

CALIFORNIA

Breast Cancer Research Program

APPLICATION INFORMATION PACKET

CYCLE X—2004

(For all award types, *except* CRCs)

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2004/CBCRP Cycle X Application Packet

Overview

This booklet provides key information on:

- What's new for 2004
- Application deadlines and PI eligibility
- CBCRP's Priority Issue research topics
- CBCRP's Award Types
- Application evaluation process
- Pre-funding and award conditions
- List of application forms
- **New!** Sample application forms used for the programmatic review

The applications forms and instructions will posted after October 6, 2003 on our Web site: www.cbcprp.org/ under the link "Apply and Reports."

Application Deadlines

The CBCRP has only one funding cycle per year. All materials, originals and copies, must arrive in our office before 6:00 PM on the date it is due.

1

Main Deadline: Thursday, January 8, 2004

ALL applications, except CRC and Joining Forces Conference Awards

Deadlines for Community Research Collaboration (CRC) and Conference awards only:

2

Community Research Collaboration Awards:

Thursday, November 6, 2003 for pre-application Concept Papers (required)

Thursday, February 26, 2004 for full applications

3

Joining Forces Conference Awards. Anytime before **July 1, 2004 (contact us before submitting)**

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CBCRP Cycle X /2004—AT-A-GLANCE

What's New

- **Note!** We are providing **examples of text for the key application forms used for the Programmatic Review**. See Sections 4 and 16.
- We have raised the maximum **award amount for Postdoctoral Fellowships to \$90,000**.
- Consistent with NIH guidelines, **indirect costs** (non-UC institutions only) are capped for **New Investigator awards at 8%**, and for **Postdoctoral Fellowships no indirect costs will be allowed**.
- The research topics listed as “bullets” under the **Earlier Detection priority issue** now includes **molecular imaging and biomarkers**.
- We have changed the **Career Enrichment award description to encourage research disciplines other than the basic and clinical sciences**.
- We require all **applicants to classify their research** according to a newly developed **Common Scientific Outline (CSO)**. This is described with the link to the CSO Web site in Sections 2 and 12, and the information is entered in the appropriate boxes on Form 1.

Priority Issues and Award Types

- Please note that **six of our research topic Priority Issues are designated as “primary”** and will receive first consideration for funding. See Section 2.
- Similarly, **five Award Types are designated “primary”** and will also be given first consideration for funding. See Section 3.
- It is the responsibility of the PI(s) to select the appropriate Award Type and Priority Issue for their application topic and research level/interests. Please **contact us** early with any questions or concerns. We're happy to help!

Application Forms

- The application forms are not included with this booklet. **The application forms** can be either **downloaded from our Web site: www.cbcprp.org/** or sent to you via **e-mail**. The forms will be available after October 6. Call us, if you have any problems: (510) 987-9884.
- We are allowing submission of Other Support and Biographical Sketch application forms using either the NIH forms or the comparable CBCRP forms.
- When preparing the application, please note that a separate group of forms are submitted as an **Executive Summary**. This document is needed for the **Programmatic Review** and special attention should be made to the content of these forms as discussed in Section 4. See Section 16 for examples.
- **The Lay Abstract content is especially important**. See Section 3 and the examples in Section 16.

Other Important Reminders

- Note the **submission deadline dates** and time. Late submissions will not be accepted. **See Section 12 for our policy on submission deadlines**.
- Submit **one single-sided original** and **eleven double-sided copies** of the complete application.
- Enclose **unopened letters** of support/recommendation in a separate envelope for Career Development applications.
- **No supplemental materials will be allowed** after the submission deadline dates—unless requested by the CBCRP.

New awards begin July 1, 2004. **We will contact you with the funding decision** in early June 2004. Information on funding status will not be provided any sooner!

1

INVITATION TO SUBMIT APPLICATIONS

The California Breast Cancer Research Program (CBCRP) is pleased to invite research grant applications for **2004 Cycle X funding**. We expect to have available approximately \$13-14 million to award **new grants beginning July 1, 2004**. In this booklet you will find information to help you select the proper research topic category (Priority Issue), award type, and understand our evaluation and funding process. We hope this will encourage you to apply and to direct your research aims to match the interests of the CBCRP. **Our overall commitment is to fund research that will result in rapid advances in breast cancer prevention, detection, treatment, and cure.** We welcome current CBCRP grant recipients to apply with new projects, and we invite researchers new to our Program to bring your expertise to our cause. The CBCRP supports research only in California from funds obtained through:

- 1) A portion of a 2 cents per pack State cigarette tax
- 2) A State income tax check-off
- 3) The generous contributions from concerned community members dedicated to defeating breast cancer

All grant applications will be first evaluated and rated for scientific merit in a **peer review** process. Applications having sufficient merit are then reviewed for **programmatic relevance** by our advisory Council. It is a combination of both scientific merit and programmatic interest that determines funding. All applicants will receive a detailed written critique.

Who May Apply?

- 1. Any individual or organization in California may submit an application.** The research must be conducted primarily in California. We welcome investigators from community organizations, public or privately-owned corporations and other businesses, volunteer health organizations, health maintenance organizations, hospitals, laboratories, research institutions, colleges, and universities.
- 2. We encourage researchers new to breast cancer to apply.** We recommend that applicants who have limited experience in scientific research or in scientific grant-writing collaborate with established researchers. Applicants are urged to consider the suitability of their research ideas under the CBCRP's collaboration award types.
- 3. Previously funded PIs.** You are welcome to submit applications for new projects with aims distinct from previously funded CBCRP grants.
- 4. Re-submissions.** Individuals who submitted "not funded" applications can revise them and re-submit in the current cycle. Already-funded PIs may submit new applications in Cycle X that are distinct from the previously funded research. Refer to the instructions in Section 12.
- 5. Multiple applications and grant limits for PIs.** An investigator may submit more than one application, but each application must have unique, specific aims. A PI can only receive one non-collaboration award type grant. In addition, a PI may also receive one grant as a co-PI for a collaboration award type (CRC, TRC, SPRC) or as a PI on a Joining Forces Conference Award (JFCA).

Note: Principal investigators with current CBCRP grant support will not be eligible to apply for additional funding unless the required scientific and fiscal reports are up-to-date. See Section 13 under "Policy on Applications from PIs with Delinquent CBCRP Grant Reports."

Application Deadlines

The CBCRP has only one funding cycle per year. **Submitted applications must be complete with all forms, copies, and in a format consistent with our instructions.** Please read our instructions carefully, and only use the new forms for this funding cycle. The application forms and instructions are available from our Web site:

www.cbcprp.org/ or by e-mail. All materials, originals and copies, must arrive in our office before 6:00 PM on the date it is due.

1 Main Deadline: **Thursday, January 8, 2004**
ALL applications, *except CRC and Joining Forces Conference Awards*

Deadlines for Community Research Collaboration (CRC) and Conference awards only:

2 **Community Research Collaboration Awards:**
Thursday, November 6, 2003 for pre-application Concept Papers (required)
Thursday, February 26, 2004 for full applications

3 **Joining Forces Conference Awards. Anytime before July 1, 2004 (contact us before submitting)**

Special exception: Recipients of Cycle IX TRC Pilot Awards may submit a full TRC Research Award application up until February 26, 2004, if a Letter of Intent is submitted by January 8, 2004. Call for instructions.

See section 12 for the deadline policy statement and the detailed submission requirements.

We encourage you to contact us with any questions about our research topic Priority Issues and/or available award types.

2

RESEARCH PRIORITY ISSUES

The **FIRST STEP** in applying to the CBCRP for grant funding is to examine our Priority Issues and Award Types. Answer the question, “How do my research interests, type of project, and career level match the CBCRP Priority Issues and Award Types?”

Funded research must address:

“The mission of the CBCRP is to eliminate breast cancer by leading innovation in research, communication, and collaboration in the California scientific and lay communities.”

To establish the CBCRP’s priorities and advance our mission, our advisory Council identified these key criteria and goals for our funded research:

- **Nurture collaboration** and synergy between California scientists, clinicians, advocates, community members, and others
- **Recruit, retain, and develop high-quality California-based investigators** who focus on breast cancer research
- Foster **innovative ideas** (i.e., new drugs, new strategies and new paradigms)
- **Address the public health outcomes** of prevention, earliest detection, effective treatments, and quality of life
- **Translate research** to more effective products, technologies, or interventions and their **application/delivery to Californians**
- **Drive policy** in both the private and public sectors on breast cancer in California
- **Reduce disparities** and/or **address the needs of the underserved** in California
- Complement, build on, and/or feed into, but **do not duplicate the research programs of other funding agencies** interested in breast cancer
- Respond to feedback and breast cancer research needs and **expectations of the CBCRP as identified by scientists and the public** in California

The **nine (9) Priority Issues** listed below are the broad research topics designated by the Program for Cycle X. They are arranged as four larger groups to better identify those that are closely related. The individual priority issues are defined and the “bullets” are some examples of research topics that are encouraged. Your application must incorporate a main research topic that corresponds to one of the CBCRP’s “Priority Issues.” If your research overlaps more than one Priority Issue, then choose the best match to enter on Forms 1 and 5. Explain the relevance of the additional Priority Issue(s) using Form 5.

Note: The CBCRP is a member of a cancer funding consortium that has developed a **research topic classification scheme and grant portfolio database** Web site: www.cancerportfolio.org/
The purpose of the CSO is to better analyze our applications and funded grant portfolio, compare our funding with other agencies, and identify promising new research topics. Thus, we require our **applicants to provide CSO (Common Scientific Outline) classification code(s) that match the main topics of the research**. There are seven numbered major categories, each with several sub-categories. These are listed and defined in the above Web site, and the existing CSO database can be searched by PI name or word to gain insight in how to classify your application. Please read though **the description of the CSO at the end of this section, and follow the instructions in Section 12 for entering the appropriate code number(s) on Form 1 (cover page). We appreciate your help.**

Primary vs. Complementary Priority Issues

Please note that six of the CBCRP priority issues are “primary” and these will be given first consideration for funding. The reasons are to:

- Encourage applications on topics that the Council has identified as **important breast cancer or scientific issues** that are critical to advancing our understanding of breast cancer
- **Support under-researched topics**. This will help achieve the goal of the Program and advisory Council to make our funding complement, and not duplicate, the funded research of other agencies to reduce overlap.

The remaining three “complementary” Priority Issues are well represented in the CBCRP funded portfolio and include topics commonly funded by other agencies. We will continue to fund applications submitted in these Priority Issues, especially those having high impact and innovation.

Note: After application submission and during the review and funding process, the **CBCRP will examine applications for their appropriate match to the selected priority issue and award type**. We reserve the right to switch applications to a different priority issue or award type. In general, this inspection occurs during the peer review, and committees have the option of changing award type and priority issue by majority vote. In addition, the Program staff and/or advisory Council can make these changes during the programmatic review.

I. The Community Impact of Breast Cancer: the social context

Overview: Beyond access to medical treatment, a woman diagnosed with breast cancer needs: (1) an effective healthcare system that meets the special needs of breast cancer patients, (2) an individualized social support framework, and (3) the recognition that key differences in various racial and ethnic groups that can serve to create disparities. The CBCRP supports research and formulation of public policy alternatives that would contribute to breast cancer prevention and improve outcome. The CBCRP recognizes the need for reducing inequities in access to prevention, detection, treatment, and survivorship services for underserved populations. Finally, we encourage sociocultural, psychological, and behavioral research to reduce the impact of breast cancer on each woman.

1. Health Policy and Health Services: Better Serving Women’s Needs

A. Health Policy

Exploring either public policy change or health outcomes with regard to breast cancer treatment, prevention, earlier detection, and racial/ethnic differences in breast cancer. Topics of special interest include:

- Research and formulation of **public policy alternatives** contributing to breast cancer prevention, e.g., precautionary principle strategies, biomonitoring, and phase-out of persistent bioaccumulative toxins
- Methods to improve **health care outcomes**, especially through public health policy initiatives
- **Economic aspects of breast cancer care**, including increased efficiency and cost-benefit ratios
- Studies of public (i.e., the lay public and policy-makers) **perceptions of breast cancer**, the burden of breast cancer in California, and **priorities for research**
- **Quality of care**, including adherence to state-of-the-art and standard of care guidelines for diagnosis, treatment, and rehabilitation
- **Impact of direct consumer marketing** of genetic testing, imaging techniques, and therapies.



B. Health Services

The development of public policy strategies to most effectively deliver services to women, including **preventing breast cancer and eliminating the barriers to service delivery**. Topics of special interest include:


 Primary

- **Reducing inequities in access** to prevention, detection (*excluding screening mammography*), treatment, and survivorship services for underserved populations
- Outcomes, quality of care, costs, and quality of life in **health service delivery systems**, including organizational models of service, networking, supportive care, support groups, feminist models of health care, and/or multi-specialty access
- Methods to **reduce costs** and/or increase **patient-physician cooperation**, and develop, implement, and evaluate **new practices/policies**
- Development of better self-reporting **patient satisfaction and quality assessment tools** covering the entire process of diagnosis, treatment and rehabilitation.

2. Sociocultural, Behavioral, and Psychological Issues Relevant to Breast Cancer: The Human Side

Qualitative or quantitative research into sociocultural, behavioral, and psychological issues affecting women with breast cancer or at high risk for the disease. Topics of special interest include:


 Primary

- Enhancing **quality of life** at diagnosis, during treatment, and afterwards
- **Survivorship** and end-of-life issues
- Patient and health care practitioner interactions and **decision-making**
- **Participation in clinical trials**/scientific research, especially to increase the participation of underserved populations

3. Racial/Ethnic Differences in Breast Cancer: Eliminating Disparity

Research addressing the underlying differences in breast cancer biology, incidence, morbidity and mortality, or treatment. Topics of special interest include:


 Primary

- Provider and **organizational factors** related to delivery and practice of screening, diagnoses, and treatment that contribute to differences in racial/ethnic groups
- **Social determinants of health** (i.e., environmental exposures, socioeconomic factors and modifiable behavioral risk factors) that contribute to disparities in breast cancer incidence, morbidity and mortality
- Identification of **protective factors** related to incidence and mortality by race and ethnicity, including smaller racial and ethnic groups found in California.
- Exploration of elevated mortality rates among **African Americans and Native Americans**
- Racial/ethnic differences in histologic, cytologic, and **molecular parameters of breast cancer** and disease progression

Note: The **Racial/Ethnic Differences** priority issue overlaps other CBCRP topics. The first bullet listed above is linked to the **Health Policy and Health Services** priority issue. The second bullet is linked to the **Sociocultural, Behavioral and Psychological Issues** priority issue. The third and fourth bullets are linked to **Etiology and Prevention**. Finally, the last bullet is linked to **Pathogenesis**.

II. Prevention and Risk Reduction: the environment of the disease

Overview: What are environmental and biological factors that interact to increase a woman's risk of developing breast cancer? The disease seemingly strikes women at random despite the efforts to identify causative genes and risk factors. We especially encourage new California-based studies to understand the environmental causes of breast cancer, and how these increase risk and impact different communities of women in California.

