormone-responsive cancer cell lines decreased. In the future, Dr. Balon plans to make compounds that will take advantage of this differential effect and inhibit the growth of tumors cells while not affecting the growth of normal cells.

estrogen

Although it has been hypothesized that lesbians are at greater risk of breast cancer than heterosexual women are; no studies have yet been reported comparing breast cancer risk factors among these groups. **Suzanne L. Dibble, D.N. Sc.** of the **University of California, San Francisco** and **Stephanie Roberts, M.D.** of the **Lyon-Martin Women's Health Services** undertook such a comparison among women, aged 35 or older, seen at Lyon-Martin. There were no significant differences between lesbian and heterosexual women in occurrence of family history of breast cancer, current alcohol usage or history of alcohol problems, age at

training

menarche and menopause, or use of hormone replacement therapy. However, lesbians reported more breast biopsies, less use of birth control pills, higher body mass index, fewer pregnancies and fewer biological children. These results suggest that, since lesbians have a higher rate of some known breast cancer risk factors, they may be at higher risk of breast cancer. Future studies are needed, and if these differences are replicated in a larger study, the next step will be to inform both lesbians and their health care providers of the potential breast cancer risks. Studies are also needed to find the best ways to reach lesbians for breast cancer screening.

Ronald Ross, M.D. at the **USC/Norris Breast Cancer Research Center** was funded to implement a formal, focused, interdisciplinary graduate research training program devoted to breast cancer research. The goal was to train graduate students in research to better understand the reasons for the underlying differences in breast cancer incidence, mortality and survival among the numerically most important racial-ethnic groups comprising Los Angeles County, the most populous and ethnically diverse County in the United States. The program is multi-faceted and involves epidemiologists and prevention scientists, behavioral scientists, tumor biologists, and molecular geneticists, and radiation, surgical and medical oncologists. The training program has been highly successful. Five trainees have been supported from among 10 highly qualified applicants each year, after careful review and scoring by senior scientists at the Center. Trainees are highly multi-disciplinary in their interests, which include pathology, molecular biology, cell biology, and cancer control. Trainees have been matched to an appropriate faculty mentor with an active breast cancer research program. This work is continuing through another three years of funding begun in June of 1998.

Research In Progress

Environment and gene/environment Interactions: Nature and Nurture

Deirdre Hill, Ph.D. of the **University of Southern California** has been funded to investigate several factors that may be related to breast cancer risk among women 40 and younger and has completed work on the first research question: do women who received diagnostic X rays or radiation therapy prior to age 20 have an increased risk of developing breast cancer at age 40 or younger? Focusing on women with a family history of breast cancer or a personal history of benign breast disease (some studies suggest a greater susceptibility to ionizing radiation among these women), they found that breast cancer risk was elevated following medical radiation received *prior to age 20* primarily among women with benign breast disease. Women who reported benign breast disease, and who received moderate radiation exposure prior to age 20, had a breast cancer risk that was 2.1 times greater than women who reported neither.

The Bovine Leukemia Virus (BLV) provides an interesting possible cause of breast cancer. The virus is present in cow's milk, but additional research needs to be performed in order to determine whether humans are actually exposed to the virus. **Gertrude Buehring, Ph.D.** of the **University of California, Berkeley** has found evidence of the presence of the virus protein in a proportion of breast tissues as well as an antibody response to the virus. This indicates that humans are indeed exposed to BLV.

Hormones and Nutrition: Understanding the Modern Woman's Lifestyle



While the exact causes of breast cancer remain unknown, certain aspects of a woman's life appear to increase her chances of breast cancer. A woman who has her first menstrual period at an early age is more likely to be diagnosed with breast cancer than a woman who has her first menstrual period at a later age. **Carol Koprowski, Ph.D.** of the **University of Southern California** analyzed data previously gathered on a total of 751 girls (4th through 7th grade) who provided information on diet and physical activity at least one time prior to experiencing their first menstrual periods. The results of this study indicated that girls who spent more hours in physical activity (13 or more hours per week) were more likely to have their first menstrual periods at later ages when compared to girls who spent fewer hours performing physical activity (less than five hours per week). Current analyses are examining the relationship between diet, physical activity and ovulatory status of a menstrual cycle (i.e., whether an egg is released during the menstrual cycle).

Recently Initiated Research

estrogen

Eight projects funded in 1999 focus on the causes of breast cancer. Given the evidence that there is a strong association between lifetime exposure to estrogen and increasing breast cancer risk, it is not surprising that six of the eight grants funded under this priority issue are aimed at understanding the role of estrogen, though their approaches differ widely. **Leslie Bernstein, Ph.D.** of the **University of Southern California** will investigate leptin, a newly discovered hormone produced by fat cells. Large amounts of adipose (fat) tissue in obese women increase circulating estrone (a form of estrogen) levels in proportion to the amount of adipose tissue. Leptin could be a factor in breast cancer etiology because of the important role that it plays in fat storage and metabolism. **Donna-Williams Hill, Ph.D.** of the **University of Southern California** will undertake to isolate the mechanisms by which exercise produces protective factor(s) against breast cancer. Many studies have been conducted, but it is not yet known what types, duration, intensity of exercise is likely to be best and for whom. By using a rat mammary model, Dr. Hill will be able to control for several of the factors (confounding variables) which to date have made interpretation of exercise studies in humans difficult. **Brian Henderson, M.D.**, also of the **University of Southern California** will look

soy

at several molecules, called insulin-like growth factors or IGFs, that collaborate in stimulating cell division by mediating the effect of estrogen. He will analyze blood samples from postmenopausal African-American, Japanese, Latina, and non-Latina White women to determine if circulating levels of IGFs and their binding proteins differ by race or ethnicity. His results will enlarge those of a previous study by a colleague showing strong positive association between IGF-1 and breast cancer in a small group of premenopausal White women. **Vicki Davis, Ph.D.** of **Cedars-Sinai Medical Center** will investigate whether it is possible to obtain protective effects against breast cancer by inhibiting estrogen action in the breast, while maintaining the important beneficial effects of estrogen such as protecting against heart disease and osteoporosis, by looking closely at a natural variant of the estrogen receptor on cells called estrogen receptor alpha.

There is strong evidence that certain dietary patterns are associated with lower breast cancer risk. Most notable of these is a diet rich in soy products which seems to lessen the impact of estrogen on breast cells. **Anna H. Wu, Ph.D.** of the **University of Southern California** will conduct a case-control study to investigate soy-estrogen metabolizing gene interaction, specifically variants of the CYP17 and COMT genes. This large study (which will result in a sample size of approximately 1300 cancer cases) is necessary to sort out the complex and interrelated lifestyle/environmental and genetic factors in breast cancer development.

Ann Hamilton, Ph.D. also of the **University of Southern California** will probe the genetic basis of estrogen's role in breast cancer from yet another direction by looking at pairs of identical twins. Using tissue from 200 pairs of identical twins, both with breast cancer, 200 pairs, one with breast cancer, and 100 pairs, neither with breast cancer, she will compare the frequency of one genetic polymorphism among these groups, called the A2 allele on the CYP 17 gene, which has been shown to be related to higher levels of estrogen.

Two studies undertake other etiologic investigations: adolescent risk factor identification, and testing hypotheses about a mechanism by which cell growth may become uncontrolled.

Georgianna Farren of **Marin Breast Cancer Watch** and **Margaret Wrensch, Ph.D.** of the **University of California, San Francisco** (co-PIs), heading a community-university collaboration, will investigate possible risk factors encountered by adult women residents of Marin County during their adolescence. An important methodological innovation is the development of survey instruments that may prove very useful in overcoming one of the most intractable barriers to such research, namely the accuracy and completeness of recall by women of events which occurred decades previously. Another study will investigate the role of the enzyme ornithine decarboxylase. Based on previous research, it appears that ornithine decarboxylase exists in rapidly growing and cancerous tissue at high levels. **Craig Byus, Ph.D.** of the **University of California, Riverside** will attempt to identify in model cell lines of human mammary tissue and carcinomas where there are genes that are turned on and off when ornithine decarboxylase is present at these high levels, as a preparatory step to understanding their function.

Prevention and Risk Reduction

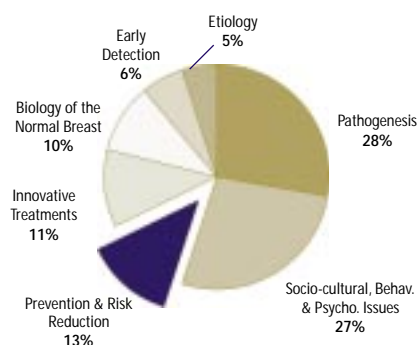
Breast Cancer

Ending the Danger of Breast Cancer

Only a maximum of 20% of breast cancer is thought to be due to inherited genes. Thus, as much as 80% of breast cancer is caused by factors other than inherited genes; namely environmental and lifestyle factors. The incidence of breast cancer thus has the potential to be reduced or avoided by alterations in our environment, our diet, physical exercise or hormone levels. Identifying prevention strategies and understanding how they interface with a woman's underlying immunological, hormonal, cellular, and genetic makeup is a BCRP Priority Issue. Much of the work that BCRP funds that looks at risk identification and risk reduction is now aimed at understanding the individual lifestyle differences between women who contract breast cancer and women who do not. Many funded projects examine specific dietary factors to understand the molecular basis for their possible components into preventative agents.

Research Conclusions

Distribution of 1999 Funds



Gary Firestone, Ph.D. from the **University of California, Berkeley** completed a 2-year IDEA project to study *Dietary Indole Inhibition of Breast Cancer*. A naturally occurring compound, called indole-3-carbinol (I3C), produced in cabbage, broccoli, and Brussels sprouts can inhibit the growth of human breast cancer cells grown in the laboratory. Dr. Firestone found that I3C works by causing a drop in the amount of a critical protein (CDK6) needed for cells to pass through a cell division checkpoint, and also causes an inhibition of a functionally related protein, called CDK2. Importantly, I3C was found effective for both tamoxifen-sensitive and tamoxifen-resistant breast cancer cells. I3C has promise both as a preventative compound and as a treatment option. For example, it could be used as adjunct therapy with tamoxifen and for breast cancers where the only current options are surgery and radiation therapy. The results of this project were published in the *Journal of Biological Chemistry* (Feb 13, 1998; 273(7): 3838-47) and in *Cancer Research* (Mar 15, 1999; 59(6): 1244-51). In 1999, the BCRP funded Dr. Firestone and a postdoctoral fellow in his lab for new grants to continue the development of this project in a pre-clinical direction.

Research in Progress

Shiuan Chen, Ph.D. at the **Beckman Research Institute of the City of Hope** is looking further into some intriguing findings that show that grape juice suppresses breast cancer cell growth. Grape juice seems to prevent the synthesis of estrogen, the female hormone linked to breast cancer. Previous experiments had demonstrated that tumors implanted in mice fed grape juice daily for 5 weeks were one-third the size of those in mice not fed grape juice. Dr. Chen is performing more extensive animal studies using mice and rats to critically evaluate these preliminary findings. During the last year, he has worked out details of the animal experiments, initiated the separation of the active components in grape juice, and found that red wine extract, but not white wine extract, contains similar chemicals that can suppress estrogen formation.

grape juice



Kent Erickson, Ph.D. at the **University of California, Davis** is continuing a project to determine how dietary fat could be altered to reduce the growth and spread of breast cancer. His first aim is to test the effects of dietary fat on metastasis, because most deaths from breast cancer are due to the spread of the tumor. He has found that when animals are fed high levels of fish oil, breast tumor growth is slower and the level of metastasis to the lungs is decreased compared to animals fed a diet containing safflower oil. This suggests that the effect of fish oil may be to decrease levels of the protein that stimulates growth of new blood

vessels into tumors. Dietary fat may also alter levels of specific enzymes associated with tumor growth and metastasis. For example, breast tumors produce an unique enzyme that is increased in animals fed the vegetable oil diets, whereas the levels of a natural inhibitor of that enzyme are increased in tumors of animals fed the fish oil diet.



Pamela Horn-Ross, Ph.D. of the **Northern California Cancer Center** is addressing two questions relevant to our understanding of diet and breast cancer. First, do estrogen-containing plant foods eaten in amounts commonly consumed by non-Asian postmenopausal women reduce breast cancer risk? Second, does obesity increase breast cancer risk only when a woman's diet does not contain a sufficient amount of plant estrogens? Preliminary analyses suggest that recent consumption (i.e., within the year prior to breast cancer diagnosis) of foods containing plant estrogens does not impact breast cancer risk in non-Asian postmenopausal women. Second, there was a tendency for obesity to increase a woman's risk of breast cancer, but only when the diet did not include a substantial amount of plant estrogen-rich foods. At present, this study suggests that foods rich in plant estrogens do not appear to be useful in breast cancer prevention at levels commonly consumed by non-Asian women.

foods

Ling Jong, Ph.D. from **SRI International** is developing a safe, effective, and reliable breast cancer preventive agent, without the undesirable side effect of tamoxifen, based on a tumor-inhibiting compound that occurs naturally in cruciferous vegetables, such as cauliflower and Brussels sprouts. This compound, called indole-3-carbinol (I3C), is known to be converted into several different active forms in the body. Dr. Jong designed and synthesized variations of 3-3'-diindolylmethane (DIM), which is a major active form of I3C, and discovered four active analogs. One analog has 15 times the growth inhibitory activity of DIM. Computer-aided molecular modeling is being used to correlate bioassay results with molecular structure. Understanding how structural changes in the compound affect anti-tumor activity will help generate more active and promising cancer preventive agents in the future.



Nurulain Zaveri, Ph.D. from **SRI International** is continuing a New Investigator project to develop and test more effective compounds based on an active anti-cancer agent from green tea, called epigallocatechin-3-gallate (EGCG). Many breast cancer survivors practice alternative therapy by using naturally occurring dietary compounds. In many cases, it is proving very difficult to extract, purify, and study these compounds using the pharmaceutical methods of Western medicine. However, these compounds, including EGCG, are excellent starting points for rational drug design. Dr. Zaveri's project is addressing the critical issues of potency and absorption properties to select EGCG derivatives as new candidate breast cancer therapeutics.