4. Etiology: Finding the Causes

Investigating breast cancer initiation that may be due to environmental exposures that subject women to agents that they, as individuals, cannot control. To date, there has been intensive study into the contributions of behavior and lifestyle to breast cancer. We wish instead to focus on the external physical factors that contribute to the disease. Our goal is to understand the underlying cancer-initiating biology that may result from exposures, which

include pesticides and other known or suspected carcinogens found in air, food, water, medications, etc. Topics of special interest include:

- Investigations of the **causal role of environmental factors** in terms of site of exposure (e.g., neighborhood, home, workplace) and stage of breast development at time of exposure (particularly adolescence, childhood or the prenatal period)
- Studies of occupational exposures and breast cancer risk
- Consequences of exposures from breast milk, second hand smoke, EMF and other exposures difficult to ameliorate by changing personal behavior
- Creating new **tools to better monitor external initiators of breast cancer**, e.g., body burden of suspected carcinogens including developmental toxicants and identification of surrogate markers of exposure
- Investigation of the human effects of exposure to chemicals currently in use that have been shown to induce mammary tumors in animals
- Identifying **gene/environment interactions** and **biomarkers** using new tools such as proteomics or genomics
- Identification of **carcinogenic agents with elevated exposures in specific populations or geographic areas**

Note: Cell and tumor model-based studies of the role of specific genes, gene combinations and cellular pathways initiating breast cancer should be submitted under the CBCRP priority issue of **Pathogenesis**.

5. Prevention and Risk Reduction: Ending the Danger of Breast Cancer

Methods to prevent breast cancer or reduce risk, including elimination of external causative factors and the identification of surrogate markers for use in prevention trials. Topics of special interest include:

- **Nutritional pathways**, possible preventative foods, and new animal models to test diet components
- Identification of **causal behaviors** that can be modified to reduce risk
- Developing new **intervention strategies**
- **Risk reduction and identification**
- Identification of **surrogate markers/outcomes** for breast cancer prevention
- **Molecular epidemiology** studies on the risk of disease associated with the presence of newly identified or suspected susceptibility genes

Note: By "Prevention," we refer only to the PRIMARY prevention of breast cancer (prevention of the occurrence of the disease).

III. Biology of the Breast Cell: the basic science of the disease

Overview: There is a need to move beyond the "static picture" of breast cancer in tumor cell lines and current animal models. New research is needed to understand the pre-neoplastic, causative events of the disease at the tissue level, including the stroma. The genetic changes in disease progression and the heterogeneity seen in the clinic need clarification at the basic science level. Lab researchers and clinicians are encouraged to engage in more "cross-disciplinary" research projects to link discovery efforts with the clinical issues important to breast cancer. We must understand the genetic and molecular signatures of the disease to treat it effectively.

6. Biology of the Normal Breast: The Starting Point

Aspects of normal breast biology that could provide insights into new approaches to prevent, detect, or treat breast cancer. Topics of special interest include:

- Development and structure of the **normal breast**
- **Cell-cell interactions and the extracellular environment** in the normal breast

- **Patterns of transition** from normal to atypical to pre-malignant breast tissue and factors influencing these transitions
- The development of **cell lines and animal models** that more closely reflect human breast development

Note: Studies that develop tumor models, analyze tumor biology, or use cell lines derived from tumors should be submitted under the **Pathogenesis** priority issue.

7. Pathogenesis: Understanding the Disease

Focus on breast cancer tumor and stromal biology, including (1) relevant proteins and genes and (2) key cell signaling, growth control, cell cycle, apoptosis, and regulatory pathways. Topics of special interest include:

- How cancer spreads: **angiogenesis, invasion, and metastasis**
- **Breast cancer specific events** in molecular genetics, DNA repair, and tumor suppressor function
- Studies using emerging **gene array and proteomic technologies**
- Establishing **potential biomarkers** for earlier detection, stage of disease, tumor progression and prognosis
- Biological factors associated with shortened or lengthened **survival**
- Basic science studies on **disease progression, especially starting at DCIS**
- Racial/ethnic differences in histologic, cytologic, and **molecular parameters of breast cancer** and disease progression (should be submitted under the CBCRP's **Racial/Ethnic Differences** priority issue)

IV. Diagnosis and Treatment: delivering clinical solutions

Overview: Early detection does not guarantee a cure. And, the limitations of mammography require women to undergo unnecessary biopsies and emotional strain. Ultimately patients and physicians have too few options for treatment. New breast cancer specific and “individualized” therapies require investigation. Lab researchers and clinicians are encouraged to engage in more “cross-disciplinary” research projects to link discovery efforts with the clinical issues important to breast cancer.

8. Earlier Detection: Improving the Chances for a Cure

Finding new, cost-effective technological and biological approaches to early detection, molecular imaging, and tumor analysis of breast cancer at the individual and population levels. Topics of special interest include:

- Developing new imaging **technologies to reveal key physiological and biological properties** for breast tumors, associated stroma, or pre-malignant lesions to better characterize stage, and to provide clinically useful information
- **Improving existing imaging technologies to improve specificity and sensitivity** of tumor detection, especially in high-risk women
- Detection of **biological markers** of pre-cancerous or early cancerous lesions
- Research into potential **surrogate markers** for the **identification of high risk women** for clinical surveillance

9. Innovative Treatment Modalities: Search for a Cure

Developing new, more effective therapies for breast cancer. Topics of special interest include:

- Complementary and **alternative medicine** and nutritional factors
- The final stages of establishing a breast cancer protein or gene target as a potential **new therapy target**
- Alternative **approaches for staging** and treating DCIS, primary breast cancer and local recurrences
- Rational **drug design** focused on breast cancer
- **Immunological approaches** for treatment and **vaccine development**
- Preclinical and early clinical studies of **promising new treatment strategies and/or agents**
- Improved management of **sequelae of breast cancer treatment**

Note: Studies of new combinations of standard chemotherapeutic agents will not be considered responsive.

Special California Data Sources for Breast Cancer Research

CBCRP encourages research that explores new hypotheses using existing data sources (from previously funded studies, tissue banks, or from databases such as the California Cancer Registry) especially that take advantage of the ethnic diversity of the state to explore differences between ethnic populations. Three opportunities are:

1. Cancer Information Service

The Cancer Information Service (CIS) at <http://cis.nci.nih.gov/> is a national information and education network, is a free public service of the National Cancer Institute. The CIS program for California is administered by the Northern California Cancer Center (NCCC). It maintains a database of CIS call and outreach contact information, and can serve as a “laboratory” for testing new interventions.

2. California Cancer Detection Section

The Cancer Detection Section (CDS) of the California Department of Health Services (www.dhs.cahwnet.gov/cancerdetection/) is pleased to announce the availability of its breast and cervical cancer early detection services data for scientific research.

Since 1991, CDS has received federal funding to implement the Breast and Cervical Cancer Control Program (BCCCP), which provides free breast and cervical cancer screening and diagnostic services to eligible women in several locations around the state. Since 1994, an increase in the state tobacco tax has funded the CDS-administered Breast Cancer Early Detection Program (BCEDP), which provides breast cancer screening and diagnostic services to eligible women throughout the state. As of October 1, 2002, the two programs’ billing and data systems have been unified into one program called *Cancer Detection Programs: Every Woman Counts*. To be eligible for breast cancer detection services, women must be 40 years or older, have a household income at or below 200% Federal Poverty Level (FPL), and have no or limited health insurance. To be eligible for cervical cancer detection services, women must meet the same income and health insurance criteria and be 25 years or older.

Since program inception (1991) to June 30, 2002, CDS has provided approximately 730,100 clinical breast exams, 653,500 mammograms and 188,000 Pap tests. Program data include procedure, date of service, outcome, cancer stage, payment, client demographics, and provider information. The most accurate historical clinical data is BCCCP screening and diagnostic outcome information. After October 1, 2002, the same information with improved data integrity will be available.

Also available from CDS is data collected from callers to CDS’ statewide consumer 800 number (1-800-511-2300). CDS has contracted with the Northern California Cancer Center (NCCC) since 1995 to operate its 800 number. Women call the 800 number to determine their eligibility for breast and cervical cancer screening services, receive a program application, and get referrals to local providers. The 800 number assists callers who speak English, Spanish, Mandarin, Cantonese, Vietnamese, and Korean.

Data from NCCC include caller demographics, reason for call, and follow-up call information. From the program inception in 1995 through August 31, 2003, there have been approximately 114,000 calls made to the toll free number; about one-half of the callers were eligible to receive breast cancer screening services.

In order to assure client privacy and compliance with HIPAA requirements, confidential client identifiers are available only for scientifically-valid research projects that have been approved by a certified Institutional Review Board (Human Subjects Committee), follow HIPAA requirements and are consistent with the CDS

mission: “saving lives by preventing and reducing the devastating effects of cancer for all Californians through early detection, diagnosis and treatment, with special emphasis on the underserved.”

CDS welcomes research ideas and analyses of CDS data for research or evaluation purposes. Due to the complexity of the CDS data, collaboration with CDS staff would be necessary to communicate the strength and limitations of the data. CDS foresees the degree CDS and researchers collaborate would vary depending on the research/evaluation project and researchers’ preference. Collaboration with CDS would be efficacious at the beginning to enable the researchers and CDS to determine the resources needed and to plan accordingly. It is expected that funding agencies, such as BCRP, should require a letter of support from CDS for proposals involving use of CDS data. To request CDS data, a request form must be completed and submitted to CDS. This form can be obtained from CDS at Department of Health Services, Cancer Detection Section, Evaluation and Research Unit, P.O. Box 942732 MS 428, Sacramento, CA 94234-7320 or can be downloaded from the Web: www.dhs.ca.gov/publications/forms/cancer.htm

3. California Health Interview Survey

The California Health Interview Survey (CHIS) is the largest telephone health survey in the country. This survey takes place every two years. The first survey, CHIS 2001, interviewed over 57,000 California adults in six languages between November 2000 and September 2001. CHIS is a random digit dial (RDD) survey incorporating a geographically stratified sample so that county-level estimates are possible for counties and groups of counties with population sizes of 100,000 or more. Additionally, CHIS 2001 over-sampled three cities (Berkeley, Pasadena, Long Beach), over-sampled California's urban and rural American Indian/Alaska Native population, as well as five Asian groups (Japanese, Korean, Vietnamese, Asian Indian, and Cambodian). Large samples of Latinos, African Americans, Chinese and Filipinos are also in the data file. An NCI sponsored cancer control topical module with breast cancer history, mammography screening, and the Gail risk model variables was included in the CHIS 2001 survey. Zip code information is collected for all respondents plus geocode coordinates for Los Angeles and San Diego counties. Detailed race/ethnic information is collected, including allowance for recording multiple race/ethnic groups. The data are weighted using the 2000 Census. Public use files are available free on the CHIS Web site. More detailed and more confidential information is accessible by application through special data access centers located at the UCLA Center for Health Policy Research in Los Angeles (fees may apply) and at the Department of Health Services in Sacramento for state researchers. An application mechanism exists for researchers to conduct follow-back studies with CHIS participants. CHIS 2003 is collecting data between August 2003 and January 2004. The CHIS 2003 survey also addresses cancer screening and will be fully geocoded statewide. For more information, go to www.chis.ucla.edu.

Interested researchers are invited to contact Walter Price at (510) 987-9886 or walter.price@ucop.edu

If a proposed project requires **access to data from the California Cancer Registry** (www.ccrca.org/), then the application must include a letter of collaboration from a Registry official. If you have questions, please contact William E. Wright, Ph.D., (916) 779-0300, Chief, Research and Surveillance Program, Department of Health Services Cancer Surveillance Section.

CSO Coding for 2004 Grant Applications

Beginning with 2004/Cycle X, the CBCRP will require all applicants to code the research area of their application using the Common Scientific Outline (CSO) classification. The requested information is mainly for statistical purposes, and is not part of the scientific review.

Background

The CSO is intended to enable funding agencies to accurately index grants in their portfolio in order to facilitate information sharing, enable informative analysis and evaluation of agency portfolios and goals, and targeting of unmet research needs.

CSO data from the CDMRP, the NCI and the Cancer Research Institute of the United Kingdom (NCRI) is online at www.cancerportfolio.org. The CBCRP will follow in the fall of 2003.

Many applicants will be familiar with the CSO code from other funding organizations. There are two coding elements: a Primary and a Secondary Code. Choose a primary code that best describes the total intent of the application. Then use a secondary code, if the research cannot be adequately described by one code.

Enter the codes for your application in the space(s) provided in the upper right hand corner of Form 1, just below the words "Cover Page".

The detailed instructions are provided in Section 12 and the instructions for Forms 1A-C.



3

OVERVIEW OF AWARD TYPES

After considering our Priority Issues in the previous section, each applicant needs to select the appropriate CBCRP award type. They fall into four broad categories: (1) multi-PI **collaboration research**, (2) **topic-targeted research** (RFAs), (3) **innovative research**, and (4) **career development**. The award types have specific caps for project duration and direct costs that are listed below.

Note: The award type budget caps are listed for direct costs only. To request **indirect costs** there are two things to keep in mind. First, we do not offer indirect costs to the nine University of California campuses. Second, indirect cost allowances and caps vary by award type. **Each non-UC institution that applies must include Form 20**, which shows the indirect rate being requested and the “base” of budget categories to be used to calculate indirect costs.

The CBCRP award types are grouped into “Primary” and “Complementary” categories:

Primary Award Types. These will be given **first consideration for funding** and include the three types of collaboration awards: Community Research Collaboration (CRC) (see below), Translational Research Collaboration (TRC), Scientific Perspectives Research Collaboration (SPRC), and Joining Forces Conference Awards (JFCA). The Requests for Applications (RFAs), also Primary Awards, are available only in the “Primary Priority Issues.”

Complementary Award Types. These include the innovative award types, IDEA and STEP; and the career development award types (postdoctoral fellowships, dissertation, new investigator awards, mentored scholar, career enrichment, and training program). Fostering innovation and careers in breast cancer research are the focus in the “complementary” category. RFAs are not available in the three Complementary Priority Issues: Earlier Detection, Innovative Treatment Modalities, or Pathogenesis.

Summary: When you prepare the application, indicate the Award Type on Form 1A or B and explain the relevance of your project or research career level to the award type selected using Form 5.

The award type descriptions are covered in the following Sections in detail. The chart below summarizes the key duration, budget, PI, and evaluation criteria distinctions.

Some key points to keep in mind while comparing the award type data are:

- The budget amounts shown are for the total project duration.
- Only non-UC institutions can request indirect costs. The term “indirect costs” used by the CBCRP refers to the Facilities and Administrative Cost Rate, or “F&A Rate.” This is a mechanism whereby the funded institution can be reimbursed for expenses incurred in providing facilities and administrative support to sponsored research.
- However, UC campuses may wish to include a sub-contract with a non-UC institution that is eligible to receive indirect costs. In this case, the direct costs budget for the UC campus can exceed the direct costs cap for the award type by the amount of the indirect costs in the sub-contract.
- Generally, the annual budgets for 2-3 year projects should be equivalent (e.g., \$100K/yr for a 3-yr New Investigator grant and \$45K/yr for a 2 year Postdoctoral Fellowship). However, yearly budgets can vary, and it is possible to request the direct cost maximum over a shorter duration (e.g., a TRC Full Award for \$500K over a two-year duration or a \$200K STEP for 18 months).
- The Merit Score criteria definitions for “innovativeness” and “career development” differ in the various award types. Refer to the definitions in the award type Sections that follow.

Overview of CBCRP Award Types and Evaluation Criteria

Community Research Collaboration (CRC) and Joining Forces Conference Awards (JFCA) are not shown. See Sections 7-8.