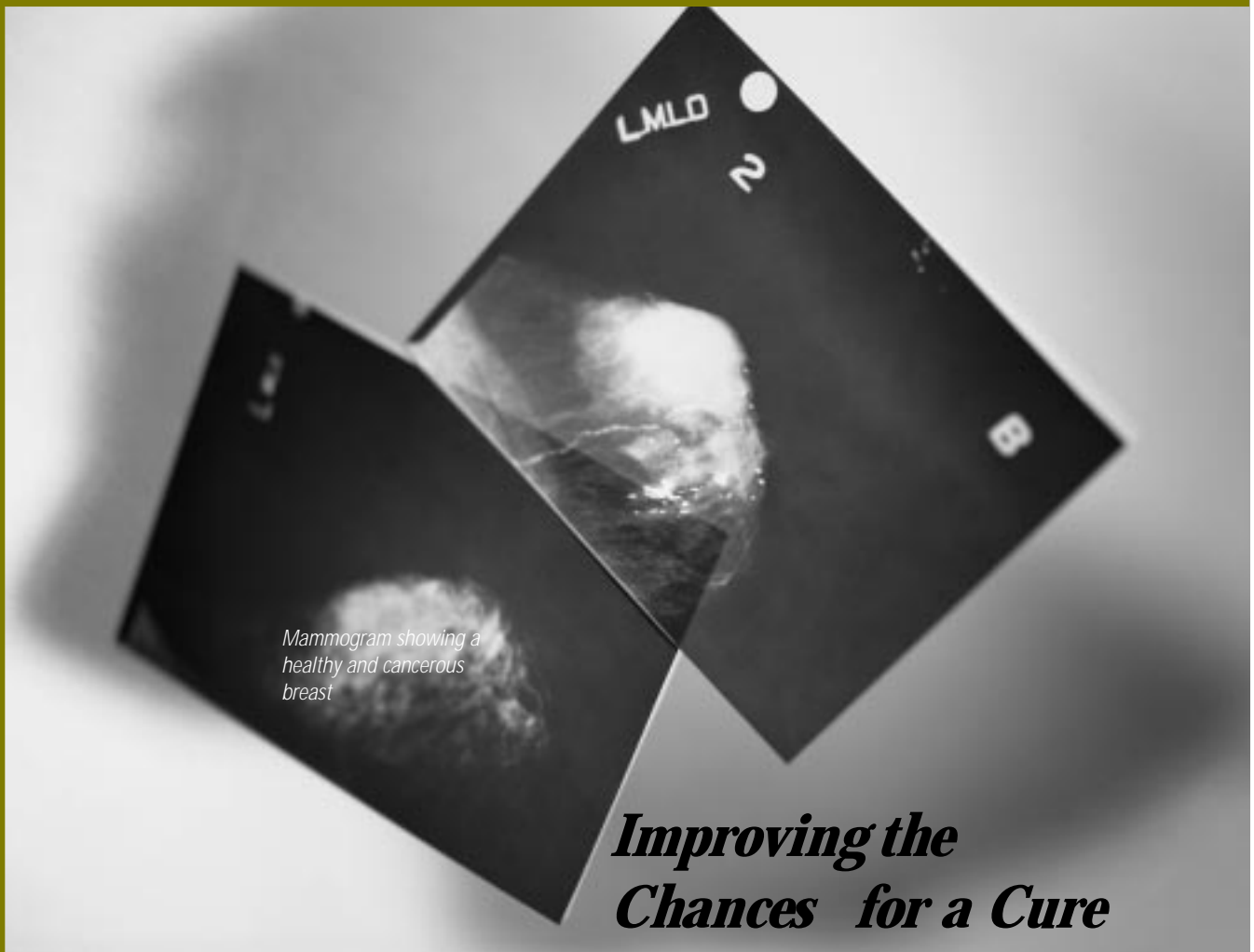
Recently Initiated Research



exercise

Three grants awarded in 1999 also address the Prevention and Risk Reduction Priority Issue. **Donna Williams-Hill, Ph.D.** at the **University of Southern California**, is investigating the mechanisms by which exercise may reduce risk of breast cancer. Many studies have been conducted, but it is not yet known what types, durations or intensities of exercise are sufficient and most effective, and for whom. By using a rat model, Dr. Hill is controlling for several of the factors that have made human studies on exercise difficult. Next, **Vicki Davis, Ph.D.**, at the **Cedars Sinai Medical Center**, is investigating whether it is possible to obtain protective effects against breast cancer by inhibiting estrogen action in the breast, while maintaining the important beneficial effects of estrogen on the rest of the body, such as protecting against heart disease and osteoporosis. She is looking closely at a natural variant of the estrogen receptor, called estrogen receptor alpha. Finally, there are indications that certain dietary patterns are associated with lower breast cancer risk. Most notable of these is a diet rich in soy products, which seems to lessen the impact of estrogen on breast cells. **Anna H. Wu, Ph.D.** from the **University of Southern California**, is conducting a case-control study to investigate soy-estrogen metabolizing gene interaction, specifically variants of the CYP17 and COMT genes. This large study (which will result in a sample size of approximately 1300 cancer cases) is necessary to sort out the complex and interrelated lifestyle/environmental and genetic factors in breast cancer development.

Breast Cancer



Mammogram showing a healthy and cancerous breast

Improving the Chances for a Cure

Until breast cancer can be prevented, detection at the earliest time possible remains an essential goal. Over the period 1988-1995, the percentage of invasive breast cancer discovered at its earliest stage (Stage I) improved almost 30% percent, from about 35% to 45%. We hope that the application of BCRP-supported research findings can contribute to the continued improvement in this trend.

Research Conclusions

Developing and Improving Imaging Technologies: Better and Easier Detection



To achieve the goal of improving chances for a cure, cancer must be found as early as possible, when the tumor is still very small and is most likely not to have produced metastasizing cells. Much of BCRP's funding of early detection technology research has been aimed at: 1) improving the sensitivity (capability of finding very small tumors) and sensitivity (capability of distinguishing between true cancers and other breast or image anomalies) of existing technologies; 2) adapting existing technologies specifically for breast imaging; 3) improving the clinical application of existing technologies; and 4) bringing new technologies closer to the point of clinical application.

William Moses, Ph.D. of the **Lawrence Berkeley National Laboratory** has been working to adapt an existing technology that uses gamma rays (Positron Emission Tomography or PET) to be more suitable for breast and axilla imaging. His original goal was to develop an instrument with higher efficiency (up to 30 times greater), finer spatial resolution (0.9 mm), and lower cost (possibly by a factor of 10) than conventional PET cameras currently in use for body imaging. To date, most of the originally proposed work has been completed: 1) many details of the detector module concept have been worked out; 2) several prototype modules have been constructed and tested, and all parts necessary to complete production are in hand; 3) the necessary electronics have been fabricated and tested (although some work is still necessary on the custom integrated circuit and one of the four types of readout circuits); and 4) preliminary versions of the software necessary to operate the camera, acquire data, calibrate the system, and reconstruct images from the data have been developed. Additional funding (from another source) has been obtained to complete the device.

Manbir Singh, Ph.D. of the **University of Southern California** was funded ("*High Resolution Breast Gamma Emission Imaging System*") to design a novel breast cancer detection system to give a three-dimensional image of small lesions in the breast after injection of a trace amount of a radiolabeled pharmaceutical. Previous studies in this field have relied upon two-dimensional "projection images" which, though limited in their accuracy, can convey very useful physiologic information to help physicians differentiate malignant from benign lesions. With the proposed three-dimensional imaging system, it was hoped that detection of smaller lesions with a volume of .05 to 0.1 cc would be possible. Experimental three-dimensional imaging studies of a test-object simulating radioactive uptake in lesions and a background region in the breast have been conducted with an array of CZT detectors representing a small-scaled version of the proposed system. Results confirm the computer simulation studies and suggest that in an imaging time ranging from 20 minutes to 1 hour,

accumulation of the radiolabeled pharmaceutical in lesions of volume 0.1 to 0.5cc would be detectable in a clinical situation. This limit is a factor of 2-4 times better than achievable with current clinical gamma imaging systems and would represent a significant improvement in the ability to distinguish malignant from benign lesions.

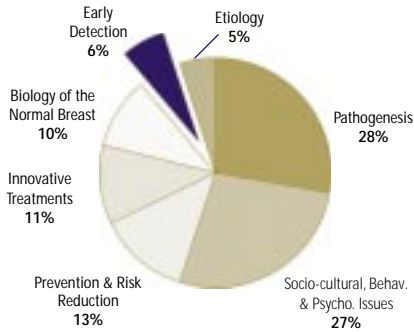


Orhan Nalcioglu, Ph.D. from the **University of California, Irvine** finished a 2-year IDEA project concerned with the *MRI Detection of Breast Cancer Blood Vessels*. The goal of this work was to develop advanced chemical agents to detect breast cancer blood vessels using Magnetic Resonance Imaging (MRI). This would allow more advanced diagnosis and visualization of breast cancer compared to traditional mammography. Dr. Nalcioglu developed an MRI contrast agent that contained protamine, which is a simple, low molecular weight protein derived from salmon sperm. It is normally used to treat patients that have been overdosed with the anti-coagulant heparin following cardiopulmonary bypass. Protamine binds to and neutralizes the activity of heparin. Dr. Nalcioglu attached protamine to an MRI contrast agent, and demonstrated an excellent detection of experimental breast tumors in rats. Apparently, the blood supply to breast tumors contains heparin exposed to the circulation, and results from this project indicate that neutralization of heparin at these sites could have a positive detection or therapeutic value.

H.K. Huang, D.Sc. of the **University of California, San Francisco** was funded to try to integrate the process of acquiring, storing, communicating, visualizing, managing, and analyzing digital mammography examinations within the operational environment of a university-based diagnostic center and a community-based general-radiologist mammography practice based some distance away. Technically, they found that the image quality of their full field digital mammography system was at least as good, if not better, than a conventional film/screen mammography system, and it took less than seven seconds to transmit a full resolution digital mammogram (40 Mbytes) between the two locations. Also, the image management system requires only two minutes to automatically archive the images after an examination and categorize them in the database for immediate distribution; and, the workstations, coupled with a dual cursor system, can be used for telediagnosis and teleconsultation between a referring physician and an expert mammographer at a different location. In summary, he and his team feel that they have developed and validated a telemammography system that can be used for the real-time off-site management and interpretation of a community-based general radiologist mammography practice by mammography specialists.

Jack Sklansky, Eng.Sc.D. of the **Charles R. Drew University of Medicine & Science** and his colleagues were funded ("A Neural Network for Case-Based Diagnosis in Digital Mammography") to help radiologists use large collections of digitized mammograms as aids in determining whether or not to recommend biopsies and to help reduce the number of unnecessary biopsies without increasing the number of missed cancers. He tested the system

Distribution of 1999 Funds



with a panel of four radiologists, using a database of “regions of interest” (ROIs) in which microcalcifications are visible, and found that the sensitivity and the specificity of each computer-aided radiologist significantly exceeded the sensitivity and specificity of each unaided radiologist and of the computer alone. He concluded that that radiologists interacting with this mapped database of proven mammographic ROIs are likely to achieve significant reductions in the number of unnecessary biopsies and the number of misdiagnosed cancers when interpreting mammograms containing images of microcalcifications.

Daniel Valentino, Ph.D. at the **University of California, Los Angeles** completed his four-year project (“*Digital Imaging for Hospital and Community-Based Mammography*”). During the final year, his team completed the development of an infrastructure for high-performance interfaces, networks and servers that enable direct digital mammography units to send images quickly to display workstations, and to store images permanently in archival devices. They also tested a high-speed ATM network (ultrafast networks using asynchronous transfer mode—ATM- technology) which can provide the bandwidth and throughput that may produce images of sufficient quality to satisfy the medical imaging community.

imaging

Improving Access to Screening: Reaching Every Woman

Stephen J. McPhee, M.D. of the **University of California, San Francisco** in his project “*Promoting Early Detection Of Breast Cancer Among Vietnamese*” sought to increase access to early breast cancer detection services by Vietnamese women through a large community intervention. Although efforts of the California Breast Cancer Early Detection Program served to increase awareness in the comparison community, thus making interpretation of results difficult, women who reported greater exposure to the various intervention elements were significantly more likely to have heard of, had, and plan a clinical breast examination and to have heard of, had, and plan a mammogram than women with lesser exposure.

The investigators conclude that, although the intervention had no beneficial effect in the community at-large, it had a modest positive impact on those women who reported exposure to the intervention.

BCRP feels that it is important that researchers developing new technology have a broader understanding of the clinical issues associated with new technologies. Many breast cancer researchers have very narrow, specialized understanding of the disease or misunderstand the relationship of their research to breast cancer detection and treatment. **Carolyn Kimme-Smith, Ph.D.** at the **University of California, Los Angeles** has completed three years of her “*UCLA Biomedical Physics Graduate Training in Breast Cancer*”. Two of the students trained in the program have specialized in developing PET and Gamma camera detectors for breast cancer, and two others specialized in Radiation Oncology for Breast Cancer. One student has specialized in Digital Mammography. In addition to this specific training, the program

provides a broad base of knowledge to allow graduates to be resources for researchers other than physicists alone, as well as become principal investigators on their own research projects.

Noreen Facione, Ph.D., R.N. of the **University of California, San Francisco**, in a study involving more than 1,000 women in the San Francisco Bay area in community based focus groups, surveys, and interviews, described how women make judgments about self-discovered breast symptoms that might signal breast cancer. The many influences on this judgment process were described in three diverse groups: women who identified themselves as Anglo/White, African American/Black, or Latino/Hispanic. The likelihood of making a judgment to delay a medical visit was correctly predicted in 31% to 66% of the women in these three cultural groups. The most influential of the variables are attitudes and beliefs that are common to the three cultural groups. These included inaccurate beliefs about the incurability of breast cancer and its presenting symptoms, perceptions of constraints on early detection associated with women's roles, immigration concerns and provider relationship issues. A proportion of this volunteer sample (13.1%) reported currently having breast symptoms and only 50% had been examined by a provider. The variables associated with a decision to delay seeking medical evaluation of symptoms correctly predicted actual delay behavior in 87% (52 or 60) of these women.

detection

California represents a major gateway for Pacific Islanders into the United States and little is known about their health beliefs, practices, and needs. **Sora Park Tanjasiri, Dr.P.H.** of the **University of California, Irvine** examined the breast cancer knowledge, attitudes and screening behaviors of two groups of Pacific Islander women — Chamorros (indigenous Guamanians) and Tongans — aged 40 and older in Los Angeles and Orange County. Among her findings was the fact that only 12.9% of Tongans had yearly clinical breast exams and only 10.2% had yearly mammograms. For Chamorros, while 66.2% had yearly clinical breast exams, only 25.3% had yearly mammograms. In addition, many barriers to screening were identified, including cost, language, and lack of knowledge for both populations.

Biomarkers and Novel Screening Approaches: Unmasking the Hidden Signs

Margaret Wrench, Ph.D. of the **University of California, San Francisco** studied breast cancer incidence in women with abnormal cytology as determined by using nipple aspirate fluid from a previous study of 6,908 women. Preliminary findings indicate that *compared with women who yielded no fluid*, women who yielded fluid had relative risks of breast cancer as follows: normal cytology, 1.5; hyperplasia, 2.2; and atypical hyperplasia 2.5. Women from whom they obtained fluid were 1.6 times as likely to develop breast cancer as women who did not yield fluid were (95%CI: 1.3-2.1).

These findings varied somewhat according to the women's family history of breast cancer or previous benign breast biopsy and provide continued strong support for the hypothesis that hyperplasia and atypical hyperplasia diagnosed in nipple aspirate fluid indicate an increased risk of breast cancer.

Research In Progress

Developing and Improving Imaging Technologies: Better and Easier Detection

Laura Esserman, M.D. of the **University of California, San Francisco** is investigating the factors required to achieve high cost-effectiveness in mammography screening in California, and then developing a plan to promote the provision of the highest quality screening services for the least possible cost. To date she has found, based on California data, that there is indeed a correlation between volume of mammograms read by a radiologist and increased sensitivity and specificity in the radiologist's interpretations. This volume-outcome relationship is at least one factor that promotes efficiency and quality in mammographic services.

Also, preliminary data from randomized controlled trials of mammography in Malmo and Stockholm suggest that sensitivity has remained constant over a 20-year period, cancer to biopsy rates increased, and both interval cancers and false-negative rates have decreased during the same period, demonstrating that increased specificity is learned over time, without impact on sensitivity.

Improving Access to Screening: Reaching Every Woman

Mary Smith, M.S., C.R.C. and Carol D'Onofrio, Dr. P.H. of the **Alta Bates Foundation** and **Northern California Cancer Center**, respectively, have undertaken a study of issues intended to increase access to breast screening for women with disabilities. The need for this study was demonstrated in a previous BCRP-funded pilot study. The work to date has involved the preparation of several large databases necessary for initial analysis and for the creation of a field survey.

Biomarkers and Novel Screening Approaches: Unmasking the Hidden Signs

David Vera, Ph.D. of the **University of California, San Diego** intends to synthesize and test a molecule that, when injected around a breast tumor, will deliver radioactivity and fluorescence to the first lymph node that receives lymph from the tumor site, thus enabling the surgeon to find this "sentinel" lymph node with the aid of an ultraviolet lamp. To date, he has synthesized the radiolabeled molecule, which can be labeled with technetium-99m and attached mannose to the chain, which permits the lymph node to avidly bind the radioactive chain.

Newly Initiated Research



BCRP funded five projects in 1999 that address earlier detection. **Carolyn Kimme-Smith, Ph.D.** of the **University of California, Los Angeles** will continue to direct a medical physics training program that exposes students to pathology, laboratory, and clinical issues relevant to breast cancer. The remaining four grants relate to biomarkers of breast cancer. First, **Jeffrey Smith, Ph.D.** will explore a novel molecular approach to detect breast tumor proteases that might be released into the blood. Second, **H. Phillip Koeffler, M.D.** is funded to use a yeast-based system to detect proteins secreted from breast cancer cells to discover potential biomarkers for future study. Third, **David Hoon, M.Sc., Ph.D.** will investigate the potential of sampling blood to isolate circulating tumor-specific DNA to test for markers associated with breast cancer. This approach has the potential to substitute for surgical biopsy in order to gain critical information regarding tumor status and possible treatment strategies. Finally, **Robert Cardiff, M.D.** will study biomarkers in mouse systems to gain information on the relationship of current and potential markers to stage and progression of breast cancer.

biomarkers

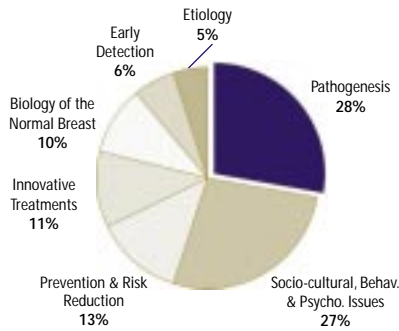
Breast Cancer

Understanding the Disease

The Pathogenesis priority issue addresses the topic of **breast tumor cell biology**. An increased understanding of the initial development and progression of breast cancer at the molecular level lays the groundwork for new approaches and therapies to treat the disease. We have organized the following descriptions into five 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**

Distribution of 1999 Funds



Pathogenesis research generally employs the modern tools of molecular biology to understand the unique genes and protein interactions that allow breast cancer cells to grow, become more aggressive, and spread in the body. This is referred to as ‘basic science,’ since the approach to the disease is at a very fundamental level. This allows scientists to integrate information from other cancer types, general cell biology, animal and lower organism model systems, and immunology to address research questions specific to breast cancer.

The **specific impact of these research projects** for women with breast cancer is not immediate. The development of basic science discoveries in a translational direction is addressed in another BCRP priority issue, Innovative Treatments. The eventual progression of new treatment approaches and therapeutics through the laboratory, pre-clinical phase, and clinical trials can take 10-15 years. The total cost of such commercial development can reach several hundred million dollars. Despite the often tangential connection of basic science to new drugs and treatments, it is well accepted that the initial research phases must occur in simple cell and animal models of breast cancer. And, the first step is the discovery of new breast cancer-related genes and proteins of interest. At each step in the drug and therapeutic development stage, hundreds of promising leads become discarded, and only a handful move on for further study. The BCRP cannot predict which of the basic science projects we fund will ultimately impact breast cancer. However, in the first five years (1995-1999) we have seen a rapid evolution of BCRP-funded basic science projects into topics of greater specificity to breast cancer. To move basic science in a direction more specific to breast cancer, the BCRP began, in 1998, to rate all applications on their potential for ‘impact’ on breast cancer. This emphasis supports “the mission of the BCRP **to reduce the impact of breast cancer in California** by supporting research on breast cancer, facilitating the dissemination of research findings, and their translation of research into public health practice.”

treatment

Unfortunately, each new gene, protein, and biochemical discovery is hailed as **the ‘next cure’ for cancer**. Over two years ago a famous Nobel Laureate predicted in the *New York Times* that the discovery of the angiogenesis inhibitors, endostatin and angiostatin, would be the cure for cancer— within two years! Such optimism leads the public to become sceptical, or even cynical, about the claims for basic science discoveries. These opinions notwithstanding, the underlying creative process to prevent and cure breast cancer is stimulated by two primary factors. First, new young investigators must be supported to start careers in breast cancer research. Secondly, research that uses innovative approaches and challenges the current dogma must be supported.

Research Conclusions

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

Pierre Desprez, Ph.D. of the **California Pacific Medical Center** completed a New Investigator Award entitled "*The Invasive Nature of Epithelial Breast Cancer Cells*", which looks at the role of a protein called Id-1 in breast cancer metastasis. Id-1 binds to specific regions of genes to regulate their tissue-specific production in many cell and cancer types. Dr. Desprez found that the presence of Id-1 is associated with breast tumors that invade their surrounding environment. He also found that when Id-1 is introduced into breast cells that are not invasive, they become invasive. Finally, the production of Id-1 is regulated by certain hormones. For example, estrogen causes the cell to make more Id-1, whereas progesterone decreases Id-1 production. These results indicate that regulation of Id-1 could be one of the important factors for determining the aggressiveness of breast cancer. Findings from this project were published in the journal *Molecular and Cellular Biology* (Aug 1998; 18(8): 4577-88).

David Rose, Ph.D., D.V.M. at **The Scripps Research Institute**, completed a 2-year Postdoctoral Fellowship on *Integrin Receptor Activation in Breast Cancer*. He examined proteins on the surface of breast cancer cells that are critical to cell migration. This tumor cell receptor, an integrin called a4b1, binds to another receptor on cells lining blood vessels, called Vascular Cell Adhesion Molecule (VCAM)-1. Mutant cell lines were developed that had altered a4b1 binding affinity and showed increased migration. It appears that a4b1 is sensitive to the intracellular signaling pathways known to be changed in breast cancer cells. Future work could reveal how a4b1 is directly associated with breast cell migration. In addition, soluble inhibitors of a4b1 adhesion could block cell movement.

Alex Strongin, Ph.D. at the **La Jolla Institute of Experimental Medicine** completed a Research Project award entitled "*How are Collagenases Involved in Breast Cancer Metastasis?*" A group of enzymes called collagenases are able to dissolve the scaffolding supporting the breast cells (extracellular matrix), thus performing a necessary step for allowing cancer cells to move from the breast to other parts of the body. Dr. Strongin is delineating the critical steps in this process and identifying the key players. He found that the activation of an enzyme called MMP-2 depends on the activity of two other proteins, MT1-MMP (a protein present in most aggressive breast tumors) and the avb3 integrin receptor. He also found that MMP-2 must be attached to the membrane of the cell in order for it to affect cell movement, cell shape and localized digestion of the extracellular matrix. Several articles were published during this project, most recently in the journal *Molecular and Cellular Biology* (Nov 1999; 17(11): 6598-608).

Karin Zeh, Ph.D. at **The Burnham Institute** began project on *Cell Adhesion Signaling Defects in Breast Cancer* was focused on investigating a gene in breast cells, called plakoglobin, that is involved in cell-cell association events to maintain the normal epithelial structure. She was developing a technology of gene knockout (i.e., gene deletion) that would be specific to the mammary gland in adult mice. She completed the initial stages of the project to develop an indicator mouse strain having the appropriate expression of a marker gene (b-galactosidase). She resigned her Fellowship after one year to pursue a career in biotechnology.

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

Myles Cabot, Ph.D. of the **John Wayne Institute for Cancer Treatment** completed a project entitled "*Nongenomic Actions of Antiestrogen*", in which he investigates the mechanism of action of agents such as tamoxifen on the components of the cellular membrane. Tamoxifen action can occur through the membrane by causing changes in the elements of the cellular membrane called second messengers. Dr. Cabot found that one of these second messengers, called PKC-epsilon, is specifically activated by tamoxifen. This pathway could be the one operating in breast cells that are estrogen receptor negative but responsive to tamoxifen. Additionally, he found that one of the actions of tamoxifen is to block glycolipid metabolism, a biochemical pathway used by the cancer cells to resist Adriamycin therapy, thus supporting the observation that tamoxifen can reverse resistance to chemotherapy. This research produced several publications, including ones in the *International Journal of Cancer* (Mar 4, 1997; 70(5): 567-74 and Sep 11, 1998; 77(6): 928-32). This initial work supported by BCRP allowed Dr. Cabot to obtain federal funding to continue research in this area.

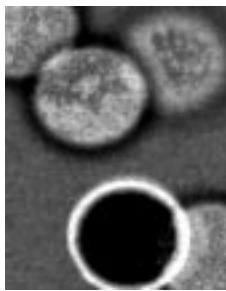
tamoxifen

Shiuan Chen, Ph.D. of the **Beckman Research Institute of the City of Hope** completed a project entitled "*Control of Estrogen Production in Breast Cancer*". He studied how estrogen is produced in fat tissues and found that cancer-free areas of the breast produce less estrogen than cancerous areas. He also found that the regulation of estrogen production by the aromatase gene was under the control of hormones in cancer-free areas, whereas a protein called cAMP regulated estrogen production in areas with cancer. Based on the analysis of the different regulatory areas of the aromatase gene, Dr. Chen hypothesizes that when cancer cells are exposed to estrogen, they produce cAMP and then the control of estrogen synthesis switches from a hormone-dependent to a cAMP-dependent process. This study may reveal a fundamental difference between benign tissue and cancerous tissue. Dr. Chen reviewed this field in the journal *Frontiers in Bioscience* (Aug 6, 1998; 3:922-33).

cell death

Michael Karin, Ph.D. at the **University of California, San Diego** completed a 3-year project on *Regaining Control over Breast Cancer Cells*. The aim was to study how breast cancer cells can survive in the presence of signals (e.g., chemotherapy and radiation) that trigger the process of apoptosis, which is programmed cell death. They found that breast cancer cells could escape death by activating the gene regulatory protein (transcription factor) called NF- κ B. This research was published in *Cell* (Nov 1 1996; 87(3): 565-76). Inhibitors of NF- κ B and its associated proteins can now be investigated as potential inhibitors of breast cancer in animal models. This approach could render breast cancer cells more sensitive to cell death caused by either chemotherapy or immune attack.

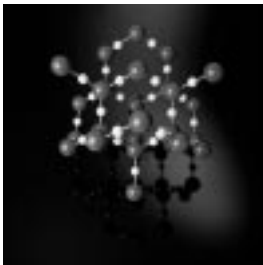
Juan Zapata, Ph.D. from **The Burnham Institute** was funded for a 2-year Postdoctoral Fellowship to study *TRAF-regulated Signal Transduction in Breast Cancer*. This project is related to Dr. Karin's project described above. In this project, Dr. Zapata studied the pathways by which apoptosis (cell death) signals are communicated within breast cancer cells. Comparing normal breast tissue and breast cancer by microscopy techniques, he found that the amounts of a protein called TRAF-4 was decreased. In further studies, he showed that mutating the cell surface receptor (CD40) for TRAF signaling would still allow the relay of other signals through alternate cell death pathways via NF- κ B (see Dr. Karin's project above). Thus, breast cancer cell death appears to be regulated by both positive (TRAF) and negative (NF- κ B) apoptosis factors. These studies were recently published in the *Journal of Biological Chemistry* (Aug 6, 1999; 274(32): 22414-22).



Sahn-Ho Kim, Ph.D. from the **Lawrence Berkeley National Laboratory** was funded for 2 years as a Postdoctoral Fellow to study *Loss of Tumor Suppressor Proteins in Breast Cancer Cells*. His initial plan to find proteins that interact with the retinoblastoma (Rb) tumor suppressor was unsuccessful. He then redirected his project to discover proteins that interact with telomeres, which are the ends of chromosomes and are critical to controlling the capacity for cells to divide indefinitely. Using the yeast two-hybrid system, he identified a telomere-associated protein called Tin2. The relationship of Tin2 to breast cancer is not yet established, but this new information could explain the capacity of cancer cells to escape the normal cell aging process.

proteins

Cary Lai, Ph.D. of **The Scripps Research Institute** completed a project entitled *The Role of a Newly Discovered Neuregulin in Breast Cancer*. This one-year award explored the possibility that a newly discovered molecule, named NRG-4, could belong to a family of genes called the neuregulins. Members of the neuregulin family are ligands (they bind to a receptor and activate it) for the ErbB family of receptors. ErbBs, particularly ErbB2 (also called Her-2/neu), have proven to play important roles in the development and treatment of breast cancer. Dr. Lai found that the NRG-4 qualifies as a member of the neuregulin family because it activates ErbB4, although it does not activate ErbB2. The identification and characterization of NRG-4 provides a more complete picture of the factors that influence treatments such as heregulin-based therapies.



Ichiro Maruyama, Ph.D. of **The Scripps Research Institute** completed a project entitled *Growth Factor Receptor Activation in Breast Cancer*, investigating how the epidermal growth factor receptor (EGFR) becomes active. The current thinking is that two molecules of EGFR come together to form the active structure (a dimer). However, by creating mutant EGFR components, Dr. Maruyama was able to show that the dimer structure can form without bound EGF. Thus, dimer formation is not sufficient for EGFR activation, but rather it is the relative orientation of two molecules in its dimer structure that is needed. This information will ultimately be helpful for guiding future research into targeting EGF-like receptors.

Alexandre Nesterov, Ph.D. of the **University of California, San Diego** completed a Postdoctoral Fellowship entitled *"Molecular Mechanisms of EGF Receptor Endocytosis"*. The goal of the research was to lay the groundwork for developing an approach to therapy that specifically targeted epidermal growth factor (EGF) - a growth hormone involved in breast cancer. The approach is based on the observation that the receptor for epidermal growth factor (EGFR) is brought inside the cell (endocytosis) from the cell surface and degraded in order to inactivate it. If this process could be accelerated specifically for EGF-like receptors in tumor cells, this could serve as a way to control tumor growth. Dr. Nesterov was able to identify a previously unknown protein called 'Catnip' that may be involved in this process. He was also able to develop a method that is being used to identify previously unknown signaling components of the epidermal growth factor receptor.

Kevin Sato, Ph.D. at **The Scripps Research Institute** finished a 2-year Postdoctoral Fellowship to investigate *Disruption of Cyclin E/Cell Cycle in Breast Cancer Cells*. The ability of cells to divide is regulated by proteins called cyclins, which are the checkpoints in the cell cycle. One of these checkpoint proteins, called Cyclin E, appears elevated in breast cancer and is associated with a partner protein, cdk2. Dr. Sato's project used both antisense (inhibitory DNA fragments) and knockout (gene deletion) approaches to reduce cyclin E amounts in cells. However, these cyclin E blocking approaches led to only modest increases in cell division times. Interestingly, in the course of these studies, the presence of a novel inhibitor of cdk2 was demonstrated. Thus, breast cancer cells that were inhibited for cyclin E possessed an unexpected ability to maintain adequate levels of cyclin E/cdk2 complex by an alternate process.

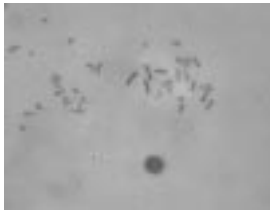
Michael Stallcup, Ph.D. of the **University of Southern California** has completed a project entitled *Estrogen Receptor-Interacting Proteins in Breast Cancer*. The goal of this project was to characterize some previously unknown proteins that could potentially be interacting with the estrogen receptor (ER) and determine whether they could regulate estrogen action by interfering with the function of the receptor. Dr. Stallcup found that the novel protein fragments he originally identified (GRIP2 and GRIP3) were not natural genes; however, he did find a portion of the natural gene GRIP1 that could preferentially block the necessary step of the

cancer
cells

Mistakes on the master blueprint: molecular genetics and gene regulation

estrogen receptor binding to its coactivator proteins. He found that GRIPI interferes with the estrogen receptor function by binding to multiple regions along the estrogen receptor. During this investigation he also discovered a novel estrogen receptor-related protein named estrogen receptor related protein 3, or ERR3, that can turn on some of the same genes as the estrogen receptor, but does not require estrogen to do so. If breast cancer cells are found to have too much ERR3, it would lend credence to the possibility that this protein is responsible for estrogen independent growth. Dr. Stallcup published work from this project in several papers, most recently in the *Journal of Biological Chemistry* (Aug 6, 1999; 274(32): 22618-26).

Robert Oshima, Ph.D. from **The Burnham Institute** completed a project to study *Oncogene Regulation in Mammary Cancer*. The focus of his research was the gene regulatory protein (transcription factor) called Ets2. Dr. Oshima tried several techniques to reduce the amounts and block the activity of this protein. Using human mammary tumors grown in mice, he found that decreasing the amount of Ets2 in cells by half resulted in much smaller tumors. These results were published in *Cancer Research* (Sep 1, 1999; 59(17): 4242-6). Many important breast tumor genes are believed to be regulated by Ets2, and further work will be needed to show how specific reductions in this protein might inhibit tumor formation.



enzymes

Philippe Pujuguet, Ph.D. from the **Lawrence Berkeley National Laboratory** completed a 2-year Postdoctoral Fellowship to investigate *ECM-Regulated Transcription in Breast Cancer*. The idea underlying this research was that the material that surrounds cells (the extracellular matrix, or ECM) interacts with breast cells to either prevent or promote their transformation into a malignant state. To study this process, Dr. Pujuguet examined how production of an important milk protein, casein, was regulated by factors (called transcription factors) that control genes. This work led him to discover that a particular enzyme that acts on histones (chromosome binding proteins) appeared to be directly associated with the presence or absence of the extracellular matrix. These findings help explain how normal breast cells maintain their morphology and synthesize proteins associated with the non-transformed state. This project was published in the journal *Molecular and Cellular Biology* (Apr 1998; 18(4): 2184-95).

David Zarling, Ph.D. at the **Pangene Corporation** was funded for a 2-year IDEA project to study *Recombination and Mutation in Breast Cancer*. He investigated how breast cancer cells can recover from DNA damage induced by either radiation or chemotherapeutic drugs. He found that a DNA recombination and repair protein, called Rad51, was induced in breast cancer cells in response to radiation. Inhibition of Rad51 by both genetic knock-outs and using novel, proprietary inhibitors developed at Pangene would make the cells much more sensitive to radiation treatment. Thus, use of these new inhibitors could increase the effectiveness of radiation therapy.