	IDEA	STEP	RFA	Post-doc	New Invest.	Career Enrich.	Dissertation	Mentor Scholar	Training	TRC-Pilot	TRC-Full	SPRC-Exploratory	SPRC-Full
Primary (P) or Complementary (C)	C	C	P	C	C	C	C	C	C	P	P	P	P
Number of Principal Investigators	1	1	1	1	1	1	1	1	1	2 or 3	2 or 3	2 or 3	2 or 3
Maximum duration	1.5 yrs	2 yrs	3 yrs	2 yrs	3 yrs	1 yr	1-2**	2 yrs	3 yrs	1.5 yrs	3 yrs	1.5 yrs	3 yrs
Maximum direct costs (total project)	\$75K to \$100K*	\$150K to \$250K*	No Cap	\$90K	\$300K	\$100K + salary	\$60K + other**	\$70K + other^	\$300K	\$100K	\$500K	\$100K	No Cap
Budget: Maximum Equipment	\$5,000	No Cap	No Cap	\$2,500	\$5,000	No Cap	None	No Cap	No Cap	No Cap	No Cap	No Cap	No Cap
Minimum PI Effort on Project	5%	5%	10%	80%	25%	25%	80%	50%	10%	10%^	10%^	10%^	10%^
Indirect Costs (non-UC only)	Full	Full	Full	None	8%	8%	None	8%	8%	Full	Full	Full	Full
Priority Issue Addressed	Any	Any	Primary Only	Any	Any	Any	Any	Any	Any	Any	Any	Any	Any
Scientific Merit Score includes the following components:													
Innovativeness	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Impact	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Approach	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Feasibility	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Career Development				<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>					
Translational Potential										<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>		
Cross-Disciplinary										<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>		
Synergistic Potential												<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

*See Section 10 for IDEA and STEP direct costs caps that depend on the usage of animal and human subjects in the project.

**1 year for master's program; 2 years for doctoral program. Maximum of \$30K/yr.

^ See Section 11 for complete budget details.

^^ For each co-PI.

4

APPLICATION EVALUATION AND AWARD PROCESS

Applicants should carefully consider how their projects will be evaluated and the criteria involved. The Program takes pride in the detail of the review process, the accuracy of review scoring, and the communication of scores and application evaluations to the PIs. The **CBCRP uses a two-tiered funding process**. First, the peer review committees rate applications for scientific merit. Second, the Program's advisory Breast Cancer Research Council evaluates those applications with "sufficient merit" for several criteria of programmatic relevance. The Council consists of 16 members from the advocacy, clinical, research, health care, and industry communities.

Peer Review Committees

Review Committees (i.e., study sections) are assembled around specific award types and/or priority issues. Scientific and breast cancer advocate reviewers are chosen from outside California to minimize possible conflicts of interest. The reviewers have demonstrated expertise in breast cancer and/or the specific research topics in the applications. Scientist reviewers are a mixture of senior and more junior researchers, and they are selected from academic, nonprofit institutions, biotech/industry, and clinical research settings. Advocates often have training and/or prior experience in application review. The Committee Chair is usually a more senior researcher with significant review committee experience. The Chair may assist in recruiting reviewers and assigning applications. The Program conducts the Review Committees consistent with NIH practice.

Applications are evaluated by three scientific reviewers (primary, secondary, and tertiary) and an advocate reviewer. Each reviewer prepares written comments that concentrate on the strengths and weaknesses of the proposed research with respect to the scientific merit scoring criteria specific for each award type. In addition, the application is read by the committee Chair. Applicants will receive a detailed written evaluation. This is primarily derived from the written comments of the assigned reviewers, but also includes key points from the committee discussion and Programmatic Review evaluation. Both funded and non-funded research stands to benefit by a careful study of the results of the review process. The Committee ballots and final score calculations are verified by the University of California Auditor.

Note: PIs that have been previously funded by the CBCRP should inspect our Web site www.cbcpr.org/research/ to read through the posted abstracts for their grant(s). Reviewers are instructed to look through previous CBCRP funding to evaluate whether applications are novel and worthwhile additions to previously funded research. We advise PIs to address the distinction of their new applications to previously-funded CBCRP grants using Form 16.

Scientific Merit Criteria

There are distinct components of scientific merit and they are scored independently by our peer reviewers to reflect the requirements inherent in each award type. The components specific to each award type are listed and compared in the Table on the preceding page. In **the award type sections to follow, these scientific merit score components are described in detail**. The use of merit score components allows the Program and the Breast Cancer Research Council to better judge the strengths and weaknesses of each application. When preparing the application, please consider how your application has addressed the specific merit score components in the award type you have chosen.

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When all applications have been peer reviewed, the Program will calculate the **average scientific merit scores** that combine all the merit components equally. The average scientific merit scores for all applications are ranked, and **the lowest third (approximately) of applications are excluded from further consideration for funding**. Thus, applications with a “sufficient scientific merit” are eligible for the Programmatic Review described below.

Note: The scientific merit assigned by review committees does not distinguish between “primary” and “complementary” Priority Issues and Award Types discussed in Sections 2 and 3. This distinction only occurs in the Programmatic Review described below.

The following will be evaluated by the scientific peer review committee and Program staff, but they are not included in the scientific merit score:

Budget/Duration and Overlap: The appropriateness of the requested direct cost budget and duration of the project will be reviewed. Awards may be made contingent upon acceptance by the investigator(s) of a revised budget, as recommended by the Review Committee. Note the specific allowed budgetary items and caps for each award type. Equipment is defined as: (1) non-expendable, tangible, personal property, (2) having an acquisition value of \$1,500 or more, (3) free standing, and (4) with a normal life expectancy of 2 years or more. The maximum allowable costs for equipment in each award type are discussed in the following sections and the instructions for Form 7.

PIs and other key personnel are required to report other non-research (Form 14) and research (Form 15) funding, and state the distinction between the application and other research funding on Form 16. The review committee and Council will examine these items and make comments on research overlap.

Research Risks: If a project proposes activities that pose unacceptable potential for human and animal subjects risks, then a recommendation either not to fund or to delay funding until the issue is resolved may result. The application information for IRB and Animal Welfare approval should be included on Forms 18 and 19 with the application. The Program will require full institutional approval prior to the release of any funds. Clinical trials may be required to provide a data and safety monitoring board (DSMB) as described in the NICI policy release, <http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm> (see also Form 18). The DSMB is in addition to institutional IRB approval, and provides a multi-disciplinary approach to ensure patient safety, confidentiality, and study monitoring.

Programmatic Review

The Programmatic Review is conducted by the advisory Breast Cancer Research Council and involves analyzing applications with a “sufficient scientific merit” score for the criteria listed below.

<u>Programmatic Criteria</u>	<u>Application Form</u>
• Priority Issue Responsiveness	Form 5
• Award Type Responsiveness	Form 5
• Multidisciplinary approach	Form 6
• Translational potential	“
• Focus on the underserved	“
• Balance in the overall portfolio	Forms 3, 4, and 16
• Emphasis on relatively underfunded areas	“
• Quality of the Lay Abstract	Form 3
• Inclusion of advocates and sensitivity to advocacy concerns	Forms 3 and 6

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The individuals on the Council performing this review include advocates, clinicians, and scientists from a variety of disciplines. In performing the Programmatic Review the advisory Council first evaluates **only a portion of the application forms**, which are submitted as an **Executive Summary**. These Forms, except for Form 4 (Scientific Abstract), should be prepared using a style and language comprehensible to the general public. Thus, **it is critical for applicant(s) to pay special attention to the instructions for these forms**. This is especially true for the Lay Abstract (Form 3), which must be a non-technical description of the research using the criteria provided in the instructions and listed on the form itself. In addition, the PI(s) must sign Form 3 to acknowledge that a failure to follow the instructions on the form could adversely affect the Programmatic Review score. On Form 5 applicants explicate the link between the proposed research and the chosen priority issue and award type. On Form 6 applicants address the issues of multidisciplinary approach, inclusion and relevance to the underserved, the translational potential, and advocacy involvement in the proposed research. Form 16 (and Form 17 for career development applications) enable the PI(s) to make a distinction of the proposed research from the other currently funded research of the PI(s) or the mentor. Applicants are encouraged to state whether they believe the research is underfunded or would contribute to the balance in the CBCRP's portfolio. The Program's funded research from the previous seven cycles is listed on our Web site: www.cbcprp.org/ under the link "Research Portfolio." The titles and detailed abstracts for more than 550 funded projects can be accessed by either Priority Issue/sub-topic or by PI.

Note: Please refer to Section 16 for examples of quality presentations on the key application forms used for the Programmatic Review. Each year we choose not to fund applications that have been assigned high peer review merit scores, but the applicant(s) fail to connect the research to the stated CBCRP research interests, funding priorities, and mission.

After the Council assigns a programmatic rating, they will then examine the peer review committee's scientific merit score. The Council assesses the ranking within each committee by award type and the strengths and weaknesses in the individual merit score components (e.g., innovativeness, impact, career development). **Thus, it is a combination of (1) the programmatic evaluation and (2) strengths and weaknesses in both the average scientific merit and individual components of scientific merit that determines a decision to recommend funding.**

Finally, the applications in the "primary" category for either the Priority Issue or the Award Type are given "first consideration for funding." This means that a decision to fund or not to fund the "primary" applications will occur prior to consideration of the "complementary" applications.

Other Funding Issues and Information

How does an applicant's choice of Priority Issue and Award Type ultimately impact funding success? First, an application is considered "primary", if it addresses either a "primary" Priority Issue or Award Type. Secondly, after application submission, and during the review and funding process, the CBCRP will examine applications for their appropriate match to the selected Priority Issue and Award Type. Thus, we reserve the right to switch applications to a different Priority Issue or Award Type. In general, this inspection occurs during the peer review, and committees have the option of changing award type and priority issue by majority vote. In addition, the Program staff and/or advisory Council can make these changes during the programmatic review.

In 2003/Cycle IX we evaluated 221 applications in peer review committees and eliminated 80 on the basis of low scientific merit. Of the remaining 141 applications having **acceptable scientific merit**, the advisory Council in its programmatic review (we omit applications falling in the bottom third of scientific merit scores from the programmatic review) recommended 50% (29) of the "primary" and 23% (19) of the "complementary" applications for funding. **A more detailed presentation of 2003 CBCRP funding will be presented in a publication called "2003 Cycle IX Compendium of Awards"** and it will be posted on our Web site under the link "Publications."

Award Decisions and Pre-Funding Requirements

The final approval for funding is made by the Executive Director of the Special Research Programs at the University of California, Office of the President, Dr. Charles L. Gruder.

Applicants will be notified by mail in early June 2004 of their funding status. The written application evaluation from the review committee, the merit score average, component scores, and percentile ranking are provided at a later time. Some applications could be placed on a 'waiting list' for possible later funding.


Pre-funding requirements: Prior to initial funding disbursement we require grant recipients and/or the contracts and grants officials to: (1) inform the Program in a timely manner of their acceptance of funding, (2) resolve any issues of research funding overlap, (3) provide up-to-date human subject and animal approval documents, (4) provide up-to-date indirect cost rate (ICR or F&A) agreements for non-UC institutions, (5) edit and submit an acceptable lay abstract and/or revised project title, and (6) resolve any issues of reduced project budget/duration or other Program requirements. Distribution of funding is done separately for each project year.

Confidentiality

The CBCRP maintains confidentiality for all submitted applications with respect to the identity of applicants and applicant organizations, all contents of every application, and the outcome of reviews.

For those applications that are funded, the CBCRP makes public the title, principal investigator(s), the name of the organization, and award amount in a Compendium of research distributed for each funding cycle. In addition, the costs (both direct and indirect) are published in the CBCRP's Annual Report. The project abstract and progress report abstracts are displayed on the CBCRP Web site. If the Program receives a request for additional information on a funded grant, the principal investigator and institution will be notified prior to the Program's response to the request. Any sensitive or proprietary intellectual property in a grant will be edited and approved by the PI(s) and institution prior to release of the requested information.

No information will be released without prior approval from the PI for any application that is not funded.



5

SCIENTIFIC PERSPECTIVES RESEARCH COLLABORATION (SPRC) AWARDS

Critical expertise to solve breast cancer exists outside of the current legion of researchers studying the disease. Thus, the CBCRP seeks to create the opportunity for breast cancer researchers and clinicians to collaborate with scientists outside the breast cancer research community to **explore creative ways to combat the disease**. The SPRC requires an **interactive partnership** between an investigator experienced in a research discipline outside breast cancer and an experienced breast cancer researcher. The project's problem or research hypothesis must be focused on breast cancer and use tools and theories from another discipline to generate and explore new paradigms. Some examples of other disciplines that might prove valuable in the fight against breast cancer include economics, sociology, mathematics, physics, engineering, environmental science, psychology, women's studies, ethnic studies, and political science. The key point is that the non-breast cancer research partner must contribute a separate body of knowledge/expertise not before utilized to tackle problems in breast cancer. We envision two major opportunities for projects using the SPRC award type approach. First, we anticipate there will be a **potential for synergism** in problem-solving and concepts that can be incorporated into such a research project. Second, individuals and groups can gain the basis for **interaction that might not otherwise be possible** from other funding agencies. We encourage our applicants for this award type to expand their research horizons to find what is possible and needed to defeat breast cancer.

As part of this initiative, a **Joining Forces Conference Award** (Section 8) is offered to stimulate ideas and interactions around breast cancer that could be the basis for SPRC collaborations.

Award Description

The SPRC Awards are designed to stimulate, facilitate and fund research that brings **insights, tools, and ideas from research disciplines not now integrated into breast cancer research** to bear on the intractable problems of breast cancer. Such disciplines could include computer modeling, mathematics, economics, sociology, physics, engineering, environmental science, social marketing, psychology, women's studies, ethnic studies, etc. To be responsive to the SPRC award type, the research partnership should: (i) define and explicate in the grant application how the collaboration is focused on breast cancer as the ultimate goal, (ii) identify the resources made possible by the interaction leading to synergism and a novel approach, and (iii) explain how this research funding would create the opportunity for such a collaboration. The SPRC award type has **two levels of support**:

The SPRC Exploratory Award is for a maximum of **\$100,000 direct costs for a period of up to 18 months** and is intended to explore the potential of the highly speculative concepts that are expected to arise from these partnerships. Activities can include supporting the initial phase of the partnership, including solidifying the organizational structure and processes of the partnership, determining the locus of the responsibility for the research efforts, detailing the research plan and methods, and collecting any pilot data necessary. An outcome of the exploratory grant would include an application for a SPRC Full Research Award or an award from another funding source.

The SPRC Full Research Award is for a period of **up to three years with no dollar cap** (a total of \$2 million will be available for these awards). The research plan should be fully developed. The purpose of the SPRC Full Research Award is to stimulate and support an innovative, synergistic research project involving a collaborative team of breast cancer researchers and scientists from other disciplines. We anticipate the goal of a SPRC award to be to create a new conceptual framework for understanding breast cancer.

Award Requirements

To be judged responsive to this award type, a SPRC application requires an **interactive research partnership** between an experienced breast cancer researcher and researcher experienced in another discipline not yet integrated into breast cancer research.

- The **breast cancer partner** should be knowledgeable in the basic science, clinical or public health aspects of breast cancer and be experienced in research in one of these areas.
- The **non-breast cancer partner** should be an accomplished researcher in a field that is not now integrated into breast cancer research (see examples above), with ideas and/or methods from his/her field that could move breast cancer research forward.

A competitive SPRC Award application must demonstrate the potential (for the Exploratory Award) or the ability (for the Full Research Award) to conduct high quality, innovative, collaborative research combined with the ability or potential to illuminate intractable problems in breast cancer with insights, tools and ideas from another discipline.