Searching the unknown: novel breast cancer genes



Terumi Kohwi-Shigematsu, Ph.D. from the **Lawrence Berkeley National Laboratory** completed a 3-year project to study *The Role of MAR-Binding Protein in Breast Cancer*. She examined the process and the proteins involved in the attachment of chromosomal DNA to the skeletal framework of the cells' nucleus. Unexpectedly, she found that a previously described DNA repair protein, called poly ADP-ribose polymerase (PARP), is present in high amounts in breast cancer and participates in chromosomal DNA attachment. This is important, because previously it was believed that PARP and its companion proteins only bound to DNA nicks associated with DNA damage. The potential role of the PARP system in breast cancer was confirmed when experiments to reduce PARP levels in breast cancer cells lines resulted in a loss of invasiveness and ability to form tumors in mice. The most recent findings for this project were published in the *Journal of Biological Chemistry* (Jul 16, 1999; [274\(29\)](#): 20521-8).

Claudia Lin, Ph.D. at the **Lawrence Berkeley National Laboratory** completed a 2-year Postdoctoral Fellowship to work on a *Targeted Search for New Transcription Factors in Breast Cells*. The overall goal was to discover how gene regulation becomes altered during the differentiation of breast cells. Previously, she had described the Id-1 transcription factor, which is being investigated by other BCRP funded projects awarded to Dr. Pierre Desprez. In Dr. Lin's research, the yeast two-hybrid method was used to find a protein binding partner of Id-1, which is called ITF-2. She found that ITF-2 binding activity towards DNA would increase significantly upon growth arrest, and that artificially increasing amounts of ITF-2 within breast cells would cause morphological changes and b-casein milk protein production. The significance of this work is that it leads to strategies to understand the normal function of breast cells, which could be maintained to prevent the development of breast cancer.

DNA

Michael Press, M.D., Ph.D. of the **University of Southern California** has completed a project entitled *Genes Which Cause Increased Cellular DNA in Breast Cancer*. Dr. Press was looking for the human gene equivalents to 'rum1', a yeast gene that regulates DNA. He found two DNA fragments in human cells that qualify as human counterparts to *rum1*, which turned out to be different parts of the same gene. The protein product of the gene could be found in all of the adult tissues and was found at similar levels in tumor tissues. There were also no mutations in the gene in any breast cancer cell line. Therefore, although this project successfully identified a human cousin to the yeast *rum1* gene, it does not appear that this gene plays a role in breast cancer development.

Mathias Treier, Ph.D. at the **University of California, San Diego** completed a 2-year Postdoctoral Fellowship on *Potential Tumor Suppressors in Breast Cancer*. This project also investigated a gene regulation process that could be more 'global' in nature. He focused on a protein that controls gene activity called the nuclear receptor corepressor (N-CoR). The importance to breast cancer is that the N-CoR is thought to form protein complexes that

modulate the estrogen receptor. Thus, any defects in the N-CoR could lead to resistance to tamoxifen therapy. Dr. Treier attempted to generate mice that lacked the N-CoR, but these animals would not survive beyond the embryonic stage. He plans to investigate this problem by surgically transplanting tissue from embryonic N-CoR-deficient mice into normal mice and allowing the genetically deficient mammary tissue to develop in a so-called 'chimeric' state. In other planned work, the role of the N-CoR will be studied in cell models.



genetics

Fabiana Guerra-Vladusic, Ph.D. of the **Lawrence Berkeley National Laboratory**

received a Postdoctoral Fellowship entitled *Characterization of Heregulin Targeted Genes*. She was able to make significant progress in her research project, which characterized the cellular and genetic effects of heregulin in breast cells. Heregulin is a molecule that binds to ErbB2 (also called Her-2/neu), a receptor that is an important protein in the development and treatment of breast cancer. Dr. Guerra-Vladusic defined the genes and proteins present when heregulin production is constantly turned on in the cell. She found that this caused the breast cells to stop dividing, increase in size and begin to die. She also found that these cells produced less ErbB2 and ErbB3, but more of a nuclear localized protein called PEA3. This observation opens up the therapeutic possibility that cells with too much ErbB2 can be induced to die by stimulating PEA3 production or activity. This research was recently published in the *International Journal of Oncology* (Nov 1999; 15(5): 883-92). Dr. Guerra-Vladusic resigned her fellowship to work in a biotechnology company.

Sergei Malkhosyan, Ph.D. at **The Burnham Institute** completed an IDEA project on

Molecular Karyotyping of Breast Cancer by DNA Fingerprinting. He developed a novel approach to detecting genetic changes associated with breast cancer, called Arbitrarily-Primed PCR (AP-PCR). About 80 different breast tumors were analyzed and the gain or loss of chromosomal regions was tallied. Gain of chromosomal segments was characteristic of chromosomes 1, 4, 8, and 10. Loss of chromosomal material was often associated with chromosomes 4, 6, 9, 10, 11, and X. The goal is localize the gains and losses to more specific regions and correlate these with already identified breast cancer genes.

Unraveling the path to breast cancer: tumor progression

Anissa Agadir, Ph.D. of **The Burnham Institute** completed a Postdoctoral Fellowship

entitled *Anti-Breast Cancer Activity of Vitamin A Derivatives*. Retinoids are Vitamin A derivative compounds that have been investigated for their cancer preventative properties. In order to optimize their usage, it is important to understand the biology of cellular functions. Retinoids are known to turn on different classes of receptors including the RAR class and the RXR class. Retinoids that operate through different families may have different biological consequences. Dr. Agadir used synthetic retinoids that specifically activate the different classes of receptors and found that the RXR pathway can cause cell growth inhibition when the RAR pathway fails. She also found that effectiveness of retinoids in blocking the TPA (a tumor

promoter) pathway may predict the success of retinoid treatment in breast cancer patients based on the RAR status. Her results indicate that synthetic retinoids that effectively and specifically block TPA-induced cell transformation are promising candidates for further study. Several publications resulted from this project, including one in the journal of *Molecular and Cellular Biology* (Nov 1997; 17(11): 6598-608).

Chin-Shwun Lin, Ph.D. at the **University of California, San Francisco** finished a 3-year project to study the *Role of L-Plastin in Breast Cancer*. The plastins are a small family of proteins that associate with the internal cytoskeleton of cells. Normal breast cells do not contain L-plastin, but breast cancer cells commonly express this protein. Dr. Lin first developed evidence showing that L-plastin can be measured in breast tumor samples using antibodies, and he showed that this protein could be a useful diagnostic marker. Secondly, he found that L-plastin was found inside breast cells at the leading edge of the cell, which indicated a role in cell invasion. This hypothesis was confirmed by introducing L-plastin into low-grade breast cancer cell lines and showing an increase in invasive properties. Thirdly, Dr. Lin found that the L-plastin gene contained estrogen responsive regions, but it could also be regulated by androgens. Work from this project was published the journal *DNA and Cell Biology* (Dec 1998; 17(12): 1041-6).

plastins

Research in Progress

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

A sampling of BCRP-funded research grants in progress under this sub-topic illustrates a diversity of approaches. These include the searching for novel motility proteins, understanding complex regulatory pathways, and discovering how tumors can grow in the body and still evade immune detection. Key players in breast cancer cell movement are the tumor-secreted proteases that digest the material that surrounds cells (the extracellular matrix). **Pierre Desprez, Ph.D.** at the **California Pacific Medical Center**, is continuing the search for a novel breast cancer metalloproteinase (MMP) that appears to be induced by the gene regulatory protein, called Id-1. Since these proteases are secreted from cells, they could represent a novel target for early detection by their presence in blood or urine. Next, **Ulla Knaus, Ph.D.** at **The Scripps Research Institute** is continuing a project to determine how an intracellular signaling pathway in breast cancer cells is associated with cell migration. She is introducing mutant forms of signaling proteins, called Rac, into breast cancer cell lines and measuring changes in the cytoskeleton and cell growth. In addition to cell movement, this project is also examining the cell cycle and other signaling pathways. Finally, an emerging field of investigation in cancer research has received considerable attention during the past two years. This is the process of angiogenesis, which is the growth of new blood vessels into tumors that allow them to increase in size beyond 1-2 mm and spread in the body. **Pragada**

tumor

Sriramarao, Ph.D. from the **La Jolla Institute of Experimental Medicine** is continuing a project focused on the vascular adhesion processes of the blood circulation within tumors. He uses small tumor spheroids that, when implanted into mice, can be visualized by special microscopy. He studies the immune regulatory factors (e.g., TNF-beta, IL-4) that allow circulating white blood cells to arrest in the tumor microcirculation. How the tumor microcirculation develops, and how it differs from the microcirculation of normal tissues is an area of active research.

Too much cell growth: defective messages and internal signaling

Several projects are progressing in this topic area. First, **Kathryn Ely, Ph.D.** from **The Burnham Institute** is funded to investigate the 3-dimensional structure of the tumor suppressor retinoblastoma (Rb) protein and its binding partner protein, called RIZ. If she can locate the critical interaction regions of these two proteins, then future work could translate these findings into drug development. Other tumor suppressors, such as p53, protect the body from unregulated cell growth, since they can trigger cell death following DNA damage by either radiation or chemotherapeutics. **Glenn Rosen, M.D.** at **Stanford University** is investigating the action of a novel drug called PG490, which appears to sensitize breast cancer cells to the actions of tumor necrosis factor (TNF). This immune factor can trigger cell death. His findings extend the work of **Drs. Karin and Zapata** (described above) by supporting the role of a gene regulatory protein, NF-kB, as a key player in allowing breast cancer cells to avoid apoptosis (i.e., cell death). Apparently, PG490 interferes with the protein pathway that links TNF and NF-kB. Dr. Rosen's research was recently published in the *Journal of Biological Chemistry* (May 7 1999; 274(19): 13451-5). Finally, **Koji Itahana, Ph.D.** from the **Lawrence Berkeley National Laboratory** is examining a novel aspect of *p53* mutations in breast cancer cells. It is known that many breast cancers are associated with mutations in *p53*. It has been assumed that these p53 mutations serve to inactivate the protein function. Challenging this paradigm, Dr. Itahana is looking for p53 mutations that have a 'gain-of-function' activity.

breast

Mistakes on the master blueprint: molecular genetics and gene regulation

Shu-ichi Matsuzawa, Ph.D. from **The Burnham Institute** is continuing to study a human homologue of a fruit fly growth arrest protein, called Siah. He has found that breast cancer cells contain all three known members of the Siah protein family. Further work will show how other proteins bind to and regulate Siah activity, and whether changes in Siah amounts will affect breast cell proliferation. **Heinz Ruffner, Ph.D.**, at **The Salk Institute for Biological Studies** has found specific sites where the BRCA-1 (breast cancer-1) protein is phosphorylated. These studies will help resolve the issue of how BRCA-1 is associated with known cell regulation pathways inside cells, and how mutations in BRCA-1 can lead to increased risk for developing breast cancer. Dr. Ruffner recently published his findings in the journal *Molecular and Cellular Biology* (Jul 1999; 19(7): 4843-54).

Searching the unknown: novel breast cancer genes

Donna Albertson, Ph.D. at the **University of California, San Francisco** is continuing a project to map and identify critical breast cancer oncogenes (i.e., cancer-inducing genes) on human chromosome 20. She has identified a potentially important mammary oncogene, called *ZNF217*. Her results were published in the *Proceedings of the National Academy of Sciences, USA* (Jul 21, 1998; 95(15): 8703-8) and *Nature Genetics* (Oct 1998; 20(2): 207-11). **Sanjeev Galande, Ph.D.** at the **Lawrence Berkeley National Laboratory** is continuing a Postdoctoral Fellowship with **Dr. Kohwi-Shigematsu** (see above) to study the chromosomal DNA attachment process in the nucleus. It appears that a type of DNA repair mechanism in normal cells becomes altered in breast cancer, and this causes abnormal gene expression and cellular functions. **Fumiichiro Yamamoto, Ph.D.** of **The Burnham Institute** is continuing his search for previously unknown genes that may be playing a role in breast cancer. He is analyzing the pattern of genes that are turned on or off by examining changes in DNA methylation. Finally, **Paul Kaufman, Ph.D.**, at the **Lawrence Berkeley National Laboratory** is funded to study cellular aging and its relationship to proteins that normally protect chromosomes. He is working on a protein called CAF-1 (chromatin assembly factor-1). Most breast cancers occur in older women, so understanding aging at the cellular and molecular level is critical in devising strategies to prevent the very early stages of cancer progression.

Unraveling the path to breast cancer: tumor progression

Older women are at greater risk for developing breast cancer. How is this increased risk associated with specific cellular and genetic changes? **Dr. Judith Campisi, Ph.D.** at the **Lawrence Berkeley National Laboratory** is continuing a project to understand how the connective tissue cells, called fibroblasts, become altered with age and contribute to localized changes to permit the neighboring breast cells to become altered. Her specific interest is the molecular communication between these two cell types that involves the secretion of a growth factor (heregulin) by the fibroblasts, and the stimulation of its receptor (Her-2) on breast cells. More information on the local environment of breast cells is critical to understanding the changes leading to breast cancer.

Normal cells have limits placed on their ability to divide; the acquisition of cell immortality is a critical step in tumor progression. **Martha Stampfer, Ph.D.** of **Lawrence Berkeley National Laboratory** is using a cultured human mammary epithelial cell (HMEC) system and microarray technology to identify those genes whose products are altered once cell become immortal. She has identified 12 genes thus far and will perform additional experiments to characterize them. As tumors become more aggressive, they begin to look and behave like immature breast cells. **G. Shyamala, Ph.D.** also at the **Lawrence Berkeley National Laboratory** is investigating the role of hormones, such as progesterone, in maintaining the maturity of breast cells. She is finding these hormones play an important role in maintaining the integrity of the surface (i.e., basement membrane) that supports the breast cells in their normal functions.

Recently Initiated Research



drugs

In 1999, the BCRP funded 18 new grants focused on breast cancer Pathogenesis. The **adhesion, migration, and spread of breast cancer cells in the body** continue to be areas of intense research interest. Many of these new projects focus on **angiogenesis**, the development of the tumor blood supply necessary for growth and metastasis. A major clinical advantage to targeting angiogenesis is the ability to attack secondary sites of tumor growth. **Jan Schnitzer, M.D.** at the **Sidney Kimmel Cancer Center** is funded to investigate the unique surface proteins on the endothelial cells that line blood vessels within tumors. The discovery of unique proteins in blood vessels that feed tumors might provide targets to selectively attack breast cancer and spare the normal tissues of the body. **Kristiina Vuori, Ph.D.**, from **The Burnham Institute** is studying a possible mechanism of action of a new anti-angiogenic drug, endostatin, which is believed to interact with a cell adhesion receptor. The major endothelial and breast tumor integrin, avb3, is the subject of two projects. First, an endothelial proteinase is being studied for its binding to this receptor by **YingQing Sun, Ph.D.** at **The Burnham Institute**. This interaction would serve to facilitate endothelial migration during angiogenesis, and could be the basis for new therapeutics, if confirmed. Secondly, **Alex Strongin, Ph.D.** at **The Burnham Institute** is studying this same protease-integrin interaction, but in breast cancer cells, in order to explain how cancer cells are capable of invasion and to explore new approaches to block this movement. **Brett Premack, Ph.D.** from the **University of California, Los Angeles** is surveying breast cancer cells for the presence of chemokines and chemokine receptors. These receptors are important for leukocyte (white blood cell) motility and invasion and, if found on breast cancer, could be functioning in a similar manner. Breast cancer cells travel to distant sites via the blood and lymph systems. **Brunhilde Felding-Habermann, Ph.D.** from **The Scripps Research Institute** is investigating the attachment of breast cancer cells to the endothelium by the combined function of the integrin avb3 on the cancer cells and another receptor, ICAM-1, on the endothelial cell. A key aspect of this research is to isolate and study circulating breast cancer cells from the blood of experimental animals. Finally, **Sanford Barsky, M.D.** from the **University of California, Los Angeles** has a unique model system in mice to study inflammatory breast carcinoma, which spreads locally in the breast via the lymph. He is investigating how this rare form of breast cancer differs from more common types of the disease.