Each co-PI must commit at least a 10% FTE research effort to the project.

The application **must identify one of the nine Program priority issues** as the prime focus of the partnership. This is performed on Form 5. Refer to the research topic examples for the different priority issues as listed in Section 2. Contact the CBCRP if you need further assistance in this phase of the application.

Evaluation Criteria

SPRC applications are peer reviewed and rated independently for **five separate components**, which collectively determine the scientific merit.

- **Innovativeness:** The originality of the research questions and the approach taken in the investigation. The unique features of the cross-disciplinary team and the integration of tools and ideas from other disciplines.
- **Impact:** The extent to which the project, if successfully carried out, would make an original and important contribution to the defeat of breast cancer.
- **Approach:** The extent to which the conceptual framework, design, methods, and analyses are developed, well-integrated, and appropriate to the aims of the project. The relative importance of the partners in the overall project. The ways the disciplines in the partnership are integrated into the overall project design and success. Is there a balance between the breast cancer expertise and issues and the capability and potential of the non-breast cancer partner?
- **Feasibility:** The extent to which the investigators have maximized their chances for success through demonstrated skill, knowledge, expertise, and appropriate resources.
- **Synergistic Potential:** The potential to open new and fruitful avenues of research. The potential for the partnership to generate new paradigms for breast cancer research. The extent to which the proposed project integrates the background, expertise, and abilities of the partners and provides the opportunity for advanced understanding of issues related to breast cancer.

The Review Committee will also evaluate the application for **budget and duration**, human/animal **research risks** and institutional approval, and **overlapping research support**.

The **Programmatic Review** is conducted by the advisory Breast Cancer Research Council and involves analyzing applications with an acceptable scientific merit score for the **programmatic review criteria as described in Section 4** and submitted by the PI as an **Executive Summary** (see Section 12). All SPRC applications are considered “primary” and will receive first consideration for funding.

6

COMMUNITY RESEARCH COLLABORATION (CRC) AWARDS

CONCEPT PAPER REQUIRED! Deadline: Thursday November 6, 2003.

Note: There is a separate 2004 CRC *Call for Applications and Application Packet & Forms*. These are provided on our Web site. The information provided below is just an overview of this award type.

The CBCRP believes that communities should be active participants in research about themselves – in deciding what issues are important and how to study them, in gathering and interpreting data, in communicating findings with other community members, and in developing ways to address community issues. The CBCRP also recognizes that scientific research, if the results are to be reliable and able to be applied to other communities, requires the expertise of well-trained and experienced research scientists.

The CRC Award was developed by the CBCRP to bring community members and experienced research scientists together to study breast cancer-related issues that are of interest to both. We believe that combining the knowledge and interest of communities with the expertise and resources of research scientists will lead to innovative and important research that will reduce the impact of breast cancer.

To support the CRC awards a **Joining Forces Conference Award (Section 8) is offered to stimulate ideas and interactions** around breast cancer that could be the basis for collaborations.

What are the CRC Awards?

The CRC Awards are grants given to teams composed of community organizations/members and experienced research scientists to perform research. There are two types of CRC Awards:

- **CRC Pilot:** Up to 18 months of support to develop the project and collect preliminary data.
- **CRC Full Research:** Up to three years to execute the research plan developed during the pilot phase.

Both Awards have the following requirements:

1. **A research question with a hypothesis and work plan.** While the specific aims and methods must be much further developed and described for the Full Research Award than for the Pilot, the presence of a hypothesis and methods to test it are critical to both applications.
2. Evidence of active **community interest and participation** in the development and implementation of the research project. This can be demonstrated by formation of a community advisory group, description of activities community members have undertaken, letters of support from community member organizations/agencies.
3. **Two or three Co-Principal Investigators.**
 - One Co-PI *must* be a **representative of the community organization** or group involved in the project. This person leads the community involvement in the project.
 - One Co-PI *must* be a **research scientist** with documented experience in the methods to be used in the research. This person is responsible for guiding the scientific aspects of the project. Other scientific expertise should be added as appropriate (as other key personnel or consultants).
 - A third community or scientist partner may be added, if desired.

Award Details

CRC Pilot Award:

- Maximum direct costs **\$100,000**.
- Indirect costs: traditional partner at its federally negotiated rate; community partner at either a flat 25% or a rate negotiated with the UC Office of Research Administration.
- Maximum duration **18 months**.

CRC Full Research Award (a previously awarded pilot project is not required):

- Maximum direct costs **\$500,000**.
- Indirect costs: traditional partner at its federally negotiated rate; community partner either at a flat 25% rate or, if applicable, a federal rate.
- Maximum duration **three years**.

Subject Matter

Applicants may apply for an award addressing **any issue that has been identified by a community as important to breast cancer in that community**. However, there must be a well-defined research question. This question could include testing of health service delivery, but priorities such as service delivery, program development, evaluation and outreach must be well justified in the context of the research question. For example, a project with service delivery as its primary objective, supplemented by a program evaluation component would not be considered appropriate for this Award. **Areas of particular interest to the CBCRP that are appropriate for a CRC Award are:**

- New methods of **dissemination of information** about breast cancer (including state-of-the-art technologies)
- New methods to **increase patient access** and accrual to breast cancer clinical trials
- New methods to improve **patient support** at diagnosis, treatment, recurrence, and in clinical trials (such as psychosocial support, provider networks, etc.)
- New or not yet established **risks for breast cancer**, including environmental factors
- Ethical use, implications, public policy, and support for **genetic testing** for breast cancer susceptibility
- Methods to **facilitate diffusion of new practices** into widespread clinical use

How to Apply and Deadlines

Contact the CBCRP to obtain the *CRC Application Packet* covering the above items in more detail. The CRC application requires special forms not present in this booklet. **CBCRP staff will meet upon request with prospective applicants to assist with any issues** they have on research topics, collaborations, and application procedures.

CRC Submission Deadlines:

November 6, 2003 (Thursday)

CRC Concept Papers due (required)

February 26, 2004 (Thursday)

CRC Applications due

7

TRANSLATIONAL RESEARCH COLLABORATION (TRC) AWARDS

The TRC award type is intended to maximize CBCRP's impact on breast cancer in California by **enabling novel research that incorporates a 'cross-disciplinary' partnership** between independent investigators experienced in at least two of the four broad scientific disciplines of interest. These disciplines include: epidemiology; social, behavioral, or psychological research; basic laboratory; or clinical research. The **collaborative partnership and research project aims must focus on translation into practical applications for combating breast cancer**. It is a combination of the 'cross-disciplinary' expertise and the research plan/translational goals that make an application responsive to the TRC award type.

To support the TRC awards a **Joining Forces Conference Award (Section 8)** is offered to stimulate ideas and interactions around breast cancer that could be the basis for collaborations.

Award Description

The purpose of the TRC Awards is to encourage inter- and intra-institutional commitment to innovative, translational research utilizing a cross-disciplinary approach. The term "translational" is intended to emphasize the closeness of research to application in a clinical, community, educational, or other appropriate setting. The intent of the TRC Award is to assist the translation of research from epidemiologic, psychological, social/behavioral, basic laboratory or clinical studies into the healthcare and lay community through a synergy of several scientific disciplines and/or organizations.

The term 'cross-disciplinary' is used instead of 'multidisciplinary' to emphasize the need to include conceptual and methodological viewpoints not normally brought together. Thus, while a typical multidisciplinary epidemiologic study of dietary factors might involve a statistician, an expert in food-intake survey instruments, and an epidemiologist, the thrust of the TRC is to encourage team building that might, for example, involve biochemists, sociologists, medical anthropologists, or social psychologists, in addition to the above-mentioned disciplines. Combinations of university research, biotechnology, and healthcare communities are especially encouraged. Carefully note the distinctions between the two levels of TRC awards.

The TRC Pilot Award is for a maximum of **\$100,000 direct costs for a period of up to 18 months**, intended to support the initial phase of the project, including solidifying the organizational structure and processes of the collaborative partnership, and determining the locus of the responsibility for the research efforts, **detailing the research plan and methods**, and collecting any pilot data necessary. Such issues might include: (1) identification and development of pertinent research issues as defining research questions, including the gathering of pilot data, or analyzing existing data, (2) full research application preparation, (3) identification of institutional and/or community resources necessary for translational research, (4) identification of the expertise needed for innovative cross-disciplinary approaches to translational research, and (5) fostering the collaboration necessary to utilize this expertise on a research question with strong translational potential. Outcomes of the pilot grant would include an application for a TRC Full Research Award, applications for other CBCRP grants, or applications to other funding sources, and an ongoing intra- or inter-institutional cross-disciplinary effort aimed at translational research in breast cancer. It is expected that awardees would be in a position to submit a future CBCRP TRC Full Research Award application or applications to other funding sources.

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The TRC Full Research Award is for a maximum of **\$500,000 direct costs for a period of up to three years**, in which a research plan that has already undergone some development (with the TRC Pilot Award or through other means) is completed. The purpose of the TRC Full Research Award is to stimulate and support innovative, **scientifically rigorous research involving a team from several disciplines with the goal of translating results of the research project into practical applications**. Research originating from epidemiologic, social/behavioral, psychological, basic laboratory, and/or clinical studies should therefore be used as the source for such studies. The expected outcome is prevention, detection, treatment or public health intervention that is intended to be rapidly implemented to improve the lives of women with, or at risk for, breast cancer. This is distinct from projects leading only to further research applications. **Thus, a TRC Full Award application that does not have a specific translational goal and would lead only to other research grant applications is not considered responsive to this award type.**

Award Requirements

To be judged responsive to this award type, a TRC application requires a **collaborative research partnership** between independent co-investigators experienced in **at least two of four broad scientific disciplines** ('cross-disciplinary') of interest:

- **Epidemiology** of breast cancer
- **Social/behavioral and/or psychological** research in breast cancer
- **Basic science** laboratory research of breast cancer
- Breast cancer-directed **clinical research**

The project focus and direction should be to **translate research** from these areas into practical applications. The co-PIs can be from the same or separate organizations, but all co-PIs must be from California. **The co-PIs must each commit at least a 10% FTE research effort to the project.**

A competitive TRC Award application must demonstrate the potential (Pilot Award) or the ability (TRC Full Research Award) to conduct high quality, innovative, collaborative research combined with the ability or potential to translate basic research findings into a clinical, community, educational, or other appropriate setting.

The application **must identify one of the nine Program priority issues** as the prime focus of the research. This is performed on Form 5. Refer to the research topic examples for the different priority issues as listed in Section 2. Contact the CBCRP if you need further assistance in this phase of the application.

Evaluation Criteria

TRC applications are peer reviewed and rated independently for **five separate components**, which collectively determine the scientific merit. Applicants should carefully consider how their project specifically addresses these criteria:

- **Innovativeness:** The originality of the research questions and the approach taken in their investigation. The unique features of the cross-disciplinary team and the translational approach. Is there a balance between innovation and the wish for translation, application, and diffusion?
- **Approach:** Integration of the cross-disciplinary approach with a coherent hypothesis, and specific aims. The importance of the research questions and their basis in the scientific literature.
- **Feasibility:** The likelihood of successful completion of the study based on the research design, background and experience of the investigators, and available resources.
- **Translational Potential:** The potential and time needed for the proposed work to have an impact on reducing the incidence, morbidity or mortality of breast cancer. The potential for general diffusion of the research results into basic research, clinical, or public health practice. The ease of translation in terms of costs and expertise needed. Potential impact for underserved populations.

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- **Cross-disciplinary nature of the research team:** The knowledge, skills, research tools and experience of the research team in relation to the scientific, translational and innovative potential of the work. The extent to which the composition of the team provides the potential for original research solutions and applications.

The Review Committee will also evaluate the application for **budget and duration**, human/animal **research risks** and institutional approval, and **overlapping research support**.

The **Programmatic Review** is conducted by the advisory Breast Cancer Research Council and involves analyzing applications with an acceptable scientific merit score for the **programmatic review criteria as described in Section 4** and submitted by the PI as an **Executive Summary** (see Section 12). All TRC applications are considered “primary” and will receive first consideration for funding.

In addition, the TRC application can include as an optional participant an advocate/community partner as a Key Personnel. This person should be experienced in breast cancer advocacy issues/concerns, and be affiliated with a community-based advocacy organization. This advocate/community partner should be listed on Form 10B, a biosketch included (Form 11), and a letter of support and project involvement included in the appendix. The advocate/community partner should be discussed using Form 5 and in the Lay and Scientific abstracts.

Note: The CBCRP will allow the recipients of Cycle IX (2003 only!) TRC Pilot Awards an extended Cycle IX application submission deadline of February 26, 2004 *only* for submission of a TRC Full Research Award based on results of the Pilot Award. The PIs must submit a Letter of Intent to the Program prior to January 8, 2004 to request this extended deadline.

8

JOINING FORCES CONFERENCE AWARDS (JFCA)

The purpose of the Joining Forces Conference Awards is to increase interest, stimulate ideas, foster research, and facilitate grant applications for the three collaboration awards offered by the CBCRP– the SPRC, CRC, and TRC awards. These meetings should have a primary focus on breast cancer and facilitate contacts between individuals capable of future collaborative research activities. We have named this award type ‘Joining Forces’ to reflect our intention to break down the barriers to multidisciplinary and cross-disciplinary research, and to recruit community and lay groups in the fight against breast cancer.

To target the **SPRC Awards** (Section 5) these conferences should be designed to:

- **Bring together** breast cancer researchers, clinicians, activists/advocates, and scientists from non-breast cancer fields to explore new ideas.
- **Develop interactions** between breast cancer researchers and other scientists to develop new paradigms and research agendas to impact breast cancer.

To target the **CRC Awards** (Section 6) these conferences should be designed to:

- **Bring together** breast cancer researchers and community organizations to discuss issues in common and explore new ideas.
- **Develop interactions** between community groups and breast cancer researchers that impact breast cancer awareness, earlier detection, prevention, treatment, and socio-cultural issues relevant to a given community.

To target the **TRC Awards** (Section 7) these conferences should be designed to:

- **Bring together** breast cancer researchers and clinicians from different disciplines to explore new ideas.
- **Develop interactions** that lead to translation, dissemination, and incorporation of new ideas to combat breast cancer and put new approaches into health care practice.

Some suggested formats for a joining forces conference are, (1) a symposium with formal presentations and targeted breakout sessions, (2) a retreat that emphasizes less formal interactions, or (3) a conference style ‘roundtable’ discussion of pertinent issues without pre-existing leadership roles established. It is expected that the CBCRP, breast cancer advocates/activists, and the general public will be included in the meeting planning, organization and participation.

The Joining Forces Conference awards are limited to \$25,000 in direct costs. **No indirect costs will be given for Conference Awards.**

Application deadline

Applications may be submitted at any time prior to July 1, 2004. Joining Forces applications will not normally be peer reviewed. Instead, they will be evaluated by the Breast Cancer Research Council and funding decisions will be made within 90 days of submission. We recommend that you submit the application six months prior to the meeting date.

Evaluation criteria

The Breast Cancer Research Council will evaluate the Joining Forces Conference Award applications according to the following **review criteria**:

- **Relevance** of the conference to CBCRP goals


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- Strength of **outreach to ensure representation from new disciplines**, especially for disciplines not now integrated into breast cancer research
- Potential of the conference and the underlying approach **to generate new ideas and facilitate collaboration**
- **Qualifications and background** of the applicants/conference organizers
- **Diversity** of the scientific and advocate/activist involvement
- **Potential to advance breast cancer research**
- Appropriateness of the **budget** for the proposed conference
- Awareness and sensitivity of the conference to **the needs of California**

Special conditions

CBCRP staff must also be integrated into conference planning and implementation, and attendance by members of CBCRP staff and Council must be permitted.

The CBCRP will require a written report upon the completion of conference activities within 60 days of the final meeting, and a fiscal report is due within 90 days.



9

REQUESTS FOR APPLICATIONS (RFAs)

RFA awards are intended to support **fully developed research proposals** for which there is solid background information and promising preliminary studies. In general, the applicant will have experience in breast cancer research and the research questions will be of central importance in a particular discipline or topic area. Projects that are: (1) more speculative or high-risk, (2) performed by research teams new to breast cancer research, or (3) from less established investigators should consider the Program's other award types, especially the Innovative Research Awards (Section 10). However, we still encourage RFA applications to address and discuss project elements related to innovativeness, multidisciplinary approach, translational goals, and the needs of women who are underserved.

RFAs must address one or more of the six "Primary" Priority Issues described in Section 2 and listed below. These are RFA research topics of special importance to the advisory Council.

- **Health Policy and Health Services**
- **Racial/Ethnic Differences in Breast Cancer**
- **Sociocultural, Behavioral and Psychological Issues Relevant to Breast Cancer**
- **Prevention and Risk Reduction**
- **Biology of the Normal Breast**
- **Etiology**

Note: RFA awards are not available on the three CBCRP "complementary" priority issues- Earlier Detection, Innovative Treatment Modalities, and Pathogenesis.

There is no specified budgetary cap on requested direct costs for the RFAs. However, approximately \$1 million is set aside for each of the six RFAs. The Program and Council will weigh the available resources versus the costs of the competitive applications submitted in making the final funding decisions. **The duration limit is three years.** The **minimum time commitment for the PI is 10% FTE.**

Evaluation Criteria

RFA applications are peer reviewed and rated independently for **four separate components**, which collectively determine the scientific merit.


- **Innovativeness:** The extent to which the basic hypothesis represents a new and potentially useful way of formulating, investigating, or evaluating the problem under consideration.
- **Impact:** The extent to which the project, if successfully carried out, would make an original and important contribution to the eradication of breast cancer. This evaluation will include issues of practicality in terms of proposed approaches. Thus, for example, an intervention for prevention should be readily available, affordable, and acceptable to the population addressed, and medically reasonable for healthy women.
- **Approach:** The extent to which the conceptual framework, design, methods, and analyses are developed, well integrated and appropriate to the aims of the project.
- **Feasibility:** The likelihood that the proposed work can be accomplished by the investigators given their documented experience and expertise, past progress, preliminary data, requested and available resources, institutional commitment, and (if appropriate) documented access to special technologies or subject populations. Are there adequate plans for the recruitment and retention of subjects (Racial/Ethnic

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Differences and Socio-cultural RFAs)? This scoring component includes consideration of the match between the resources and the scope of the proposed work.

The Review Committee will also evaluate the application for **budget and duration**, human/animal **research risks** and institutional approval, and **overlapping research support**.

The **Programmatic Review** is conducted by the advisory Breast Cancer Research Council and involves analyzing applications with an acceptable scientific merit score for the **programmatic review criteria as described in Section 4** and submitted by the PI as an **Executive Summary** (see Section 12). All RFA applications are considered “primary” and will receive first consideration for funding.



10

INNOVATIVE RESEARCH AWARDS

The intent of these CBCRP innovative awards is to encourage our applicants to think beyond the conservative, “incremental advances” that are typical of most research proposals. Thus, we are receptive to funding research, although untested, may reveal **breakthroughs or new avenues of investigation**. For the purpose of the Program “innovative” is defined as:

- Applying **novel methods and approaches** to breast cancer research.
- Challenging existing paradigms or developing **new paradigms**.
- Considering an existing problem from a **new perspective**.

The Innovative Research Awards allow established researchers to **enter the breast cancer field**, and it allows existing breast cancer researchers to **try new methods and approaches** to study the disease.

These projects should represent hypothesis-driven research. They are not intended: (1) to fund smaller portions of a larger, R-01-type project, (2) for data collecting, incremental, or correlative research aims, or (3) for the compression of a larger project into a smaller time frame. Think of these projects as ‘high risk/high reward.’

There are **two distinct innovative research award types**:

The **Innovative, Developmental, and Exploratory Award (IDEA)** is targeted to highly *speculative, exploratory, high-risk research* that may not have pilot data, but that has a potential for high scientific payoff. The final results should either be completed in **18 months** or yield pilot data that then can be used for a STEP Award or full research project application to the CBCRP or another agency. It is intended for topics new to breast cancer. Note that feasibility (see below) is addressed by ‘maximizing the chances for success’. This allows the project to emphasize innovativeness and engage in speculative research goals. The **direct cost cap is either \$75,000 or \$100,000**. The higher amount is restricted to projects that use animal models or human subjects (see below).

The **STEP Award** is intended for innovative, *developmental projects* that are in exceptionally promising topics **having some pilot data in breast cancer** (such as that obtained with an IDEA), but are not yet sufficiently mature to compete successfully for funding for a full-scale study. The STEP Award is for a period up to **two years**. The **direct cost cap is \$150,000, or \$200,000 (animal subjects), or \$250,000 (human subjects)**.

Note: Researchers who are testing new hypotheses in breast cancer that are based on research (1) on another cancer type or (2) from a non-breast cancer research area should apply for the IDEA. In contrast, the STEP Award should be based on preliminary data in breast cancer developed by the PI’s own laboratory or research group.

Note to basic science applicants: If a molecular pathway has not been established to be relevant to breast cancer, then the primary point of the study should be to test this relevance. Make this aim #1 in your application!

Upon project completion of either of these award types the PI should have either: (1) opened a new area of investigation, (2) satisfactorily tested a novel or innovative hypothesis, or (3) have viable data for preparation of a full-scale research grant application to the Program or other agency.

Award Cap Guidelines

IDEA and STEP Award applications using **human and/or vertebrate animal subjects** may request a higher award cap. Use the following guidelines for placing your project into the appropriate award cap category:

Higher cap: IDEA is \$100,000 (animal or human subjects) and STEP Award is \$200,000 (animal) or \$250,000 (human subjects) for studies where the use of human or vertebrate subjects is integral to the specific aims of the project. Specifically:

- Human Subjects studies, surveys, and data acquisition requiring institutional IRB-approval and an informed consent form.
- Use of vertebrate subjects and experiments that require an institutional animal assurance approval. This would include animal tumor and metastasis models, 'knock-out mice', and studies where tumor growth/metastasis is inhibited by novel therapies.

Lower cap: IDEA is \$75,000 and STEP Award is \$150,000 is for:

- Uses vertebrate subjects in a minor portion of the project, such as generation of antibodies.
- Using existing data sources, such as patient and cancer databases.
- The basic science uses of archival breast cancer material, such as ATCC-type cell lines or stored tumor materials, generally under the 'exempt' categories of IRB approval.

The application **must identify one of the nine Program priority issues** (Section 2) as the prime focus of the research. This is performed on Form 5. Refer to the research topic examples for the different priority issues listed in Section 2.

The **minimum PI effort must be at least 5% FTE** of total research effort. Allowable expenses include salaries, fringe benefits, domestic travel, and a **\$5,000 maximum for equipment** for IDEAs. Full indirect costs (non-UC only) are allowed for IDEA and STEP awards.

Evaluation Criteria

IDEA and STEP Award applications are peer reviewed and rated independently for **four separate components**, which collectively determine the scientific merit.

- **Innovativeness:** The extent to which the basic concept and hypotheses are speculative, exploratory, develop new paradigms, and are high risk/high reward.
- **Impact:** The extent to which the project, if successfully carried out, would make an original and important contribution to the defeat of breast cancer. Note to basic science applicants: If a molecular pathway has not been established to be relevant to breast cancer, then the primary point of the study should be to test this relevance.
- **Approach:** The extent to which the conceptual framework, design, methods and analyses are developed, well integrated and appropriate to the aims of the project.
- **Feasibility:** For the IDEA and STEP Award it is the extent to which the investigators have maximized their chances for success through demonstrated skill, knowledge, expertise, appropriate resources, and collaborations. For STEP Awards this criterion also includes the relevance of the preliminary data in breast cancer.

The Review Committee will also evaluate the application for **budget and duration**, human/animal **research risks** and institutional approval.

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The **Programmatic Review** is conducted by the advisory Breast Cancer Research Council and involves analyzing applications with an acceptable scientific merit score for the **programmatic review criteria as described in Section 4** and submitted by the PI as an **Executive Summary** (see Section 12). IDEA and STEP applications can be classified as “primary” only if they address one of the six “primary” CBCRP priority issues (see Section 2). Otherwise, all other IDEA and STEP applications are classified as “complementary.” For example, a STEP application in the Pathogenesis priority issue is classified as “complementary”, while a STEP application in Prevention and Risk Reduction is classified as “primary.”

11

CAREER DEVELOPMENT AWARDS

The CBCRP strongly supports opportunities in career development for established researchers, new investigators, postdoctoral fellows, and for the training of undergraduate and graduate students. This brings fresh ideas and approaches to our evolving understanding of the disease.

The CBCRP offers six distinct types of career development awards to support:

- **New Investigators** to initiate independent careers in breast cancer research
- **Postdoctoral Fellows** to gain training that is focused on breast cancer
- Institutional **Training Programs** for undergraduate and graduate students
- Established researchers for **Career Enrichment** in a new discipline or technique
- Graduate students to complete the final year of masters, or two years for doctoral or equivalent degree requirement in breast cancer research using a **Dissertation Award**
- Researchers without postdoctoral training to become **Mentored Scholars** to work in breast cancer research under the direction of an experienced researcher to gain independence. Applicants must have a new (within the past two years) faculty appointment (or equivalent).

Note: We require that Postdoctoral Fellowship, Dissertation, and Mentored Scholar application abstracts (Forms 3 & 4), Forms 5 & 6, the Research Plan (Form 12), and Career Plan (Form 17) be prepared by the applicant. It is appropriate for the mentor to: (1) assist the applicant in prioritizing the aims, (2) help organize a training plan that focuses on breast cancer, (3) match the scope of work to the duration and skills of the applicant and research group, and (4) help with “grantsmanship” issues.

New Investigator Awards: to support newly independent investigators to enable them to initiate their own research programs in breast cancer. Applicants must have an advanced degree and have **less than three years experience as an independent investigator** (either less than three years from completion of training, or less than three years from a change in career that involves beginning independent research). Eligible applicants cannot have received prior funding as principal investigators for major research grants, such as NIH ‘R-01-type’ awards; New Investigator awards from the CBCRP, other UC Special Research Programs, or similar funding from other agencies. Allowable prior funding would include this Program’s awards, postdoctoral fellowships, and similar smaller-scale grants. The institution sponsoring the applicant must provide a non-temporary appointment indicating **research independence** and sufficient resources and support to the applicant in a research program. A **letter of support from the applicant’s departmental director** addresses the issues of research independence, facilities available, and institutional support. This award provides direct costs of up to **\$300,000 for up to three years**. The PI must devote at least **25% FTE** to the project. Allowable expenses include salaries, supplies, fringe benefits, travel, and a \$5,000 maximum for equipment. **Indirect costs are capped at 8% for non-UC institutions.** The award is not transferable to another PI.

Postdoctoral Fellowship Awards: for individuals with current or expected (before 12/31/04) doctoral degrees (Ph.D. or M.D.) to obtain research training in a field of breast cancer research with a designated mentor for **up to two years and \$45,000 (average costs) per year**. The letter of support from the mentor will address the issues of the applicant’s background, role in the laboratory, focus of the project and laboratory on breast cancer, commitment of the mentor, and the PI’s potential for developing a career in breast cancer. Applicants are eligible if they have served in prior fellowships and been awarded funding. However, the Review Committee will examine the prior postdoctoral training/funding of the applicant to assess the additional career development potential of the present CBCRP application and training. Prior recipients of CBCRP postdoctoral

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funding are not eligible under this award type. **The proposed project must be distinct from the work of the mentor and the application must be prepared by the prospective fellow.** The PI must devote at least **80% FTE** to the project. Allowable expenses include salaries, fringe benefits, travel, and a \$2,500 maximum for equipment. The student stipend request for the budget should be consistent with NIH National Research Service Award (NRSA) stipend levels (<http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03-033.html>). **No indirect costs are allowed for postdoctoral fellowships.** The award is not transferable to another PI.

Note: Postdoctoral fellows can delay the start of their project for up to 6 months to finish another funded project or to complete their doctoral training. They must notify the program in writing after an offer of funding (June 2004) to execute a delayed start date.

Training Program Awards: to defined educational programs to train graduate and/or undergraduate students for research careers in disciplines that are important to breast cancer research. The goal is to **increase the pool of excellent researchers** working on the problems associated with breast cancer. The budget limits are **\$300,000 direct costs for a maximum of three years**. The student stipend request in the budget should be consistent with NIH National Research Service Award (NRSA) stipend levels (<http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-03-033.html>). Thus to reflect possible future increases in NIH levels, we are capping CBCRP Training Program support at \$10,000 per year for undergraduate students and \$20,000 per year for graduate students. **This support is restricted for stipend and fringe benefits only.** The Training Program budget should specify support for 3-5 trainees for up to **three years**. Travel costs for the PI is limited to \$1,300/yr, and for students to \$1,000/yr. An additional 10% of the total direct costs budget is allowed for Training Program administration. The PI must commit at least **5% FTE** to the training program. The PI should have demonstrated experience both in the breast cancer topics associated with the program and in training student/researchers in areas relevant to breast cancer. The CBCRP is most interested in: (1) the use of a **multidisciplinary approach** in the training effort, (2) recruiting trainees from **different research disciplines**, (3) recruiting **diversity** in the pool of trainees selected, (4) developing a **commitment of the trainees** to breast cancer research, and (5) fostering **awareness of the breast cancer advocacy issues** that created the opportunity for this type of funding. The **trainees must commit at least 50% FTE** to the training program. **Indirect costs are allowed to a maximum of 8% (non-UC institutions).**

Career Enrichment Awards: to support established researchers or clinicians (5 or more years as a clinician or an independent investigator) to gain experience in a new breast cancer field under the direction of a colleague/mentor in the new discipline. Clinicians that are not currently involved in research projects are encouraged to apply. We encourage researchers to experience an alternate discipline to enhance their capacity to engage in new projects. The maximum duration is **one year** and direct costs **budget cap is full salary support** and up to **\$100,000** for travel, research supplies, and housing. The **PI must commit at least 25% FTE** to the project. **Indirect costs are allowed to a maximum of 8% (non-UC institutions).** The award is not transferable to another PI.

If the PI is leaving California to train elsewhere, then the award will be made to the applicant's California institution and paid by subcontract, as appropriate, to an outside institution.

Dissertation Awards: to support the dissertation research of masters or doctoral candidates who wish to pursue breast cancer-related topics. The awards are designated specifically for students who have advanced to candidacy by the award start date (July 1, 2004) and who are initiating their dissertation research. Thus, the research to be supported by the award should be sufficient to complete this portion of the PI's degree requirement. The applicant and their mentor must be affiliated with an academic research institution in California, and the candidate must be directly supervised by the mentor who is eligible to be a Principal Investigator at the applicant institution. The Principal Investigator of the application is the masters/doctoral candidate, who must prepare the application including the Research Plan.