Newly funded research under the topic of **breast cancer cell growth regulation** focuses both on the intracellular regulatory systems linked to growth factors and how breast cells evade signals that cause cell death (apoptosis) for normal cells. **Elena Pasquale, Ph.D.** at **The Burnham Institute** is funded to study a new breast cancer messenger protein within cells for the ability to contribute to growth, metastasis, and tumor progression. The oncogene growth receptor Her-2 is present in about 30% of cancers, and is associated with a poor prognosis.

estrogen

Although the new therapeutic Herceptin was released last year, this topic is of continued research interest. **Janis Jackson, M.D.** at **The Scripps Research Institute** is investigating how Her-2 and related growth receptors signal through various signaling kinases, the Ras oncogene family. **Ronald Weigel, M.D., Ph.D.** from **Stanford University** is studying how gene regulation proteins (i.e., transcription factors) serve to mediate the estrogen response. Such proteins could become surrogate markers to evaluate the effectiveness of estrogen receptor-based therapies (e.g., tamoxifen and raloxifene). New aspirin-like drugs offer interesting new avenues to treat cancer. **Youngsoo Kim, Ph.D.** at **The Burnham Institute** is focused on the role of COX-2, a target of aspirin-like drugs, for its presence in breast cancer and association with apoptosis pathways. Finally, **Heimo Strohmaier, Ph.D.** at **The Scripps Research Institute** is funded to study the degradation of a cell cycle regulation protein. A failure to regulate the amount of this protein in breast cancer could lead to excess cell growth by permitting cells to pass through cell cycle checkpoints in an uncontrolled manner.

defects

It is well accepted that **genetic differences**, both subtle and dramatic, underlie the initiation and progression of breast cancer. Two newly-funded projects are examining genes involved in breast cancer growth. First, **Devon Thompson, Ph.D.** from **Stanford University** has found a new gene, called *hAG-2*, that appears to associate with the estrogen receptor and could underlie resistance to anti-estrogen therapy. Secondly, **Katherine Ely, Ph.D.** at **The Burnham Institute** is conducting structural analysis of an apoptosis-associated gene, *BAG-1*, for its indirect association with the estrogen receptor, which also could be involved in anti-estrogen resistance. Genetic repair and recombination within and between different chromosomes lead to severe genetic defects that characterize advanced forms of breast cancer. **Joanna Albala, Ph.D.**, working at the **Lawrence Livermore National Laboratory** has discovered and is characterizing a new chromosome recombination gene, *RAD51B*, which appears to be capable of associating with the hereditary breast cancer genes, *BRCA1* and *BRCA2*. DNA damage from environmental causes, such as radiation and chemical mutagens, must be repaired correctly for cells to remain normal. Thus, there is interest in how acquired defects in normal DNA repair systems could lead to breast cancer. **Eric Brown, Ph.D.** from the **California Institute of Technology** is studying a potential DNA damage repair gene, called *ATR*, for its role in breast cancer and its association with *BRCA1* and the tumor suppressor, *p53*. Progression of breast cancer involves processes of differentiation, which are permanent cell changes in gene expression and phenotype. Two newly funded projects are examining how certain proteins that determine whether a gene is utilized to make protein are related to breast cancer. **Bogi Andersen, M.D.** at the **University of California, San Diego** is investigating a gene regulation protein, *LMO-4*, which is involved in white blood cell differentiation and is thought to be associated with breast cancer progression. Finally, **Pierre Desprez, Ph.D.** from the **California Pacific Medical Center** is funded to continue his studies on a novel gene regulation protein, called *Id-1*, which appears to be essential for the expression of cell invasion proteases involved in breast cancer cell migration.

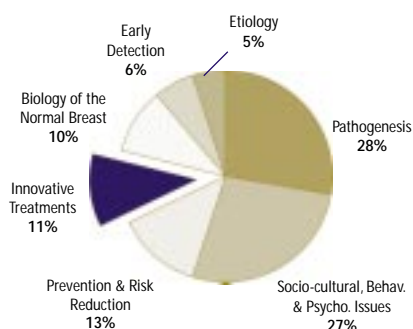
Search for the Cure

A critical goal of the BCRP is to move basic science as quickly into the clinic as possible. The Innovative Treatments priority issue offers the opportunity for researchers, both clinical and basic science, to undertake innovative projects that could improve breast cancer therapy. These research projects often represent a critical 'bridge' from the bench to the bedside.

Breast Cancer

Research Conclusions

Gene therapy and other treatments: new frontiers



Distribution of 1999 Funds

Robert Debs, M.D. at the **California Pacific Medical Center** completed a 2-year project to investigate *Gene Therapy for Breast Cancer*. The focus of this grant was to use microscopic fat globules, called liposomes, as a vehicle to deliver genes that block angiogenesis (the process of new blood vessel growth) to the sites of breast cancers. Using this approach, he was able to show a prolonged anti-tumor effect using both the angiostatin gene (the anti-angiogenesis protein that has received extensive press coverage) and the *p53* gene (a commonly defective tumor suppressor gene in breast cancer). The results of this project were published in the *Journal of Biological Chemistry* (May 7, 1999; 274(19): 13338-44). Thus, the actively dividing endothelial cells that allow angiogenesis in tumors are an attractive new target for gene therapy. Using support from the BCRP for this ‘high risk/high reward’ project, Dr. Debs was able to validate his innovative approach, publish his findings, and compete successfully for an NIH grant to continue this project on a much larger scale.

Herve LeCalvez, Ph.D. from **The Burnham Institute** completed a 2-year Postdoctoral Fellowship to study *The Role of Meltrin-alpha in Breast Cancer-Associated Bone Loss*. Meltrin-alpha is a protein on the surface of bone cells that allows them to fuse together to form bone-destroying osteoclast cells. Osteoclast formation is a common side-effect in breast cancer and causes high blood calcium levels, which can be a fatal complication of the disease. Dr. LeCalvez used molecular biology techniques to understand the protein domain structure of meltrin-alpha. First, he found a region of meltrin-alpha that would support cell fusion. Second, he found another region that might inhibit cell binding, but this segment of meltrin-alpha did not appear to interact with cell lines chosen for this study. More work is needed to manipulate and express meltrin-alpha in model cell lines to confirm this preliminary structural information.

Boris Rubinsky, Ph.D. of the **University of California, Berkeley** completed a project entitled “*Pre-Clinical Cryosurgery Testing in Breast Cancer Treatment*”. He performed pre-clinical studies to determine the parameters required for complete destruction of breast tumor through cryosurgery, which is a minimally invasive technique. Dr. Rubinsky used a small probe to freeze breast tumors and found that mouse tumors that were frozen to -40°C at a rate of $5^{\circ}\text{C}/\text{min}$ still had surviving cells after one freezing cycle, but that destruction of the tumors occurred after two rounds of freezing. He also found that cryosurgery in the presence of a class of proteins call “antifreeze proteins” can completely destroy tumor cells, even if the conditions are otherwise sub-optimal. This approach may provide a new, less invasive way to perform breast cancer surgery.

Marc Shuman, M.D., Randall Hawkins, M.D., Ph.D., and Laura Esserman, M.D. at the **University of California, San Francisco** completed a pilot grant on the *Inhibition of*

angiogenesis

Angiogenesis in Breast Cancer. The development of the blood supply for tumors, called angiogenesis, is critical for growth and spread in the body. This project involved, first, a new way to block angiogenesis by using an inhibitory monoclonal antibody to an angiogenesis protein, called VEGF. Secondly, they explored state-of-the-art imaging technologies (MRI and PET) to observe the clinical effects of treatment. They found that a new method of MRI imaging, called Triple Acquisition Rapid Gradient Echo Technique (TARGET), could reproducibly detect changes in breast cancers with 48 hours of treating mice with the anti-VEGF antibody. In other experiments, these investigators surveyed human breast cancer cell lines and found important differences for the specific angiogenesis factors critical to their growth. This indicates that human breast tumors may differ in response to anti-angiogenesis therapy, so the TARGET method could give a rapid 'read out' of efficacy.

Robert Stern, M.D. from the **University of California, San Francisco** was funded for a 3-year project to investigate *The Breast Tumor Suppressor Function of Hyaluronidase*. Hyaluronic acid (HA) is a component of the extracellular matrix, and it opens up tissue spaces to promote cell movement. The amount of hyaluronic acid on the surface of breast cancer cells correlates with tumor aggressiveness. Thus, the enzyme that degrades hyaluronic acid, hyaluronidase, has potential as a breast cancer therapeutic. Using support from the BCRP, Dr. Stern published the purification, protein sequencing, and cloning of hyaluronidase in the journal *FEBS Letters* (Nov 17, 1997; 417(3): 307-10). And, in completely new and unexpected results, the relationship of hyaluronidase to an already sequenced tumor suppressor was published in the journal *Genomics* (Feb 15, 1998; 48(1): 63-70). Hyaluronidase is found in normal breast cells. Dr. Stern found that increasing the amount of hyaluronidase in aggressive breast cancer cells lines slows cancer cell growth. In addition, injecting hyaluronidase protein into animals with experimental tumors reduces the size of the tumors. Dr. Stern is continuing this work by performing "knock outs" of the hyaluronidase gene in mice and exploring the relationship of this cell surface tumor suppressor activity with other known tumor suppressors, such as *p53*. Even more than when this project was funded in 1995, it appears that hyaluronidase has a potential to treat breast cancer.

mental function

Mary Wieneke, Ph.D. of the **California School of Professional Psychology** looked at the long-term effects on brain functioning of conventional chemotherapy and Tamoxifen for early stage breast cancer, and tried to identify the contribution of psychological and emotional distress such as depression/anxiety, to mental functioning. Women in the study were newly diagnosed with early stage (I or II) breast cancer and received either adjuvant chemotherapy (with or without Tamoxifen), or only Tamoxifen. A third group, with no chemotherapy or drug treatment, served as the comparison group. Women were tested shortly after diagnosis (baseline), shortly after completion of treatment, and about one year after the second test, or about eighteen months post-diagnosis.

brain

At baseline, psychological measures revealed a range of mild depression in the majority of the women (69%). Anxiety levels were significantly elevated at first testing, with results further suggesting that elevated anxiety levels may impair overall cognitive functioning at this time. This would have implications for decision-making and how newly diagnosed patients take in and process information at this critical time. At the third measurement, anxiety/depression levels had fallen close to or within normal range. Anxiety level was still elevated for the chemotherapy group, and the least comparative cognitive improvement over time was seen in the chemotherapy group. Thus, anxiety may indeed be a factor in cancer patients' cognitive functioning and ability to comprehensively process critical information at time of diagnosis and initial treatment planning. Some areas of cognitive functioning had not returned to "normal" 18 months after diagnosis. A longer time may be needed to evaluate long-term treatment effects of adjuvant chemotherapy and tamoxifen upon cognitive functioning.

We currently have no way to predict which women with breast cancer will benefit from chemotherapy and which women will not benefit. Therefore, current practice is to give chemotherapy to almost all women diagnosed with breast cancer, thus subjecting many patients to painful and risky therapies to benefit only some of them. Recent evidence suggests that a woman's specific tumor marker profile may be an important predictor of response to adjuvant therapy. **Drs. Shelley Enger**, of **Kaiser Permanente, Southern California** and **Michael Press** of the **University of Southern California** conducted a pilot study to lay the groundwork for a full research study to definitively assess the value of breast tumor markers in predicting response to adjuvant therapy regimens. The investigators worked together to resolve problems encountered during the course of the study and they evaluated the resulting data to assess the feasibility of carrying out a large-scale study of breast tumor markers and therapeutic response. Their results confirmed the prognostic significance of the molecular markers; *HER2/neu* and *p53* expression and *BCL2* non-expression were clearly associated with poor outcome in the study population. They also confirmed that there is significant variation in treatment in this population, and this variability is not related to differences in molecular marker status. These results enabled them to be awarded a full grant the following year to examine whether molecular markers can predict the response to different therapies.

Hormone and chemotherapy targets: improving today's arsenal

Joel Gottesfeld, Ph.D. at **The Scripps Research Institute** completed a 2-year project to study *Inhibitors of the Breast Cancer Her-2/neu Gene*. With his colleague, Dr. Peter Dervan, at the California Institute of Technology, he developed novel DNA-binding molecules, called pyrrole-imidazole polyamines, to block a critical gene needed for breast cancer growth. Their target was the regulatory region (TATA-box) of the *Her-2/neu* gene. Their laboratory experiments demonstrated that a normal TATA-box regulatory protein was blocked by the polyamines. Then, the ability of polyamines to inhibit *Her-2/neu* synthesis and decrease motility in breast cancer cell lines was demonstrated. Thus, this project showed promising

results using a novel means of inhibiting critical genes, and the treatment did not show toxicity and unwanted side-effects in cell models. More work will be needed to (i) validate these findings using animal models of breast cancer, and (ii) optimize the structure of the polyamines and specify the DNA sequence to be targeted.

Richard Pietras, M.D., Ph.D. of the **University of California at Los Angeles** completed a project entitled *"New Endocrine Strategy to Prevent Breast Cancer Progression"*. Dr. Pietras investigated the role that HER-2 has in regulating how breast tumors respond to estrogen and to drugs that block estrogen (anti-estrogens). He found that breast cancer cells with high levels of HER-2 are much less sensitive to estrogen and to tamoxifen than similar cells with low levels of HER-2 gene. He also found that stimulating the HER-2 receptor leads to activation of the estrogen receptor even in the absence of estrogen. This process circumvents the regulation of tumor growth by estrogen and could provide a biological basis for tamoxifen resistance in breast tumors with large amounts of HER-2. Resistance of these cancer cells to tamoxifen can be reversed by treatment with an antibody, such as Herceptin, that counteracts the ill effects of the HER-2 protein.

Paul Webb, Ph.D. of the **University of California, San Francisco** completed a New Investigator Award entitled *"Understanding Tamoxifen - A Drug for Breast Cancer"*. This project investigated the mechanism of tamoxifen action by examining its interaction with AP-1 (a set of proteins responsible for cell growth and implicated in cancer). Dr. Webb has found that the estrogen receptor binds to AP-1 in the presence of tamoxifen by way of a "molecular sandwich" in which the estrogen receptor binds the coactivator p160, which binds the coactivator CBP, which binds AP-1. Tamoxifen and estrogen activate this complex differently; however, tamoxifen causes the estrogen receptor to stimulate the activity of p160 component of the sandwich. This cascade partially explains the estrogen-like effect of tamoxifen on cell growth. The second form of the estrogen receptor that was discovered during the span of this grant, ER-beta, stimulated the antiestrogen component of the complex, indicating that it may be one of the mechanisms for resistance to treatment with anti-estrogens. This investigation has led to at least three scientific publications: *Science* 1997, 5; 277(5331): 1508-10; *Mol Endocrinol* 1998 Oct; 12(10): 1605-18; and *Endocrinology* 1997 Jul; 138(7): 2900-8.

Thomas Kipps, M.D., Ph.D. of the **University of California, San Diego** completed a project entitled *"Peptide Vaccines for Immunoprevention of Breast Cancer"*. The object of this grant was to develop a breast cancer vaccine by devising new ways to make the immune system sensitive to a protein found on some tumors called erbB2. Dr. Kipps used short chains of amino acids (peptides) as well as DNA as the means for stimulating the immune system. He found a sequence of amino acids that caused the production of antibodies, but did not protect mice from developing breast cancer. He was more successful with DNA vaccines that coded most or all of the erbB2 protein. Dr. Kipps found that tumors containing the erbB2 protein did not grow well in mice vaccinated with the DNA-based vaccines.

Immune therapy: Mobilizing the body's defenses

anti-estrogens

immune therapy

Sherie Morrison, Ph.D. of the **University of California, Los Angeles** completed a project entitled "*Antibody Fusion Proteins for the Therapy of Breast Cancer*". Dr. Morrison used genetic engineering techniques to fuse antibodies that recognize a protein (Her-2/neu) found in many breast tumors with molecules that stimulate the immune system (B7.1, IL-2, IL-12 and GM-CSF). All of the combinations were able to stimulate immune cells in culture at similar levels to the immune stimulatory proteins alone. She found that the fusion proteins of anti-HER-2/neu and IL2 or B57.1 were able to retard tumor growth in mice, and the anti-HER-2/neu-IL12 fusion protein could stop the growth or cause the regression of new tumors. These are promising results for the possibility of using fusion antibodies to treat breast tumors that have high amounts of HER-2/neu. This investigation has led to the publication of at least five journal articles: *Journal of Immunology*, 1999, 163:250-258; *Lab Animal Science*, 1999, 49:179-188; *Journal of Immunology*, 1998, 161:3729-3736; *Journal of Interferon Cytokine Research* 1998, 18:597-607; and *Journal of Immunology*, 1998, 160:3419-26.

Michael Roth, M.D. from the **University of California, Los Angeles** completed a 2-year project to investigate *A New Approach to Immune Therapy for Breast Cancer*. Breast cancer patients appear to inactivate a key cell type in the immune response, the dendritic cell. Dr. Roth removed dendritic cells from the blood of breast cancer patients and re-energized them with a cytokine (immune cell regulatory protein), called IL-7. He also worked to stimulate the response of dendritic cells to a major breast cancer oncogene, *Her-2*. In this project the potential for the technique was validated. However, future work is needed using gene therapy approaches to develop a more permanent dendritic cell response by enabling them to produce their own cytokines, and for them to more strongly respond to breast tumor antigens.

Jeffrey Smith, Ph.D. of the **Burnham Institute** completed a project entitled "*Targeting T Cells to Breast Cancer*", in which he investigated the viability of certain immune cells (T Cells) engineered to specifically attack breast cancer cells. During this project, Dr. Smith was able to advance the technology for generating breast cancer-specific proteins. However they were not able to graft these proteins onto T Cells and make the T Cells breast cancer specific. These studies were able to rule out the use of the loop grafting technique as a general method for re-engineering T Cell receptors. Dr. Smith was able to create fusion proteins between the T Cell receptor and breast cancer antigens, which may ultimately be useful for targeting T Cells to breast cancers.

New Drug Design

Joseph Couto, Ph.D. and **Jerry Peterson, Ph.D.** of **The Cancer Research Fund of Contra Costa** completed a project entitled "*Molecular Design for Prevention of Breast Cancer Progression*". The goal of the research was to develop novel IFab2 fragments (pieces of antibodies) that could be connected to radioisotopes and targeted to breast cancer metastases. They found that in mice the fragment localized to the tumor better than whole antibodies and were cleared from the body just as well. They published these results in two

scientific journals *Hybridoma* (16/243-248, 1997) and *Molecular Immunology* (33:1095-1102, 1996). These researchers are finding that the whole antibody is yielding a measurable response in Phase I trials in humans (funded by a different grant). Dr. Peterson has designed humanized versions of the IFab2 fragments and, based on the results from the mouse studies, these fragments should improve upon the success of the whole antibody in humans, both in terms of specific targeting to the tumor and reduced toxicity.



snake venom

Dr. Qing Zhou, Ph.D. at the **University of Southern California** completed a 2-year Postdoctoral Fellowship to study *Breast Cancer Gene Therapy Using a Metastasis Inhibitor*. This challenging project succeeded in cloning the gene for contortrostatin (CN), a possible anti-tumor protein derived from snake venom. Dr. Zhou was able to deduce protein sequence and structure of contortrostatin, and to express the protein. However, issues of protein folding and activity need to be addressed in more refined protein expression systems prior to beginning gene therapy experiments.

Francis Markland, Jr., Ph.D. from the **University of Southern California** completed a 3-year project looking at this same potential anti-tumor agent in *Breast Cancer Progression and the Extracellular Matrix*. The goal was to explore the potential of the snake venom protein, contortrostatin, for prevention of metastasis and growth of breast cancer in mice.

Contortrostatin blocks the adhesion of cells by interfering with a group of receptors, the integrins. An interesting discovery in this project was the finding that contortrostatin served to both (i) arrest breast cancer cell growth, and (ii) block the development of the tumor blood supply by the process of angiogenesis. Dr. Markland was funded by the BCRP in 1998 to explore pre-clinical development of contortrostatin using both a liposome delivery strategy and modifying it as a synthetic peptide.

Renata Pasqualini, Ph.D. from **The Burnham Institute** completed a 2-year project to develop *Superfibronectin: a Novel Anti-Breast Cancer Agent*. Fibronectin is a protein found in the material that surrounds cells (the extracellular matrix) of breast cells and circulating in the blood. Dr. Pasqualini studied the effect of a polymerized form of fibronectin, called superfibronectin, for inhibition of breast cancer spread in animal tumor models. She found that superfibronectin could be absorbed into the circulation from the peritoneal cavity, did not stimulate an immune response in the host animal, and showed in preliminary experiments that both tumor growth and metastasis were inhibited. Thus, it is clear that breast cancer cells use attachment to fibronectin for growth and spread, and blocking this process represents a potential therapy for treating the disease.

Research In Progress

Gene therapy and other treatments: new frontiers

Two of the grants currently in progress may offer ways for to make the initial surgery in breast cancer more effective. **Shanaz Dairkee, Ph.D.** of the **California Pacific Medical Center** is investigating whether she can identify areas around the margins of a breast tumor that look physiologically normal, but are genetically predisposed to forming tumors. This will allow pathologists to determine if not only all cancer cells, but also other cells that may appear normal but actually be cancerous or pre-cancerous, have been removed in surgery. She has optimized the procedure for analyzing DNA taken from tumors and their adjacent sections of tissue and identified the particular cases that will give the most informative data for this study. **Hillary Klonoff-Cohen, Ph.D.** of the **University of California, San Diego**, and **Helena Chang, M.D., Ph.D.** and **Hungyi Shau, Ph.D.** of the **University of California, Los Angeles** have teamed up to undertake a 3-year Translational Research Collaboration project. The goal of their project is to determine whether the timing of breast surgery during the phase of a patient's menstrual cycle will affect the likelihood of successful treatment. They have pilot tested their forms: coordinated their surgeons, centers, and data collections and begun to enroll participants. The outcome of this study may provide surgeons with a guideline for optimizing the timing for performing breast cancer surgery.

surgery

Hormone and chemotherapy targets: improving today's arsenal

Silvia Formenti, M.D., Peter Danenberg, Ph.D. and **Franco Muggia, M.D.** at the **University of Southern California** are undertaking studies that will help physicians identify the patients that will benefit from chemotherapy or chemotherapy and radiation treatments together. They are identifying the tumor characteristics that indicate a predisposition to respond to the chemotherapeutic agent, paclitaxel. The investigators have accrued most of the patients for the study and have begun to look at the biological correlates. They have also begun to look at whether the biological correlates will predict tumor response to paclitaxel and radiation.

Immune therapy: Mobilizing the body's defenses



Some BCRP-funded investigators are actively exploring the potential power of the immune system in treating breast cancer. **Yoko Fujita-Yamaguchi, Ph.D.** of the **Beckman Research Institute – City of Hope** is exploring an approach to target the receptor for insulin-like growth factor, IGFR. The hypothesis is that tumor cells require insulin-like growth factor for growth, so blocking this receptor and shutting off the insulin-like growth factor signals should stop cancer cell growth. Dr. Fujita-Yamaguchi has successfully constructed alpha-IGFRs that block the insulin-like growth factor receptor and is testing their effectiveness in blocking tumor growth in mice. **Joseph Lustgarten, Ph.D.** at the **Sidney Kimmel Cancer Center** is continuing a new investigator award to train T cells to specifically recognize tumors by making a fusion protein of Her-2/neu (a protein found in many breast

cancers) and IL-2 (a factor that attracts white blood cells). They have found that in the presence of these fusion proteins, T cells are capable of killing all Her-2/neu, Her-3 positive tumor cells tested in cell culture and delayed the growth of tumors in mice.

Studies of the physiology of tumors can lead to clues to eradicate them. One type of breast cancer (medullary breast cancer) is characterized by having large numbers of white blood cells (B cells) infiltrating them. Medullary breast cancer is typically less aggressive than other breast cancer. **Henrik Ditzel, M.D., Ph.D.** of **The Scripps Research Institute** is investigating whether these B cells contribute to the control of medullary tumor growth. He has found that these B cells are producing specific types of antibodies and is in the process of characterizing the antibodies to determine whether they can ultimately be used as a basis for designing a vaccine.

New Drug Design



Several projects have made progress in exploring new sources for drugs to treat breast cancer. **Kent Erickson, Ph.D.** of the **University of California, Davis** is exploring the potential of a specific type of dietary fat (conjugated linoleic acid, or CLA) to reduce and prevent the spread of breast cancer to other parts of the body. He has looked at how very low dietary concentrations of conjugated linoleic acid may reduce or prevent breast cancer metastasis by adding small amounts of conjugated linoleic acid to a high fat polyunsaturated diet. Tumor growth in mice is significantly reduced by addition of conjugated linoleic acid to their diets. (Previous work has shown that experimental animals' diets containing high levels of polyunsaturated vegetable oils increased the incidence, growth and spread of breast tumors.) Tumor spread is significantly decreased when even a very small amount of conjugated linoleic acid is added to the diet. Moreover, the total amount of tumor in the body was decreased in animals fed the conjugated linoleic acid. While the means by which conjugated linoleic acid reduces cancer spread are unknown, Dr. Erickson has assessed whether certain proteins important for invasion during tumor growth and spread are altered by conjugated linoleic acid.

Nurulain Zaveri, Ph.D., at **SRI International** is continuing a project to develop small molecule inhibitors of a breast cancer enzyme involved in tumor cell invasion. Interestingly, this enzyme, stromelysin-3, does not directly degrade the extracellular matrix; instead it destroys a protein that blocks other matrix-destroying enzymes. It also allows breast cancer cells to respond to other growth factors. Dr. Zaveri is using 'rational drug design' both to target the active site of stromelysin-3 with high affinity and to avoid inhibiting other, related enzymes. The test compounds are ready for animal experiments. **Daryl Drummond, Ph.D.**, from the **California Pacific Medical Center** is using a novel combination of technologies to deliver chemotherapeutics to breast cancer cells. He 'packages' the drug inside of liposome particles, and he targets breast cancer cells by placing a Her-2 antibody on the outside of the liposome. An especially novel element is the use of acid-sensitive lipids, which are expected to release the

chemotherapeutic only when the liposome is absorbed into breast cancer cells. Thus, the drug concentration inside the cancer cells will be very high, but elsewhere in the body the concentration will be low, avoiding the toxic effects of chemotherapy on the body.

Newly Initiated Awards

The BCRP funded 11 new grants for innovative treatments of breast cancer in Cycle V. These projects cover a wide range of topics from uses of Chinese herbs to the emerging technology of 'gene chips' for the diagnosis of breast cancer. With the explosion of new genetic information, many of these projects work at the gene level. This is a tremendous improvement over the previous simple endpoints of growth, metastasis, and cell death for therapeutic evaluation. Thus, as more genetic information on breast cancer becomes available these findings will fill in the genetic puzzle of the disease. It is clear that there will not be one, single effective therapeutic or preventative strategy for all breast cancer(s). Treatments of the 21st century will recognize the diversity of the disease and approach it from many opportunistic angles. Both patients and physicians will be offered many choices that combine the need to eliminate the cancer and to maintain the quality of life.

herbs



The discovery of new drug compounds, refining their key structural elements and mode of action, and exploring the appropriate clinical uses continue to be major areas of investigation. Traditional medicines are recognized as potentially safe and effective treatment methods. Unfortunately, Western medicine has not yet been able to tap this reservoir of new drug options. Perhaps as many as 50% of breast cancer patients and survivors use herbs, green tea, and other plant compounds to self-medicate as an adjunct therapy. **Debasish Tripathy, M.D.** of the **University of California, San Francisco** is funded to study traditional Chinese medicine by investigating botanicals used in Chinese medicine for anti-tumor activity. The aim is to gain more information on which agents are most effective as a first-step for additional clinical studies. **Michelle Tabb, Ph.D.** of the **University of California, Irvine** is investigating a novel intracellular protein that could provide a key common link between the action of phytoestrogens (i.e., plant estrogens), the drug tamoxifen, and Vitamin A in regulating breast cancer cell growth. This project could clear up confusion about why seemingly unrelated compounds act to control cancer. Two newly-funded projects investigate compounds derived from cruciferous vegetables (e.g., brussel sprouts) for their effect on breast cancer. **Gary Firestone, Ph.D.** of the **University of California, Berkeley** is continuing a project initially supported by the BCRP in 1997 to investigate indole-3-carbinol (I3C). This compound will inhibit breast cancer cell growth and it appears to work effectively in estrogen-independent tumors. He plans to develop derivatives of I3C to overcome hurdles of potency and bioavailability in tumor models representative of the human disease. Working with Dr.

Firestone is **Liquan Zhang, Ph.D.**, who is funded to examine how I3C works at the molecular level in breast cancer cells. It appears that I3C inhibits the passage of cells through checkpoints necessary for cell division and growth. Finally, **Mai Nguyen, M.D.** of the **University of California, Los Angeles** is funded to purify and study novel compounds derived from a Chinese palm tree for their activity in inhibiting the process of blood vessel growth, which is necessary for metastasis and tumor growth.

Two newly-funded projects focus on detecting and evaluating biomarkers for breast cancer that are associated with clinical diagnosis and treatment, rather than earlier detection. First, **Stefanie Jeffrey, M.D.** of **Stanford University** will use gene chips to survey breast cancer samples for gene expression patterns. These gene chips have thousands of human gene sequences, and they can simultaneously detect increases and decreases in gene expression in a rapid, automated fashion. Dr. Jeffrey's interest is whether this technology can be applied to smaller biopsy samples from patients at a point where therapy and treatment decisions are critical to a successful outcome. Secondly, **Shelley Enger, Ph.D.** of **Kaiser Permanente Southern California** and **Michael Press, M.D., Ph.D.** of the **University of Southern California (co-PIs)** are funded to study the relationship of existing biomarkers, such as Her-2 and p53, in predicting the success of different adjuvant therapies from large numbers of women diagnosed and treated for breast cancer in the Kaiser Permanente and University of Southern California systems. It is critical to know how women respond to chemo-, radio-, and hormonal treatments following their diagnosis. Women who have breast cancer with the Her-2 growth receptor oncogene have new therapies (i.e., the Herceptin monoclonal antibody) available. But, research continues on Her-2 to better target and treat breast cancer. **Michael Campbell, Ph.D.** at the **University of California, San Francisco** is exploring a molecular approach to combine parts of the Her-2 protein with a virus in an attempt to create a novel immunovaccine. **Richard Pietras, M.D., Ph.D.** of the **University of Southern California** will study how radiation therapy can be combined with Herceptin treatment, and how this combined treatment works on the intracellular signaling pathways inside of breast cancer cells.

The BCRP funded two research projects that explore the use of radiotherapy to target and treat breast cancer. First, **Xiaofei Wang, Ph.D.** of **The Scripps Research Institute** is examining how radiation-induced DNA damage leads to DNA repair. If these intracellular signaling proteins could be rendered inactive, then breast cancers could be made much more radiosensitive prior to therapy. Finally, **Michelle Winthrop, Ph.D.** of the **University of California, Davis** is funded to target radionuclides (i.e., radioactive molecules, rather than externally applied iodizing radiation) to breast cancer. Her approach is to make bispecific antibodies that both will transport the radionuclide and will selectively bind to cancer when injected into the circulation.

detection

Breast Cancer



Meeting a Woman's Needs

Research has demonstrated over and over again that access to, and utilization of, medical services are not uniform in our population. While BCRP is working to advance new prevention strategies and treatments for breast cancer, we are also committed to investing in research that will make these available and acceptable to all populations in California. Despite the small number of grants BCRP has funded in the Health Policy Area, its interest in funding such research remains keen and it will continue to solicit and encourage applications in this area.

Research Conclusions

The Medical System

Breast-conserving surgery (BCS) is an equally effective alternative to mastectomy for most women with stage I or II breast cancer, and is now the recommended alternative for these cases. However, 37% of women with small early stage tumors still received a mastectomy in 1996. The physical and psychological impact associated with unnecessary mastectomies represent a human cost that can be minimized by understanding which factors affect the choice of surgical treatment. **Cyllene R. Morris, DVM, MPVM, Ph.D.** of the **Public Health Institute** undertook to: 1) determine statewide trends of utilization of breast-conserving surgery; 2) determine the most significant predictors of choice of surgery for women who are eligible for breast-conserving surgery; and 3) compare the five-year survival experience of women receiving breast-conserving surgery to the survival of women eligible for breast-conserving surgery who receive mastectomies.

Her analysis indicated that women who are of Asian or Hispanic race/ethnicity, 65 years and older, currently married, diagnosed with a centrally located, stage II lobular or comedo carcinoma, residing in less affluent areas, or in a county without a radiation facility are the least likely to receive breast-conserving surgery in California. On the other hand, African American women are more likely to receive breast-conserving surgery than women of any other race/ethnicity were. Despite these differences, use of breast-conserving surgery is increasing steadily in California. The rate of increase in breast-conserving surgery is similar among women of all race/ethnic groups, and is also similar regardless of the socioeconomic status in the patient's neighborhood. Further analysis of these data is underway and will be published shortly.