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The student stipend request for the budget should be consistent with NIH National Research Service Award (NRSA) stipend levels (<http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-02-028.html>). Thus to reflect possible increases in NIH levels for 2003-2005, we are capping allowable expenses at **\$30,000 per year for stipend/fringe benefits, tuition/fee remission, supplies, and domestic travel**. Follow the instructions for Form 7 to divide the requested amounts appropriately into the budget categories. The maximum duration is **one year for a master's candidate and two years for a doctoral candidate**. **No equipment purchases and no indirect costs** are allowed. **The PI must commit at least 80% FTE** to the dissertation project. The award is not transferable to another PI.

Mentored Scholar Awards: for researchers without postdoctoral training have a new (within the past two years) faculty appointment (or equivalent), but are not yet ready to become independent investigators. The award allows the applicant to work in breast cancer research under the direction of a mentor in order to gain experience, faculty rank, publications, and other skills necessary to achieve independence. Applications in health policy, economics and social sciences (anthropology, sociology, psychology, etc.), as well as nursing, especially encouraged. The intent of the Mentored Scholar award is to offer career support, equivalent to postdoctoral fellowships for Ph.D./M.D. recipients in the basic and clinical sciences, but in disciplines not normally requiring postdoctoral training. Applicants cannot have received prior funding as principal investigators for major research grants, such as NIH 'R-01-type' awards; New Investigator awards from the CBCRP, other UC Special Research Programs, or similar funding from other agencies. Allowable prior funding would include smaller-scale grants, such as the CBCRP's IDEA. The institution sponsoring the applicant must provide a non-temporary appointment with sufficient resources and support for the applicant to conduct the research project. The mentor for these awards should be a senior faculty or departmental head that currently supplies the PI's salary and research support, and under whom the PI is currently working. The mentor should be eligible to be a principal investigator at the applicant institution. The letter of support from the mentor will address the issues of the applicant's background, role in the research group, focus of the project and laboratory on breast cancer, commitment of the mentor, and the PI's potential for developing a career in breast cancer. The proposed project must be distinct from the work of the mentor and the application must be prepared by PI.

The direct costs budget cap is **\$70,000 per year for PI salary and \$10,000 per year for all other budget items**. The **maximum duration is two years**. The PI must devote at least **50% FTE** to the project. **Indirect costs are allowed (non-UC only) to a maximum of 8%**. The award is not transferable to another PI.

All career development applications **must identify one of the nine Program priority issues** as the prime focus of the research, training program, or enrichment topic. This is performed on Form 5. Refer to the research topic examples for the different priority issues listed in Section 2. Contact the CBCRP if you need further assistance in this phase of the application.

Evaluation Criteria

Note: There are key differences in the evaluation criteria definitions for the various award types in this Section.

I. New Investigator, Postdoctoral Fellowship, and Mentored Scholar Awards:

These applications are peer reviewed and rated independently for **five separate components**, which collectively determine the scientific merit.

- **Innovativeness:** The extent to which the basic concept and hypotheses are novel approaches to breast cancer research.
- **Impact:** The extent to which the project, if successfully carried out, would make an original and important contribution to the defeat of breast cancer. Note to basic science applicants: If a molecular

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pathway has not been established to be relevant to breast cancer, then the primary point of the study should be to test this relevance.

- **Approach:** The extent to which the conceptual framework, design, methods and analyses are developed, well integrated and appropriate to the aims of the project.
- **Feasibility:** The extent to which the investigators have maximized their chances for success, including the incorporation of the appropriate resources and collaborations.
- **Career Development:** Letters of recommendation/support are required these award types. These along with the Career Plan statement on Form 17 (see below) address this issue.
New Investigator: The potential of the research problem and institutional environment to foster an independent career in breast cancer for the investigator.
Postdoctoral Fellow: The applicant's potential for conducting research in breast cancer, the likelihood that the proposed training will develop this potential, and the mentor's commitment to the candidate.
- **Mentored Scholar:** The potential to develop the PI's skills, professional experience, and qualifications for independent research.

II. Training Program Awards:

Training program applications are peer reviewed and rated independently for **four separate components**, which collectively determine the scientific merit.

- **Innovativeness:** The extent to which the Training Program represents a new way of educating breast cancer scientists. The ability to recruit a trainee pool representative of the diversity in California.
- **Impact:** The extent to which the Training Program would make an original and important contribution to increasing the pool of breast cancer researchers to contribute to the defeat of breast cancer. Will the research proposed and training plan allow the trainees to pursue a career in breast cancer research?
- **Approach:** The extent to which the plan for the Training Program is developed, well integrated and appropriate to the aims of the program. Included is the nature of the proposed training experience, the qualifications of the faculty, and the general pool and selection of trainees.
- **Feasibility:** The likelihood that trainees can be recruited and will pursue research careers in breast cancer. The ability of the training goals to assist in the development of a pool of new breast cancer researchers.

III. Career Enrichment Awards:

Career Enrichment applications are peer reviewed and rated independently for **five separate components**, which collectively determine the scientific merit.

- **Innovativeness:** The extent to which the training will expose the PI to techniques and disciplines for breast cancer research.
- **Impact:** The extent to which the training would make a contribution to increasing the pool of competitive breast cancer researchers.
- **Approach:** The extent to which the training is integrated into the background of the PI, research skills of the mentor, and the PI's stated research goals in breast cancer.
- **Feasibility:** The extent to which the investigators have maximized their chances for success, including the incorporation of the appropriate resources and collaborations.
- **Career Development:** The extent to which the training will foster and add to the PI's research capabilities related to breast cancer.

IV. Dissertation Awards:

Dissertation applications are peer reviewed and rated independently for **five separate components**, which collectively determine the scientific merit.

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- **Innovativeness:** The quality of the research training and environment. The extent to which the applicant will be trained in current research techniques and analytical methods.
- **Impact:** The specificity of the project to an important breast cancer research topic.
- **Approach:** The quality, organization, and presentation of the research plan. Are the hypothesis and specific aims well described and logical?
- **Feasibility:** The extent to which the training and research environment will allow the project to be completed.
- **Career Development:** The mentor's commitment to the candidate. The extent to which the training will enable the PI to become competitive in the next career phase.

The Review Committee will also evaluate the application for **budget and duration**, human/animal **research risks** and institutional approval.

The **Programmatic Review** is conducted by the advisory Breast Cancer Research Council and involves analyzing applications with an acceptable scientific merit score for the **programmatic review criteria as described in Section 4** and submitted by the PI as an **Executive Summary** (see Section 12). Career development applications can be classified as "primary" only if they address one of the six "primary" CBCRP priority issues (see Section 2). Otherwise, all other career development applications are classified as "complementary." For example, a Postdoctoral application in the Pathogenesis priority issue is classified as "complementary", while a Postdoctoral application in Prevention and Risk Reduction is classified as "primary."

Notes: Letters of support/recommendation should be arranged prior to the submission of the application on January 8, 2004. Have your references mail these letters to you and include them unopened in their sealed envelopes with the application at the time of submission. Refer to the instruction page at the end of the Forms section.

In general, the **letters of support will include one (1) principal reference** (i.e., mentor for a postdoc, dissertation, career enrichment, mentored scholar; the unit or department head for a new investigator); and 2-3 additional references for all career development (except training program) applications.

List all of the individuals submitting letters using Form 1D.

Career Enrichment: Letters for out-of-state candidates should detail the expected benefits to the residents of California institution in particular and research in the state in general. The out-of-state applicant should be a resource for knowledge, skills, or experience not found in California.

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SUBMISSION REQUIREMENTS AND REVISED APPLICATIONS

It is the responsibility of the applicant(s) to include the appropriate forms, follow the detailed instructions for preparing the forms, submit a signed original and the correct number of copies, and meet the submission deadline.

General items

- The complete application (original, copies, appendices, and Executive Summaries) must arrive at the CBCRP office by regular mail, express delivery, or by hand delivery. **No fax, e-mail, or Internet submissions will be accepted.**
- All applications must be in **English**.
- Applications and copies must be **typed and legible**. Follow these format requirements, which are consistent with the NIH's 398 form instructions:

#1. All applicant-prepared page sections (i.e., those pages that are not CBCRP application forms) of the grant (e.g., Biographical Sketch, Budget Justification, Research Plan, and any continuation or appendix pages (except publication reprints) must conform to the following four requirements: 1. The height of the letters must not be smaller than 10 point; **Times New Roman or Arial 11- or 12-point are the suggested fonts**. 2. Type density, including characters and spaces, must be no more than 15 characters per inch (cpi). 3. No more than 6 lines of type within a vertical inch; 4. Page margins, in all directions, must be at least ½ inch.

#2. Deviations from the font size specifications and page limitations, especially the page limit for the Research Plan, will be grounds for the CBCRP to reject and return the entire application without peer review.

#3. Do not use photo reduction for preparing either the original application or the photocopies. Prepare all graphs, diagrams, tables, and charts in black ink.

#4. The application must contain only material that reproduces well when photocopied in black and white. Glossy photographs or other materials that cannot be easily photocopied should be submitted in the appendix.

- Applications must be completed on original or duplicated CBCRP **forms from the current Cycle X format**. Forms from previous years or altered forms will not be accepted.
- The **Principal Investigators' name(s)** (last name, first name, middle initial) must appear in the **upper right hand corner** of each page (use last name of all co-PIs for TRC and SPRC Awards).
- Duplicate copies of applications and all appendices should be double-sided.
- **Use the Table of Contents (Form 2) as a checklist** to ensure that a complete application is submitted.
- **Do not use binders or covers** for the application materials. Use only staples or clips to bind each copy. Appendices should be attached to the Forms section by a removable clamp or rubber band.

The complete application submission

Please submit the following:

- **One (1) original, single-sided with original signatures on the cover page and Form 3, and one appendix, if applicable**

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- **Eleven (11) double-sided duplicate copies** of the application and **eleven (11) copies of any appendix items**
- Two (2) single-sided copies of the **Executive Summary** (see below for content)
- **Envelope containing sealed Letters of Support/Recommendation (Postdoctoral Fellowship, New Investigator, Dissertation, Mentored Scholar, and Career Enrichment Awards only)**

Joining Forces Conference award application need to include one single-sided signed original and 20 double-sided copies.

Appendix Guidelines

The Research Plan (Form 12) should be self-contained and understandable without referring to the appendix. The appendix is used for human and vertebrate animal subjects approval documents, any contractual budget, letters of collaboration, and ‘supporting materials’. These items are described in more detail on Form 21. The ‘supporting materials’ could include supplemental tables or figures related to the project background and preliminary data, and publications and pre-prints to support the investigator’s background and capability to conduct the research. **The appendix should be not more than 1-inch thick.**

Each appendix copy should begin with Form 21 to list the contents. Attach the appendix copy to the original application and the 11 application copies with a removable clamp or rubber band.

Do not staple the application forms and appendix copies together!

Executive summary (for the Programmatic Review)

Two **single-sided copies** of an Executive Summary must be submitted with the application. The following Forms are required for the Executive Summary:

<u>Form Number</u>	<u>Form Name</u>
1A or 1B	Cover page, 1B is for TRC and SPRC only.
3 & 4	Lay and Scientific abstracts.
5	Priority Issues and Award Type Responsiveness
6	Statements for the Additional Criteria
8	Budget Summary
16	Distinction from Other Funded Work
17	Career Plan- career development applications, except Training Program.

No executive summary is required for Joining Forces Conference award applications.

Required Signatures

The principal investigator(s) must sign the original copy Form 1A, B, or C (Cover Page) and Form 3 (Lay Abstract). If the application is submitted by an organization, it must be **approved by the applicant organization’s contracts and grants office, or comparable unit, and signed by a designated institutional official on Form 1A, B, or C (Cover Page).** “Proxy” signatures are not accepted.

CSO Coding Instructions for Forms 1A-C

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Enter the CSO codes for your application's research topic in the space(s) provided in the upper right hand corner of Form 1, just below the words "Cover Page." Coding is best done by the individual writing the research plan and abstracts. To identify the best CSO code match, please consider:

- “why” the research is being done, or the total intent of the research;
- “what” the research is investigating, the particular aspects of breast cancer being studied;
- “how” the research is being carried out.

The CSO coding scheme is presented in the Web site: www.cancerportfolio.org/cso.jsp There are seven major CSO categories, and each of these is divided into 4-9 sub-categories. First, familiarize yourself with the major heading under which you think your research belongs. For example, CBCRP's priority issue "Pathogenesis" matched the CSO category of "Biology". Epidemiology studies most likely will be under either "Etiology" or "Prevention." There may not be an exact CSO and CBCRP topic correspondence, but the bullets on the CSO Web site and those under our priority issues listings in Section 2 should allow you to make a rational selection.

Next, you can use either one or two CSO codes to best categorize your application:

- Use a Primary CSO code which best describes the total intent of the application. **Many applications are adequately characterized by one code.**
- The Secondary code should represent a different, but integral part of the research, not a contingency aim, and represent some minimum of the total effort. If you would identify this effort as a separate aim, then code it. Many of our grants under the priority issue of Innovative Treatment Modalities (CSO major category #5) would also receive a secondary code assignment under the CSO “Biology” category (#1), because the project involves some component for advancing basic tumor biology gene or protein mechanism/function.

Here are two examples from CBCRP's grant coding:

- "Understanding Tamoxifen-A Drug for Breast Cancer", studied tamoxifen activity on AP-1 in cell culture and then used genetic and biochemical approaches to understand how tamoxifen stimulates AP-1, and how the estrogen-like effects of tamoxifen on cancer growth might arise. We coded this grant as a 1.1 (Primary Code) & 1.3 (Secondary Code).
- "Pre-clinical Cryosurgery Testing in Breast Cancer Treatment" proposed to establish the use of imaging monitored cryosurgery for treatment of breast cancer. This was satisfactorily coded using the single 5.1 code.

DEADLINE FOR RECEIPT OF APPLICATIONS POLICY STATEMENT

Applications must be received by 6:00 P.M. on the specified dates. Because unforeseen circumstances can occur and because we cannot extend the deadline, **we recommend that you allow at least 48 hours for express delivery.** Applicants who choose to hand deliver the materials to us will not be allowed extra time due to traffic, copying problems, or other issues that could have been avoided by more timely preparation. An application received after the deadline may be acceptable if it carries, or if the applicant can provide upon request, a legible proof-of-mailing date assigned by the carrier and **the proof-of-mailing date is not later than 2 days prior to the deadline date.** Private postage meter marks are not acceptable. Deliver all applications to:

**California Breast Cancer Research Program
University of California, Office of the President
300 Lakeside Drive, 6th Floor
Oakland, CA 94612-3550
(510) 987-9884**

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We are located in the Kaiser Building, three blocks East (towards Lake Merritt) from the 19th Street BART station when traveling on 20th St. If you drive, then short-term parking is available in front of the building off Lakeside Drive and in the adjacent parking garage.

Submission of Additional Materials

No supplemental application materials (e.g., manuscripts or publications) will be accepted after the deadline, unless explicitly requested and approved in advance by the CBCRP.

Revised Application Guidelines

A revised application requests support for research that was **reviewed previously, but not funded**. Applicants who wish to submit a revised application should review the award types available in Cycle X and note changes from previous cycles. Revised applications may be submitted under a different award type, but should be appropriate for that award type.