Research In Progress

Reducing Inequities

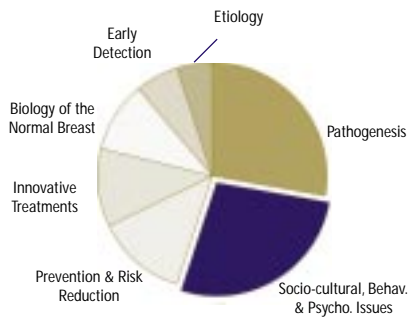
Despite the high incidence of breast cancer and low levels of both awareness and utilization of screening and early detection examinations, no educational programs have been tested among Samoan women. **Shiraz I. Mishra, M.D., Ph.D.** of the **University of California, Irvine** and **Pat Luce-Aoelua, M.S.**, **National Office of Samoan Affairs** are implementing an innovative, theory-based, culturally sensitive and linguistically appropriate breast cancer educational program specially developed for Samoan women. They are implementing the intervention and evaluating its effectiveness in enhancing knowledge, modifying attitudes, and most importantly, effecting positive behavior change. During the first year, they developed the educational program, constituted the sample frame of 68 Samoan speaking churches in Los Angeles and Orange counties, and began implementation of the study in 11 of these churches.

Breast Cancer

Issues Relevant to Breast Cancer

While we search for new prevention and treatment strategies, we cannot ignore the social and cultural context in which women who are faced with breast cancer live and make decisions. These aspects of human life influence health-related behavior, quality of life, and the biological response to breast cancer. Understanding these aspects will help us to further reduce the human cost of breast cancer in California.

Research Conclusions



Distribution of 1999 Funds

Karyn Angell, Ph.D. of the **Stanford University School of Medicine** investigated whether social stress and social support influence a woman's delay in seeking treatment for symptoms of breast cancer. Results from her postdoctoral study revealed that women who experience the death of a parent or close family member during the year before diagnosis are over 7 times more likely to delay treatment for breast cancer, and women with severe chronic stressors of two or more years duration are 4 times more likely to delay treatment. The presence of close friends or relatives in whom a woman can confide does not predict less delay in seeking treatment. However, women whose social network includes people who are critical or demanding are 2.5 times more likely to delay treatment for their breast cancer. These results suggest that even though a woman may know about symptoms of breast cancer and have access to medical care, her decision to seek medical care for herself is strongly influenced by the social and emotional demands of close friends and family members. Thus, this study, (which should be replicated with a larger and more ethnically diverse group of women) points to the importance of a woman's social environment in affecting the way she takes care of herself. We cannot ignore the role of a woman's social network in our treatment and prevention efforts.

social
stress

Long-term survival: Socio-cultural, behavioral, and psychological factors

People have suspected for some time that stress affects well being, but new evidence suggests that expression of stress-related emotions might also affect length of survival in cancer patients. **Janine Giese-Davis, Ph.D.** of **Stanford University** coded the emotional expression and talk-time from videotape as women participated over time in Dr. David Spiegel's supportive-expressive group for metastatic breast cancer. Her preliminary results indicate that the mean survival time is doubled for women who do not constrain anger (3.7 years compared with 1.8). This is the first behavioral study in a relatively naturalistic setting which links bottling up anger with shorter survival. It appears also that women with a healthy, responsive, stress-hormone (cortisol) level benefit from the group intervention by living longer if over time in the group they 1) increase the duration of moments of genuine positive emotional expression, particularly affection, or 2) express longer moments of direct anger, fear, and sadness. The data also suggest that women with a flat or unresponsive stress hormone level do not improve their survival through emotional expression in the group. They appear rigid in their emotional coping style in a way not modified by the group. These results indicate that the physiologically unresponsive women need either an additional or quite different kind of therapy.

emotions

Mary Anne Kreshka, at **Sierra College** in Nevada City and **Cheryl Koopman, M.D., Ph.D.** of **Stanford University** used BCRP's CRC pilot award mechanism to form a collaborative partnership to investigate whether a workbook-journal could help fill a social and

support

psychological support need experienced by many women in rural California. Based on focus groups and the psychological literature on the subject, they developed the journal, entitled "One in Eight," which addresses such topics as how to relate to doctors and medical technicians, how to talk to family and friends, and how to cope with hair loss, energy loss, and other side-effects of chemotherapy and other issues important to newly diagnosed breast cancer patients. They found that women who received the journal showed a significantly greater reduction in their traumatic stress symptoms related to having cancer compared with women who did not receive it. These women also experienced significantly greater increases in fighting spirit toward having breast cancer as well as greater decreases in feeling fatalistic regarding their breast cancer. The partnership was able to build on this experience and receive a full BCRP CRC award to study women who live in urban areas but who nonetheless may be isolated for reasons of disability, age, income, and other factors.

Decision-making and Issues of Genetic Testing

Susan Stewart, Ph.D., Marion Lee, Ph.D., and Joan Bloom, Ph.D. of the **Northern California Cancer Center**, the **University of California, Berkeley** and the **University of California, San Francisco**, respectively, are conducting a study to test a telephone counseling strategy for women that are at higher than average risk for breast cancer. During the first year, the multi-disciplinary, multi-ethnic research team designed an assessment tool which will assist the telephone counselor to understand the psychosocial and emotional needs of the women who will be involved in the study. Previous research has found that most sisters of women who have had breast cancer will over-estimate their own chances of having a breast cancer diagnosis, perhaps resulting in increased anxieties and worries. To this end, the team has developed counseling messages that will support and promote positive breast health behavior and reduce both system and psychosocial barriers to an affirmative approach to breast health care.

Nangel Lindberg, Ph.D. a postdoctoral fellow at the **University of California, Los Angeles** is studying factors among high-risk women that affect their attendance to preventive programs and their compliance with medical recommendations. During the first year, Dr. Lindberg has begun to characterize the clinic population. Initial survey results indicate that about half of participants report having made minimal to moderate changes in their daily routines as a result of a relative's breast cancer, but no changes in their long-range life plans. 40% reported minimal to moderate changes in their long range plans, and over 7% reported extensive life changes as a result of their relative's illness. Many clinic patients have seen the results of their relative's surgery; among them, about half described that experience as traumatic; while most feel they have adjusted, a third report having continuous feelings of distress. One third of patients report slight to extreme changes in their own body image, including changes in sexual functioning, as a result of their relative's breast cancer. Participants experience minimal levels of anxiety about getting a pap smear, but significantly more about obtaining a mammogram or performing breast self-exams. This anxiety is significantly higher for women whose relative has died from breast cancer.

Recently Initiated Research

Seven studies look at various dimension of social support. The first three address social support related to issues of education and screening in special populations: African immigrants, Hmong Women (and Men), and survivor's of Hodgkin's disease. **Yewoubdar Beyene, Ph.D.** of the **University of California, San Francisco** will conduct an anthropological study to explore differences in perceived risk of breast cancer and related cultural factors in a sample of African immigrant women in order to make recommendations about what would and what would not be appropriate mechanisms to employ when interacting with African immigrant women about breast cancer risks, and early detection. **Marjorie Kagawa-Singer, Ph.D., R.N., M.N.**, of the **University of California, Los Angeles**, **Mary Anne Foo, M.P.H.** of the **Orange County Asian & Pacific Islander Health Alliance** and **Sora Park Tanjasiri, Dr.P.H.** of the **University of California, Irvine** (co-PIs) will investigate whether, and what elements of, a culturally-tailored health promotion would best motivate the hard-to-reach Hmong population to be more aware of breast cancer screening issues and obtain mammograms. **Steven Hancock, M.D.** of **Stanford University** will examine: the emotional impact of being notified of an increased risk of cancer due to prior treatment for Hodgkin's disease; whether risk notification leads more women to screening behaviors; and whether mammograms contribute meaningfully to identifying early, curable tumors in younger Hodgkin's survivors (who have a higher-than-average risk for breast cancer). **Nilsa Gallardo, Psy.D.** of the **University of California, Los Angeles** will look at the manner in which Latinas, who have been diagnosed with a breast abnormality suspicious for cancer, define and use social support during the period in which they are undergoing treatment and awaiting a final diagnosis. By developing an assessment tailored to Latina women, she hopes to measure the impact of social support on psychological well-being, and provide clinicians with information useful in identifying women at risk for emotional distress and potentially negative health-seeking behaviors. **Diane Estrin** of the **Women's Cancer Resource Center** and **Rani Eversley, Ph.D.** of the **University of California, San Francisco** (co-PIs) will look at social support issues in the workplace. At present, little is known about: the relationship between the responsiveness of the workplace to women's needs after undergoing surgery and women's ability to return to work; possible ethnic differences in this factor (African American women appear to encounter more difficulties in their ability to return to work, as measured by the rate of return, three-months post surgery); or, about the relationship between return to work and quality of life among women who have undergone breast cancer surgery, or how this differs among ethnic groups.

Matthew Cordova, Ph.D. of **Stanford University** and **Morton Lieberman, Ph.D.** of the **University of California, San Francisco** will look at organized support groups. Dr Cordova is interested in which specific aspects of the therapeutic group support process are the most important, especially among a group of women who have had some prior psychological

cultural
factors

well being

trauma; Dr. Lieberman will explore the feasibility and effectiveness of the online support groups for women with breast cancer which are becoming more popular. Three other studies, those of **Jay Azarow, Ph.D.** of **Stanford University**, **Beth Meyerowitz, Ph.D.** of the **University of Southern California** and colleagues, and **Cheryl Koopman, M.D., Ph.D.** of **Stanford University** and **Mary Anne Kreshka** (co-PIs), will look at the personal and familial dimensions of support. Dr. Azarow will examine how it is that many women with breast cancer are able to elicit a commitment to the creative re-examination and pursuit of what is subjectively most important in their lives, and whether the ability to find positive meaning in illness is, in fact, a key predictor of psychological well-being and improved quality of life. Dr. Meyerowitz and colleagues will investigate how partners' reactions during the immediate post-treatment period relate to patients' quality of life, relationship adjustment, personal growth, and coping. With support from federally-supported research, they also intend to develop and evaluate a brief videotape intervention to prepare women for the transition from treatment to survivorship and to help partners understand the difficulties facing patients at the completion of treatment, so that their partners will be more likely to be able to provide helpful support. Koopman and Kreshka will also explore efficacy in self-support, specifically the extent and effectiveness of a workbook journal developed in a previous BCRP study. Women who may be psychologically, socially, or physically isolated will be targeted-an extension of the geographic isolation studied in the previous study. Finally, **Debra MacDonald, R.N., M.S.**, of the **City of Hope National Medical Center** and **Joy Melnikow, M.D., M.P.H.** of the **University of California, Davis** will examine how best to support women in personal decision-making, specifically with respect to cancer-risk assessment and risk-reduction. Dr. MacDonald will endeavor to learn more about women of diverse socio-economic status who are seeking genetic counseling. She will compare among women appropriate for counseling, those who choose to undergo counseling and those who don't, measure impact of counseling, with the aim of helping clinicians in referral decisions. Dr. Melnikow intends to develop a deeper understanding of how women eligible to take tamoxifen prophylaxis weigh risks versus benefits in their decisions.

Relationship between Federal and State Funding for Breast Cancer

Breast Cancer

“This is one of the most important contributions of BCRP...to fund projects at a very early stage to promote innovation and to permit breakthroughs from the established or faltering current protocols. The breast cancer field will benefit greatly from the Program”.

Funding



Funding

Funding for breast cancer research in the U.S. is available through a variety of sources:

- ♦ federal agencies (National Institutes of Health, Department of Defense), which receive funding through Congress from the national budget and from voluntary purchase of more expensive postage stamps;
- ♦ national voluntary health organizations (American Cancer Society, Komen Foundation, etc.), which receive funding through charitable contributions from individuals, events, corporations and foundations;
- ♦ regional non-profit organizations (Entertainment Industry Foundation, The Wellness Foundation, etc.), which also receive funding through charitable contributions from individuals, events, corporations and foundations;
- ♦ state agencies (New Jersey Commission on Cancer, Massachusetts Department of Public Health, etc.) who receive funding primarily from state general funds and voluntary charitable donations from individuals on state income tax returns.

The California Breast Cancer Research Program is unique in its funding sources. The large majority of BCRP funds comes from a portion of the revenue from a two-cent State tax on cigarettes. Thus, these funds do not come from the State's General Fund, nor are they dependent on voluntary charitable contributions. They are, however, dependent on the consumption of cigarettes in California — a declining and temporary source. BCRP also receives funding through charitable contributions from two sources: voluntary donations by individuals on the California state income tax return, and individual contributions sent directly to the Program.

Research Priorities



Research

One of BCRP's mandates is to "fund innovative and creative research, with a special emphasis on research that complements, rather than duplicates, the research funded by the federal government." BCRP fulfills this mandate in three ways:

1. by identifying gaps in the priority issues and award types funded by the federal government, and developing specific priority issues and award types for BCRP that address these gaps;
2. by having expert reviewers from across the U.S. review grant applications for the innovativeness and uniqueness of each research topic; and
3. by reviewing each application chosen for funding for overlap with existing and pending funding from other agencies.

Identifying Gaps



The federal government funds most health-related research through the National Institutes of Health. The vast majority of research grants funded by NIH are chosen not because they address a particular disease or problem that NIH has identified as important, but rather are chosen based on the scientific merit of projects that lie in the interest of the applicant. In the NIH view, “capitalizing on scientific opportunity depends, in part, on individual scientists designing specific research projects they believe have the greatest significance and offer the best chance of producing important knowledge. Therefore, the NIH places great reliance on investigator-initiated research.” “Only a small percentage of funds is spent on research generated in response” to specific priority issues established by NIH. The majority of the NIH budget supports the “best” research grant proposals regardless of specific applicability to prevention and treatment of a disease.

In contrast, all BCRP funds are directed to specific priority issues developed and selected by the Breast Cancer Research Council. The Council collects information from a variety of sources to inform its priority-setting process:

- ♦ opinions of national breast cancer experts;
- ♦ opinions of California stakeholders, including advocates and activists, health care providers, public health practitioners, community leaders, biotechnology scientists, and academic researchers;
- ♦ current literature on breast cancer and current gaps in knowledge



Thus, the Council attempts to identify and fill important gaps in knowledge about breast cancer that are not being addressed by other agencies. The BCRP priority issues are reviewed and adjusted each year in light of changes in the field, successes and failures of previous initiatives, and results of previous funding cycles.

An indication that BCRP has succeeded in identifying such gaps was provided by the 1998 publication of the NIH’s “Charting the Course: Priorities for Breast Cancer Research.” This report, written by an external group of national experts in breast cancer, identified and prioritized the scientific opportunities and needs that must be addressed to continue and accelerate progress in preventing and treating breast cancer over the next decade. Of thirteen critical gaps in federal funding identified by this group of experts, BCRP had already identified and chosen for funding the following eight:

1. biology of the normal breast
2. better model systems for pre-cancer and cancer
3. biology of pre-cancer
4. biomarkers
5. translational research partnerships
6. patient and survivor needs and concerns
7. multidisciplinary training
8. seed money for innovative, higher-risk ideas

Of the remaining five areas identified by NIH as critical to progress over the next decade, three involved national policy and infrastructure, and only two were research topics that BCRP had not already identified.

It is expected that NIH will begin to offer funding in some of these critical areas over the coming years. As these areas receive more support from federal agencies, BCRP will adjust its priorities and fill new gaps to complement federal funding.

Identifying Innovation and Impact

Over the past three years, BCRP has developed, tested and phased in a scoring system that allows our expert reviewers to better differentiate applications that are especially innovative and that have the most potential impact on breast cancer. This has improved the Program's ability to emphasize innovation and creativity in the research it funds.

In the past, the majority of research funders, including BCRP and the National Institutes of Health, have used a scoring method in which a single overall score for scientific merit is given to each application. With this method, an application that contained an idea that was not particularly novel, but an excellent research plan to test the idea, could receive the same score as an application that contained a very creative idea, but a flawed research plan. BCRP developed a scoring method that could distinguish these two applications. In the new scoring method, every application is scored separately for innovation, impact, approach, and feasibility. These separate scores are used by the Council to arrive at funding recommendations.

Review for Overlap



As a final step to ensuring that BCRP's funds support research that does not duplicate federal funding, all grants recommended for funding are carefully reviewed by both external scientific reviewers and staff scientists for overlap with current and pending federal grants. If any overlap is identified before funding, or during the period of the BCRP grant, the overlapping grant (or portion thereof) is not funded.



Forty-two percent (26 of 62) of the grants that BCRP awarded in 1999 studied either women or tissues from women, while the remaining 58% were laboratory studies that did not directly involve women or tissues from women. .Of the 26 grants that involved women or tissues from women, 69% (18) had women as participants in the study and 31% (8) used tissues or tumor samples. 85% (22) of these studies included underserved women in the study (the remaining four are using tissues that were not specifically collected for their studies) and 19% (5) are focused on underserved women.

The following are grants with a primary emphasis on minority and/or underserved women:

- ♦ A Support Group Alternative for Rural and Isolated Women
- ♦ Social Support and Breast Cancer Control Among Latinas
- ♦ Estrogen metabolizing genes, soy and breast cancer in Asians
- ♦ Beliefs and Risks of Breast Cancer Among African Immigrants
- ♦ Breast Cancer Screening in Women Surviving Hodgkin's Disease



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

Research Administrators



Walter Price, Dr. P.H.
Research Administrator



Laurence Fitzgerald, Ph.D.
Research Administrator



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The Breast Cancer Research Council

Breast Cancer

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 currently 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.



Chair and Vice Chair



**ROBERT ERWIN
CHAIR**
(7/1/96 - 6/30/99)

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

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



**SUZETTE WRIGHT
VICE CHAIR**
(7/1/96 - 4/3/99) *deceased*

Advocates

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



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

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.



VICKI BORIAK
(10/15/99 - 6/30/02)

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.

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.



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

Advocates

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.



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



ARLYNE DRAPER
(7/1/96 - 6/30/99)

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

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 Organization (CABCO). Ms. Rakoff has participated in the Department of Defense (DOD) Breast Cancer Research Program and the California Breast Cancer Research Program (BCRP) grant review process as a consumer advocate. She continues to work for the passage of legislation to increase research funding and to ensure access of care for all women. dedicated to patient care and psychosocial programs, she is the Director of Breast Friends, a peer support mentoring program, at Long Beach Memorial Breast Center.



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

Ex-Officio Members



LIANA LIANOV
(2/15/94 — Ongoing)

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

sharing

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



JACQUOLYN DUERR
(2/15/94 — Ongoing)

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, 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.



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

Medical Specialists



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 Organizations



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."

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.



FELICIA HODGE
(7/1/99 - 6/30/02)

community



HOLLY MITCHELL
(7/1/98 - 6/30/01)

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

Scientist/Clinicians

SHELLEY ADLER

(7/1/96 - 6/30/99)

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



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 (MPH) 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.

SUSAN BLALOCK

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

research

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.



HODA-ANTON CULVER

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

Scientist/Clinicians



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.

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



SUSAN M. LOVE
(7/1/96 - 6/30/99)



MARIA PELLEGRINI
(7/1/96 - 6/30/99)

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

Scientist/Clinicians

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



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

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 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.

advocacy

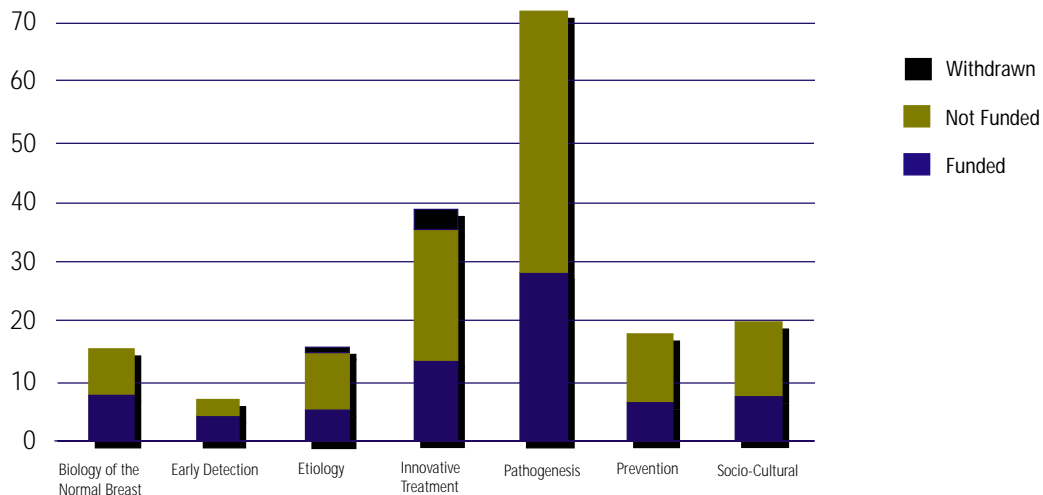


ANNE WALLACE
(8/27/97 - 6/30/00)

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 the patient participation under her direction. She is a member of the UCSD Cancer Center Protocol Review Committee, which is a body that evaluates the protocols for grant applications from the entire Cancer Center. She also collaborates on research projects that investigate the basic biology of breast cancer. She has a profound interest in funding forward thinking research that is maximally beneficial to breast cancer patients.

Summary of 1999 Research Awards

Funding Success for Priority Issues by Numbers



Research Awards

1999 was the California Breast Cancer Research Program's fifth year of operation, and marked another year of important achievements and growth for the BCRP. With a budget of \$17,432,000, BCRP was able to award 62 new projects across the state. The projects include work in the areas of:

- ♦ the biology of the normal breast,
- ♦ factors that increase the risk of breast cancer,
- ♦ ways to reduce the risk of breast cancer,
- ♦ understanding how breast cancer develops,
- ♦ developing new treatments for breast cancer,
- ♦ detecting breast cancer earlier.
- ♦ exploring socio-cultural, behavioral, and psychological aspects of breast cancer,

	Duration	Direct Cost	Indirect Cost	Total
California Institute of Technology				
Brown , Eric Role of a DNA Damage Response Gene in Breast Cancer	2	\$70,000	\$0	\$70,000
Cal. Pacific Medical Center Research Institute				
Desprez , Pierre-Yves Id-1 Expression During Breast Cancer Progression	1	\$49,988	\$28,043	\$78,031
Singh , Jarnail Identification of Novel Id-1 Regulated Genes in Breast Cells	2	\$70,000	\$5,600	\$75,600
<i>Subtotal</i>		<u>\$119,988</u>	<u>\$33,634</u>	<u>\$153,631</u>
Cedars-Sinai Medical Center				
Davis , Vicki Breast Cancer Prevention by a Dominant Negative ER Variant	2	\$199,989	\$102,994	\$302,983
Koeffler , H. Phillip Identification of Novel Secreted Proteins of Breast Cancer	1	\$50,000	\$25,750	\$75,750
<i>Subtotal</i>		<u>\$249,989</u>	<u>\$128,744</u>	<u>\$378,733</u>
City of Hope National Medical Center				
MacDonald , Deborah Communication, Content & Impact of Genetics in Breast Cancer	3	\$427,442	\$203,732	\$631,174
John Wayne Cancer Institute				
Hoon , Dave Clinical Utility of Breast Cancer DNA Markers in Plasma	2	\$197,762	\$175,613	\$373,375
Kaiser Permanente Southern California				
Enger , Shelley Can Molecular Markers Predict Response to Adjuvant Therapy?	3	\$206,166	\$66,486	\$272,652
La Loba Support Group				
Kreshka , Mary Anne (Sub-contract to Stanford University)	3	\$0	\$0	\$0

	Duration	Direct Cost	Indirect Cost	Total
Lawrence Berkeley National Laboratory				
Hagos , Carmen Hox Genes in Normal Breast Development and Breast Cancer	2	\$70,000	\$0	\$70,000
Lawrence Livermore National Laboratory				
Albala, Joanna A Role for Rad51B in Breast Cancer	3	\$225,000	\$182,787	\$407,787
Marin Breast Cancer Watch				
Farren , Georgianna Marin County Breast Cancer Study of Adolescent Risk Factors	2.5	\$215,000	\$31,800	\$246,800
Molecular Medicine Research Institute				
Beyene , Yewoubdar Belief and Risks of Breast Cancer Among African Immigrants	2	\$236,873	\$0	\$236,873
Orange County Asian and Pacific Com.				
Mary Anne Foo / Sora Park Tanjasiri Belief and Risks of Breast Cancer Among African Immigrants (Sub-contract to University of California, Los Angeles)	3	\$0	\$0	\$0
Salk Institute for Biological Studies				
Xie , Wen ACTR/A1B1 in Mammary Gland Development and Tumorigenesis	2	\$70,000	\$5,600	\$75,600
Scripps Research Institute				
Felding-Habermann , Brunhilde Breast Cancer Cell Binding to the Endothelium	2	\$197,759	\$129,133	\$326,892
Jackson , Janis Specificity of Ras Signaling in Breast Cancer	2	\$150,000	\$114,450	\$264,450
Strohmaier , Heimo Proteolysis of Cyclin E in Normal and Malignant Breast Cells	2	\$70,000	\$5,600	\$75,600
Wang , Xiaofei Mechanism of Radiosensitivity in Breast Cancer Cells	2	\$70,000	\$5,600	\$75,600
<i>Subtotal</i>		<u>\$487,759</u>	<u>\$254,783</u>	<u>\$742,542</u>
Sidney Kimmel Cancer Center				
Schnitzer , Jan Targeting Breast Cancer Blood Vessels	2	\$200,000	\$192,600	\$392,600

	Duration	Direct Cost	Indirect Cost	Total
Stanford University				
Cordova , Matthew Do Community Cancer Groups Enhance Well-being?	2	\$70,000	\$5,600	\$75,600
Hancock , Steven Breast Cancer Screening in Women Surviving Hodgkin's Disease	3	\$716,626	\$319,320	\$1,035,946
Jackson , Peter Role of the POP1 Gene in Breast Cancer Genomic Stability	1	\$75,000	\$41,535	\$116,535
Jeffrey , Stefanie Breast Cancer Gene Expression Using Amplified Core Biopsy	1	\$100,000	\$58,500	\$158,500
Koopman , Cheryl A Support Group Alternative for Rural and Isolated Women	3	\$491,009	\$97,322	\$588,331
Thompson , Devon Characterization of hAG-2 and Its Role in Breast Cancer	3	\$225,000	\$130,749	\$355,749
Weigel , Ronald GATA-3 Expression of Hormone Responsive Breast Cancer	2	\$150,000	\$84,825	\$234,825
Zhang , Hong Cloning of Senescence Genes in Mammary Epithelial Cells	2	\$70,000	\$5,600	\$75,600
<i>Subtotal</i>		<u>\$1,897,635</u>	<u>\$743,451</u>	<u>\$2,641,086</u>
The Burnham Institute				
Ely , Kathryn Molecular Structure of BAG-1: a New Protein in Breast Cancer	2	\$149,630	\$142,148	\$291,778
Kim , Youngsoo COX-2 and Apoptosis Regulation in Breast Cancer	2	\$70,000	\$5,600	\$75,600
Vuori , Kristiina	2	\$150,022	\$142,521	\$292,543
Pasquale , Elena Role of the EphB4 Receptor Tyrosine Kinase in Breast Cancer	2	\$199,876	\$189,882	\$389,758
Smith , Jeffrey Protease Fingerprinting to Diagnose Breast Cancer	2	\$148,895	\$136,510	\$285,405
Strongin , Alex Spatial Control of Matrix Proteolysis in Breast Cancer	2	\$174,555	\$165,828	\$340,383
Sun , YingQing A Novel Inhibitor of Breast Tumor Angiogenesis	2	\$70,000	\$5,600	\$75,600
Vuori , Kristiina How Does Endostatin Inhibit Breast Cancer Angiogenesis?	2	\$150,022	\$142,521	\$292,543
<i>Subtotal</i>		<u>\$692,978</u>	<u>\$788,089</u>	<u>\$1,751,067</u>

	Duration	Direct Cost	Indirect Cost	Total
University of California, Berkeley				
Firestone , Gary Indole Derivatives as Novel Breast Cancer Therapeutics	2	\$150,000	\$0	\$150,000
Miller , Sheldon Mechanisms of Fluid Transport in Human Mammary Epithelium	2	\$149,822	\$0	\$149,822
Zhang , Liqun JoAnn How Indole-3 Carbinol Inhibits Breast Cancer Cell Growth	2	\$70,000	\$0	\$70,000
<i>Subtotal</i>		<u>\$369,822</u>	<u>\$0</u>	<u>\$369,822</u>
University of California, Davis				
Cardiff , Robert Oncogenes: Progression and Biomarkers	2	\$144,609	\$0	\$144,609
Melnikow , Joy Tamoxifen Prevention: Is it Acceptable to Women at Risk?	2	\$321,373	\$0	\$321,373
Winthrop , Michelle Bispecific Antibodies for Radiotherapy of Breast Cancer	2	\$70,000	\$0	\$70,000
<i>Subtotal</i>		<u>\$535,982</u>	<u>\$0</u>	<u>\$535,982</u>
University of California, Irvine				
Michelle Tabb SXR: A Novel Target for Breast Cancer Therapeutics	2	\$70,000	\$0	\$70,000
University of California, Los Angeles				
Barsky , Sanford A New Model for Inflammatory Breast Carcinoma	2	\$200,000	\$0	\$200,000
Gallardo , Nilsa Social Support and Breast Cancer Control Among Latinas	2	\$70,000	\$0	\$70,000
Kagawa-Singer , Marjorie Breast Health Project for Hmong Women and Men	3	\$500,000	\$0	\$500,000
Kimme-Smith , Carolyn UCLA Biomedical Physics Graduate Training in Breast Cancer	3	\$189,206	\$0	\$189,206
Nguyen , Mai Novel Breast Cancer Anti-Angiogenic Compounds	1	\$69,227	\$0	\$69,227
Pietras , Richard New Radiation Therapy for HER-2-overexpressing Breast Cancer	2	\$200,000	\$0	\$200,000
Premack , Brett Role of Chemokine Receptors in Breast Cancer Metastasis	1	\$49,966	\$0	\$49,966
<i>Subtotal</i>		<u>\$1,278,399</u>	<u>\$0</u>	<u>\$1,578,399</u>

	Duration	Direct Cost	Indirect Cost	Total
University of California, Riverside				
Byus , Craig Unique Genes Expressed in Cancer Cells	2	\$150,000	\$0	\$150,000
University of California, San Diego				
Andersen , Bogi New Gene Regulation Factor, LMO-4, in Breast Cancer	2	\$190,000	\$0	\$190,000
MacLeod , Carol The Role of Nitric Oxide and Arginine in the Normal and Tumorous Breast	2	\$200,000	\$0	\$200,000
Xu , Yang The Regulation of p53 Activity in Breast Cancer	2	\$181,560	\$0	\$181,560
<i>Subtotal</i>		<u>\$571,560</u>	<u>\$0</u>	<u>\$571,560</u>
University of California, San Francisco				
Beyene , Yewoubdar Beliefs and Risks of Breast Cancer Among African Immigrants	2	\$112,620	\$0	\$112,620
Campbell , Michael HER2/Neu DNA Vaccines for Breast Cancer	2	\$197,249	\$0	\$197,249
Lieberman , Morton Effectiveness of Electronic Support Groups for Breast Cancer	1	\$100,000	\$0	\$100,000
Tripathy , Debasish Laboratory Testing of Chinese Herbs Used for Breast Cancer	1	\$95,593	\$0	\$95,593
Wrench , Margaret Marin County Breast Cancer Study of Adolescent Risk Factors	2.5	\$284,905	\$0	\$284,905
<i>Subtotal</i>		<u>\$865,277</u>	<u>\$11,237</u>	<u>\$876,514</u>
University of Southern California				
Bernstein , Leslie Postmenopausal Breast Cancer: Obesity and the Leptin Receptor Gene	1	\$74,938	\$47,586	\$122,524
Hamilton , Ann Breast Cancer Susceptibility Genes in Very High Risk Women	1	\$80,243	\$50,954	\$131,197
Henderson , Brian IGF System and Breast Cancer in Postmenopausal Women	1	\$74,956	\$47,597	\$122,553
Meyerowitz , Beth Breast Cancer Survivorship: Partner's Role in Recovery	3	\$468,018	\$150,320	\$618,338
Press , Michael Can Molecular Marks Predict Response to Adjuvant Therapy?	3	\$312,670	\$198,085	\$510,755
Williams-Hill , Donna Exercise, Hormones and Breast Cancer Prevention	1	\$87,126	\$55,325	\$142,451
Wu , Anna Estrogen-metabolizing Genes, Soy and Breast Cancer in Asians	3	\$1,023,306	\$646,221	\$1,669,527
<i>Subtotal</i>		<u>\$2,121,257</u>	<u>1,196,088</u>	<u>\$3,317,345</u>

	Duration	Direct Cost	Indirect Cost	Total
Women's Cancer Resource Center				
Estrin , Diane Returning to Work and Quality of Life After Breast Cancer	1	\$74,910	\$11,237	\$86,147
Eversley , Rani (University of California, San Francisco) - Sub-contract to Women's Cancer Resource Center	1	<u>\$0</u>	<u>\$0</u>	<u>\$0</u>
<i>Subtotal</i>		<u>\$74,910</u>	<u>\$11,237</u>	<u>\$86,147</u>



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