A revised application must have the same principal investigator as the original application. When possible it should have the **same title as the original application**. However, if the specific aims of the project have changed sufficiently, or if the original title does not fit the qualifications required for Cycle X, a modified title may be chosen.

A revision must include a section of not more than 2 pages immediately preceding the Plan for Research (Form 12). This section is a **summary of the substantial additions, deletions, and changes** that have been made. It must also include responses to criticisms in the previous Review Committee evaluation. This material does not count towards the normal page limit for the Research Plan. We also recommend emphasizing in the Research Plan any relevant work done since the previous application.

Investigators submitting revised applications are advised to carefully review this application packet. There are new elements and guidelines for Cycle X.



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CONDITIONS OF AWARDS

Details concerning the requirements for grant recipients are available in a separate Program publication, the University of California, Office of the President, Special Research Programs *Grant Administration Manual 2003-2004*. This Manual will be updated and re-issued yearly. It is sent to every grant recipient principal investigator, contracts and grants official, and the accounting contact. The Manual can be obtained from the Program's office or viewed on our Web site: www.cbcprp.org/reports/grantManual.php

Policy on Grants Allowed per PI

We limit the number of grants that a PI can receive in any single funding cycle. We have revised our policy in Cycle X to allow a PI to receive more than one grant, but the rules are very specific. A PI can only receive one grant for all non-collaboration award types. In addition, a PI may receive one grant as a co-PI for a collaboration award type (CRC, TRC, or SPRC) or as a PI for a Joining Forces Conference Award (JFCA). If you intend to submit more than one application in Cycle X, we encourage you to discuss this issue with the Program.

Policy on Applications from PIs with Delinquent CBCRP Grant Reports

PIs with current CBCRP grant support will not be eligible to apply for additional funding unless the required scientific and fiscal reports on their existing grants are up-to-date. This means that **Progress/Final Scientific Reports or Fiscal Reports that are more than one month overdue may subject a Cycle X application to possible disqualification** unless the issue is either, (i) addressed by the PI and Institution within one month of notification, or (ii) the PI and Institution have received written permission from the CBCRP to allow an extension of any report deadlines.

General Conditions of Award

The Program encumbers all funds for a grant in the year it is awarded; thus full funding of a multi-year project is assured.

Enabling legislation (AB 2055 and AB 478 of 1993, as amended by AB 3391 of 1994) authorizes the appropriation of public monies to the University of California for the CBCRP. Awardees are expected to account for the expenditure of grant funds and for the performance of work as agreed upon in a timely manner, so that the CBCRP may file reports and answer inquiries from the legislature and the public. They are also expected to adhere to the stated goals of the legislation, which include the systematic dissemination of research results to the public and to the healthcare community and the facilitation of translation of research results into commercial, alternate technological, and other applications. The Institutional Official's and Principal Investigator's **signatures on the cover page of the application signify that the individuals are aware of the conditions for receiving a grant** from the Program.

Grants to conduct research or research career development activities in California may be awarded to qualifying (see below) California individuals or organizations, which may be public or private, for-profit or not-for-profit. Eligible organizational awardees include, but are not limited to: community organizations, publicly or privately owned corporations and other businesses, volunteer health organizations, health maintenance organizations, hospitals, laboratories, research institutions, colleges, and universities. Applicants who have limited experience in scientific research or in scientific grant writing are encouraged to collaborate with established researchers in the

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design of studies and the preparation of applications in order to present the most well designed application possible. The CRC, TRC, and SPRC award mechanisms provide new opportunities for such collaboration.

To ensure the proper management of these public funds (as described above), a prospective grant recipient must satisfy the **following standard requirements** before an award will be made:

- Have adequate organizational, management, and accounting systems to administer the award and assure compliance with award terms and conditions.
- Have adequate financial resources, equipment, facilities, and technical skills to perform the proposed work, or the ability to obtain them.
- Be able to perform the proposed work within the approved time frame, taking into consideration all existing commitments.
- Have a satisfactory record of integrity and business ethics.
- Maintain mechanisms to assure integrity and honesty in the conduct of research, safe conduct of research, and fair practice for all employees and research subjects.
- Certify that none of the key personnel on the grant are barred by the U.S. Public Health Services Office on Research Integrity from performing comparable roles on federally funded grants.

A grant recipient may satisfy modified requirements, if this is determined to be appropriate upon review by the University of California's Office of Research Administration, Office of Risk Management and General Counsel. Individuals who are to be awarded grants may meet these requirements directly or by making arrangements with a research organization that does. These requirements include satisfactory fiscal management, accounting practices, liability insurance, bonding, indemnification of the UC Regents, nondiscrimination in employment, and assurances regarding the treatment of animal or human subjects and research safety and ethics.

Though the research must be conducted primarily in California by California investigators, part of the work may be done outside California if the need to do so is well justified (i.e., it is integral to the achievement of a specific aim and cannot reasonably be performed in California) and the results of such work may be applied to furthering the achievement of the Program's goals and Priority Issues.

Grant awardees must agree to:

- Use award funds only as approved by the CBCRP. The Program must approve changes in the specific aims of a grant.
- Maintain accounts, records and other evidence pertaining to work performed and costs incurred.
- File annual progress reports and a final scientific report.
- File annual fiscal reports and a final fiscal report.
- Participate in CBCRP sponsored activities to disseminate research results as able and as requested.
- Make good faith efforts to ensure the timely translation of research results into commercial applications and report these efforts to the Program.
- Make good faith efforts to communicate with the public about the funded work.
- Attend CBCRP research symposiums, if scheduled.

Following notification by the CBCRP of an offer of funding, the PI and applicant organization must accept and satisfy normal funding requirements in a timely manner. Common pre-funding items include:

- Up-to-date human IRB and animal assurance documents from a federally licensed review board must be on file for each grant.
- Modify the titles and lay abstract, if requested.
- Agree to any changes in specific aims, award budget, or duration as recommended by the Review Committee and Program.
- Resolve conflicts in Other Support and percent FTE.
- Supply any missing Forms or materials from the original application.

- Supply up-to-date documentation for approved indirect rate agreements and any derived calculations.

Award Period and Indirect Costs

The start date for the CBCRP Cycle X awards will be July 1, 2004. Continuation funding for additional project years is released upon receipt of an Annual Progress Report showing research effort/progress, no overlap with Other Support, maintenance of sufficient FTE% by the (PIs), continuing approval of Human and Animal subjects use, submission of publications copies, and reporting any changes in Key Personnel. If funding is delayed or if all funds are not expended in the normal award period, then the investigator(s) may request a no-cost time extension for a maximum of one year in order to complete the project.

Postdoctoral fellows can delay the start of their project for up to 6 months to finish another project or to complete their doctoral training. They must notify the program in writing to activate a delayed start. However, the fiscal year will remain July 1-June 30, and a no-cost extension will be needed to finish a full 2-year project.

The CBCRP encumbers the funds for all approved years of an award from the appropriation in the year the grant is awarded; thus full funding of a multi-year project is assured, dependent only on timely submission of the required reports. Funds will be disbursed annually, contingent on receipt of required progress and fiscal reports. For one-year projects, and for the final budget year of multiyear projects, 20% of the approved budget is withheld (non-UC institutions only) and paid in arrears upon receipt and acceptance by the Program of all required final reports.

Direct Costs

CBCRP award funds may be used only for expenditures necessary to carry out the approved project, as specified in the approved budget. Significant changes in proposed expenditures must be approved in advance by a CBCRP Research Administrator. Please follow the guidelines in the SRP Grant Administration Manual.

Allowable direct cost expenditures may include administrative costs only if the following two conditions are satisfied: a) the services, functions, or activities are directly necessary for the conduct of the grant research and (b) these administrative costs have not been included in the calculation of the recipient institutions indirect cost rate agreement approved by the Federal government. In other words, the Program policy does not prohibit administrative costs, but it is careful to ensure that costs meet both conditions (a) and (b).

Indirect (F&A) Costs

Individuals without an institutional affiliation will not be eligible for indirect costs as grant recipients or subcontractors.

Non-UC Institutions:

For organizations other than University of California Campuses the CBCRP will pay indirect costs (overhead) based on the approved direct cost budget. Full indirect costs on SPRC, CRC, TRC, IDEA/STEP, and RFA Awards are computed on a "direct cost basis" at the recipient organization's appropriate federally approved indirect cost recovery ("indirect" or F&A) rate. If the institution has an approved rate from the Department of Health and Human Services, it must be used. In the absence of a federally approved rate, an alternative documented indirect rate for the institution may be used. In the absence of any documented indirect rate, one will be negotiated by the University and the recipient organization.

Indirect costs on New Investigator, Mentored Scholar, Training Program, and Career Enrichment Awards will be capped at a rate of 8% of the total direct costs (excluding equipment).

No indirect costs will be allowed for the Postdoctoral Fellowship, Dissertation, and Joining Forces Conference Awards.

Provisional or pending increases in indirect rates will be included in awards only if they are documented prior to execution of the award agreement and disbursement of year #1 funding. The maximum indirect costs which CBCRP pays is the lesser of (a) the federally approved rate current for the budget year or (b) the rate provided for in the final approved budget.

Under no circumstances will funded projects be supplemented to reflect an unanticipated increase in the indirect rate; nor can funds originally awarded as direct costs be shifted to cover increases in the indirect rate. If the indirect rate decreases below that provided for in the approved budget, the CBCRP will pay overhead at the new lower rate starting on the date of change, and will decrease the award to the institution by the difference between the originally approved amount and the amount to be accrued at the new rate.

Both to initiate funding and for continuation funding of existing awards, **the Program requires a copy of the institution's current indirect cost agreement annually.**

University of California Campuses:

Campuses of the University of California will not be paid indirect costs as grant recipients or as subcontractors. Research institutes and foundations that are affiliated with the University of California, but which are legally separate entities (e.g., National Laboratories), may be paid indirect costs.

In accord with University of California policy, investigators who are University employees and who receive any part of their salary through the University must submit grant proposals through their campus contracts and grants office ("Policy on the Requirement to Submit Proposals and to Receive Awards for Grants and Contracts through the University," Office of the President, December 15, 1994). Exceptions must be approved by the UC campus where the investigator is employed.

Policy Regarding Scientific Misconduct

The University of California manages the California CBCRP, Tobacco-Related Disease Research Program (TRDRP), and the Universitywide AIDS Research Program (UARP) within its Special Research Programs in general accord with the policies and procedures employed by the National Institutes of Health (NIH), including those that apply to scientific misconduct. The Department of Health and Human Services' (HHS) Office of Research Integrity is responsible for implementing HHS regulations regarding scientific misconduct in research conducted with NIH and other support from the US Public Health Service.

The administrative actions imposed by HHS include the following: correction of the scientific literature; special plan of supervision to ensure integrity of the scientific research; certification of the accuracy of the scientific data; certification of the accuracy of sources and contributions for scientific ideas and writings; prohibition against service on PHS advisory committees or as a consultant; and, debarment from receipt of Federal funds. These actions are for a specified duration, depending on the nature and seriousness of the misconduct.

Applicants for or recipients of grants from the Special Research Programs (SRP) must promptly inform the University of an administrative action for scientific misconduct that is imposed by HHS by providing a copy of the final notice of the administrative action (i.e., after the disposition of any appeal), either at the time of application or within 30 days of the imposition of the administrative action. In general, the University will apply the same administrative action. For example, if HHS has debarred an investigator from applying for or receiving NIH awards for a specified period of time, that investigator would also be excluded from applying for or receiving awards from any of the SRP programs. To take another example, if an investigator has entered into a voluntary agreement with

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HHS for special oversight and supervision of the investigator's grant applications, research, and publications, that agreement would apply to that investigator's grant applications to, or awards from, the SRP.


Grant applicants or recipients may request that HHS administrative actions be waived or modified with respect to a grant application or award from the SRP. In such case, the applicant must present a justification for the request.

Fraud or Misuse of CBCRP Funds

Report fraud or misuse of CBCRP funds to either the CBCRP Director, Dr. Marion Kavanaugh-Lynch, at (510) 987-9878, or to the Office of the University Auditor, at (510) 987-0478 or www.ucop.edu/audit/

For-Profit Reimbursement of Awards

It is the goal of the CBCRP to discover new information, which can lead to the prevention, control and eradication of breast cancer. Hence, it is anticipated that some CBCRP grant recipients will conduct clinical trials and ultimately develop profitable products or services from work funded in part or in whole by the CBCRP. The Program strongly encourages, but does not require that, such individuals or institutions/companies consider:

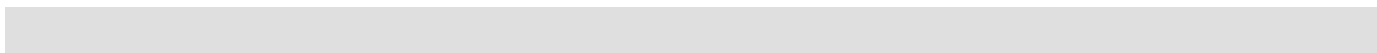
- **Donating to the CBCRP** to further advances in breast cancer research
 - **Making experimental therapies available on a compassionate access** protocol during clinical trials
 - Providing **assistance to low-income women** in gaining access to therapy
- 

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APPEALS

An appeal regarding the funding decision of a grant application may be made *only* on the basis of an alleged error in, or deviation from, a stated procedure (e.g., undeclared reviewer conflict of interest or mishandling of an application). Details concerning the appeals procedure may be obtained from the appropriate Research Administrator (with whom the applicant is encouraged to discuss his/her concerns), the Director, or by contacting us through the CBCRP Web site: www.cbcprp.org/. The **period open for the appeal process is within 90 days of receipt of the application evaluation** from the Program office.

Applicants who disagree with the scientific review evaluation are invited to submit revised applications in a subsequent grant cycle with a detailed response to the review.



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APPLICATION FORM OVERVIEW

Application forms can be downloaded after October 6th from our web site: www.cbcpr.org/ under the link "Apply and Reports." In addition, we can e-mail these forms to you, if you send a request to cbcpr@ucop.edu.

The forms themselves do not contain detailed instructions. All the instructions are provided separately, and you are responsible for reading and following these instructions. Contact us if you have any questions on form preparation, which forms are needed for a particular award type, and the application deadlines and submission requirements.

Remember: we do not allow submission of supplemental materials, unless requested by us, after the deadline dates.

Below is the list of CBCRP application forms for Cycle X:

Form Number	Form Name	Award Type
1A	Cover Page	All, except TRC, SPRC and Conference Awards
1B	TRC/SPRC Cover Page	TRC/SPRC Pilot and Full Research Awards
1C	Conference Award Cover Page	Joining Forces Conference Award
1D	Signature List	Career Development, except Training Program
2	Table of Contents	All, except Conference Awards
3	Lay Abstract	All
4	Scientific Abstract	All, except Conference Awards
5	Responsiveness	All
6	Additional Criteria	All, except Conference Awards
7A, B, C	Annual Budgets	All, except IDEA
8	Budget Summary	All, except Conference Awards
9	Budget Justification	All
10A	Key Personnel	All, except TRC/ SPRC
10B	TRC/SPRC- Key Personnel	TRC/SPRC Pilot and Full Research Awards
11*	Biographical Sketches	All
12	Research Plan	All (instructions are on a separate page)
13	Facilities and Resources	All, except IDEA
14	Other Support, non-research	All, except IDEA and Conference Awards
15*	“ “ , research	All, except IDEA and Conference Awards
16	Distinction from Other Funding	All, except Conference Awards
17	Career Plan	Career Development, except Training Program
18	Human Subjects	All, but only if Human Subjects are used
19	Vertebrate Animals	All, but only if Vertebrate Animals are used
20	Organizational Profile	All, except IDEA (only for <u>non-UC</u> institutions)
21	Appendix Cover Sheet	All, but only if using an appendix
-	Letter Attachment	Career Development, except Training Program

* We will allow submission of the comparable NIH 398 Forms for Biosketch and Other Support as accessed from the NIH Website: <http://grants1.nih.gov/grants/funding/phs398/phs398.html#forms>

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EXAMPLES OF PROGRAMMATIC REVIEW FORMS

We have included examples from two funded applications. The CBCRP thanks Dr. Paul Henderson at Lawrence Livermore National Laboratory and Dr. Peter Vogt at the Scripps Research Institute for allowing us to use this material.

Example #1/New Investigator

Project Title: *Role of Oxidative DNA Damage in Breast Tumor Progression*

FORM 3 LAY ABSTRACT

Non-technical introduction to the research topics:

An early theory of carcinogenesis proposes that DNA is damaged by environmental factors, which lead to changes in the DNA code. These changes are called mutations. Once enough mutations accumulate, cells can no longer function properly, and cancer arises. The facts that smoking causes lung cancer, and that sunlight exposure causes skin cancer support this theory. However, such a direct environmental link is not evident for breast cancer in humans. A more recent theory suggests that the metabolism of oxygen produces free radicals that cause carcinogenic DNA damage. In order to validate the latter theory, it is necessary to measure the products of free radical damage in cells. Damage to cells caused by reactive oxygen is called oxidation. In some breast cancers, increased levels of oxidative DNA damage have been associated with tumor progression. However, the most commonly used marker of DNA oxidation, called 8-oxoG, is known to be chemically unstable, and is difficult to measure accurately. Importantly, 8-oxoG is itself easily oxidized to form several secondary oxidation products. I spent most of the last three years determining that these secondary products are chemically stable, and that they are highly mutagenic. However, the products have not been studied in breast cancer, since they are difficult to detect with current technology. I propose to develop new technology that will allow detection of the products in rat and human breast cancer cells. Such an assay can be used as a foundation for making diagnostics for use in future human clinical and epidemiological studies. An additional benefit of these biomarkers will be their eventual application to chemoprevention in animals and humans.

The question(s) or central hypotheses of the research in non-technical terms:

Do certain types of oxidative DNA damage exist in breast cancer cells that are not in normal tissues? Can the oxidation products of 8-oxodG be developed as breast cancer biomarkers?

The general methodology in non-technical terms:

We will chemically synthesize a radioactively labeled DNA building block. The radioactive label is easy to detect, and will allow very low concentrations of DNA damage to be assayed. The building block will be fed to breast cancer cells, and which will incorporate it into new DNA during tumor growth. We expect that the radioactive building block will be damaged by free radicals inside the cancer cell, and that the damage products will contribute to the progression of the cancer. After isolation of DNA from the cells, the radioactive label will be used to determine how much of the building block has been incorporated into the cell, and to what extent the DNA of the cell is damaged. The technology will be developed using human breast cancer cells grown on a dish, which are easy to handle. Then, as a model of human disease, breast cancer-prone rats will be fed the building block. At different times during breast cancer development in the rats, their breast tissue will be isolated and tested for oxidized DNA damage.

Innovative elements of the project in non-technical terms:

The proposed stable radioactively-labeled biomarkers can be detected at remarkably low levels, which will allow the study of the typical real life concentrations of DNA damage. Previously, a few other types of oxidative DNA damage have been intensely studied due to ease of detection rather than how mutagenic they are. The identity and mutagenic potential of the proposed markers were only recently discovered, which is why we could not have previously addressed this problem. Lawrence Livermore National Laboratory is a world leader in biological applications of radiolabel detection, which is the most sensitive method currently capable of detecting the types of DNA damage outlined in this proposal. Once developed, the new assay could later be combined with environmental studies to determine if known carcinogens affect the load of oxidative damage in breast tissue, to correlate geographic or racial differences to biomarker levels, and to detect variations in the DNA repair capacity.

FORM 4 SCIENTIFIC ABSTRACT

Background:

It has been postulated that DNA base damage causes mutations that subsequently can be carcinogenic. Of primary importance are base lesions-formed by reactive oxygen species. One of the most common oxidized base lesions is 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), a mildly premutagenic lesion that results in G to T transversions. Organisms from bacteria to humans have developed efficient mechanisms for repairing 8-oxoG, primarily through base excision repair. Even though 8-oxoG is well repaired, spontaneous transversion mutations have been observed in proto-oncogenes and the tumor suppressor gene, p53, a commonly mutated gene in various forms of cancer, including breast malignancies. Importantly, 8-oxodG is more readily oxidized than normal DNA bases, and can form stable secondary lesions that are refractory to DNA repair. These observations indicate that lesions other than 8-oxoG are responsible for mutations that lead to carcinogenesis.

Hypothesis:

Our overall hypothesis is that highly mutagenic DNA oxidation products are formed from 8-oxodG, a known DNA damage product in breast cells, and that these products play a role in tumor initiation and progression towards malignancy. This molecular pathway has not been established in breast cancer, since the lesions of interest are difficult to detect by standard methodologies. An assumption of this hypothesis is that further oxidation of 8oxoG occurs in vivo. However, all of the stable secondary products of 8-oxoG oxidation have been isolated from in vitro studies, and were demonstrated to be mutagenic in *E. coli*. Because 8-oxodG is readily repaired and is subject to degradation during workup, it is a poor cancer biomarker. We shall develop a highly sensitive and specific assay to determine if a link exists between oxidized 8-oxodG lesions and breast carcinogenesis.

Objectives/Aims:

Specific Aim 1. Synthesis of a ^{14}C -Labeled 8-OxoG to Serve as a Probe for Stable Guanine Oxidation Product Formation in vivo. The nucleoside 8-oxodG will be synthesized with a ^{14}C -label from commercially available starting materials. The nucleoside will be a new compound in the sense that a ^{14}C -label has never been incorporated into the molecule. The probe will serve as a reporter for 8-oxodG oxidation in cancer cells.

Specific Aim 2. Assay Development Using MCF-7 Human Breast Cancer Cells. Cells will be grown in the presence of the radiolabeled 8-oxodG nucleoside. Upon incorporation into the cellular genome, the 8-oxoG will be a substrate for either DNA repair or oxidation to stable secondary lesions. DNA will be isolated and the lesions separated by HPLC and quantified with accelerator mass spectrometry, which is sensitive to ^{14}C . The use of cultured cells will allow for determination of 8-oxodG oxidation product formation in vivo.

Specific Aim 3. Determination of Adduct Load in Rat Breast Cancer. Breast cancer will be induced in Sprague-Dawley rats by a dose of a carcinogen. The induced rats will be fed radiolabeled 8-oxodG, and sacrificed over the course of 12 weeks. Breast tissue and tumors will be assayed for oxidative DNA damage using the assay from Specific Aim 2. The results will allow better understanding of breast cancer pathogenesis.

Methods:

Synthesis: Standard synthetic organic chemistry methodology will be applied to making the radiolabeled 8oxodG. Assay Development: Cell culture methods will be used to grow and maintain MCF-7 cells. Cell lysis and DNA isolation will be performed using optimal methods for handling ^{14}C -containing material. Nuclease and phosphatase

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digestion will liberate lesion-containing nucleosides. Lesion separation will be performed by HPLC using co-injection with known amounts of synthetic standards. Accelerator mass spectrometry will allow determination of the ^{14}C concentration in each sample.

Rat Models: Carcinogen-induced Sprague-Dawley rats will be fed with radiolabeled 8-oxodG and sacrificed over a time course of twelve weeks. Initially, the dosing will be optimized for maximal 8-oxodG incorporation into DNA. Breast ductal tissue and tumors will be isolated and assayed for DNA lesion content.

Impact on breast cancer:

In order to use oxidative DNA adducts as markers of tumor progression extremely sensitive and specific analytical methods must be developed. The methodology proposed will provide a general metric that can be applied to breast cancer pathogenesis by measuring quantifiable molecular signatures rather than with histology, which requires a significant amount of tissue. The technology can also be applied to determining the relationship between risk and exposure to environmental chemicals. Since there are many unknown chemicals in the environment, and individuals respond to toxic stresses differently, detection of a standard set of oxidation-related markers that are present to some degree in all individuals will be useful as a metric that can be applied.

FORM 5**1. Explain the application's responsiveness to the Priority Issue.**

The proposed research aims to understand the underlying molecular signatures of breast cancer, particularly with regard to identifying new biomarkers that will indicate the causative events in the disease, or at least an early signal that such events have occurred. We propose to detect and quantify new DNA-based biomarkers that will be correlated with stage, progression and prognosis of breast cancer in a human breast in vitro in cancer cell line and in vivo in a breast cancer-prone mouse model. Once the assay has been developed, we expect that clear changes will be observed between normal tissue, adenoma, in situ and invasive carcinoma. However, it will be interesting to determine how early in the tumor progression can significant differences in biomarker levels be detected. Because of uncertainty in the limit of biomarker detection, we believe that Pathogenesis priority issue is most appropriate, but that there is significant potential overlap with the Etiology priority issue.

2. Explain the application's responsiveness to the Award Type.

The Principle Investigator is a new appointee to the Biology and Biotechnology Research Program at the UC Lawrence Livermore National Laboratory (started in November, 2002). I am a new PI, initiating the project with preliminary data and materials, and the total project duration will be three years. These elements justify a New Investigator Award.

FORM 6 ADDITIONAL CRITERIA**Multidisciplinary Approach:** (incorporation of researchers and methods from several fields)

One of my collaborators, Professor Natalya Tretyakova (U. Minnesota Cancer Center), has already detected one of the proposed DNA damage products in rat liver cells (personal communication), which is the first time any of the proposed products has been detected in a cell. Professor Tretyakova is an expert in analytical methodology related to the detection of DNA damage products. She will provide a sample of the standard that she used in her recent experiments. Another collaborator, Professor Cynthia Burrows (U. Utah), is a chemist who specializes in the synthesis and characterization of oxidized DNA base derivatives. She will provide two of the standards needed for the project. Importantly, Professor Burrows will also provide expertise in synthesis and purification of the standards that I will make. A third collaborator, Professor Steven Tannenbaum (MIT), will provide some standards and purification advice, but is also a mass spectrometry expert. He will give technical advice should I have problems separating the expected DNA damage products from the mix of cellular components that will derive from the cell-based assays. All but two of the needed standards have already been synthesized.

My graduate studies at Georgia Tech focused on applying organic synthetic chemistry to in vitro DNA modification. As a postdoctoral fellow at MIT I learned biological engineering by incorporating oxidative DNA

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damage into viral vectors that were transfected into bacterial and mammalian cells for mutagenesis studies. The damaged DNA was characterized by state-of-the-art mass spectrometry and nuclear magnetic resonance spectrometry techniques, and the effect of the damage on cells was determined by developing novel molecular biology methods. The application of synthetic and analytical chemistry to cell biology will be a constant theme throughout the project. I have also shared lab space and group meetings with several breast and prostate cancer researchers (funded by the Komen Foundation, CapCure, the American Cancer Society, and the NIH/NCI), who were using human cell lines and rodent cancer models to test rationally designed anticancer drugs. I will use all of these multidisciplinary skills and experiences for the proposed work.

Translational Potential: (potential to be used for direct and immediate impact on breast cancer)

A significant advantage of the proposed assay is that it may predict susceptibility to cancer, much like a cholesterol test does for vascular disease. One can imagine a scenario in which a patient donates a few breast cells by nipple aspiration. The cells can be tested for oxidative DNA damage and a relative number assigned which correlates to the risk of getting breast cancer. If a patient has a high load of oxidative DNA damage in breast tissue, then antioxidants and increased surveillance may be prescribed. We do not propose to develop the technology to such a high level in this round of funding, but such a potential application is a motivating factor for the basic research we are proposing.

Focus on Underserved Populations: (potential to reduce racial/ethnic differences in incidence and treatment)

The technology will provide a metric based on established chemistry that should occur in all individuals regardless of race or ethnicity. However, the extent to which a given biomarker occurs may vary dramatically depending on the genetic predisposition of an individual or group of individuals towards the repair of oxidative DNA damage. If the biomarker can be detected early enough, then the gap in incidence between racial and ethnic groups (or at least the gap in the rate of dying from breast cancer) can be reduced or eliminated. Another factor in certain populations, although indirectly related to ethnic differences, is geographic location and exposure to environmental chemicals. Ethnic and racial groups that are disproportionately exposed to chemicals such as agricultural pesticides or industrial emissions may be served by the detection of oxidation-based biomarkers.

Advocacy Involvement in the Research: (advocacy participation or how the project addresses human needs and concerns related to breast cancer)

An effective assay for breast cancer biomarkers that relies on molecular signature would prevent unnecessary emotional strain that may be caused, for example, by a borderline diagnosis from a mammogram in an otherwise healthy patient. Likewise for a patient diagnosed with breast cancer, a concrete number that can be used to track the efficacy of a breast cancer treatment may cause a positive therapeutic psychological benefit.

FORM 16 DISTINCTION FROM OTHER FUNDING

The PI is not funded by any other grant to study oxidative DNA damage. Therefore, the work described is distinct from all other funding. The PI's other funding includes grants to investigate food mutagens such as the dietary carcinogen PhIP and to establish assays of PhIP exposure, which requires the development of technology that will enable proposals to be made related to DNA oxidation and carcinogenesis once the goals of the current proposal are met. The PI is also funded to develop Accelerator Mass Spectrometry as a routine tool for biomedical research. Therefore, the funded work is complementary to the research proposed in this application.

FORM 17 CAREER PLAN

During my PhD and post-doctoral training, I have gained extensive experience in development of assays to measure oxidative DNA damage in vitro and in vivo. I have demonstrated success in applying my skills as an organic chemist to a variety of basic biological problems that are relevant to carcinogenesis. In graduate school, I proposed and supported experimentally a mechanism by which electrons travel through DNA, which is likely the cause of sequence-specific mutations such as those frequently observed in protooncogenes. As a postdoctoral fellow funded by the NCI, I determined specific types of DNA oxidation damage that are potentially mutagenic. I now wish to move

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that technology towards applications that will help breast cancer patients. I believe the studies in which I participated on DNA damage were basic, but only slightly ahead of their time. I came to Lawrence Livermore National Laboratory in part because of a technique they developed for biological systems called Accelerator Mass Spectrometry (AMS). AMS is a technique for measuring attomole (10^{-18} mole) levels of isotope labeled chemicals in biological samples. The technology has the sensitivity to interrogate processes at the single-cell level, which is the key to understanding cancer initiation and progression with respect to DNA damage and mutagenesis. AMS will provide the tools by which technologies will be developed that can directly help patients in areas such as chemoprevention and early detection. AMS is an invaluable tool in understanding the fate and distribution of chemicals in vivo, as well as in the development of sensitive biomarker assays. Therefore, one of my aims over the next several years is to characterize the oxidation products adducts formed in the DNA of breast cancer cells and to then develop an assay for measuring them in humans. I also plan to continue pursue research to establish chemopreventive strategies for breast cancer in cells and animal model systems, which could then be translated to a clinical or preventive setting.

Example #2/ STEP Award

Project Title: *Inhibitors of Myc: Novel Drugs for Breast Cancer*

FORM 3 LAY ABSTRACT**Non-technical introduction to the research topics:**

Breast cancer cells are characterized by changes in the levels and activities of growth regulatory proteins. One of these proteins is Myc which shows enhanced function in about 50 percent of breast cancers. High Myc activity is correlated with the more aggressive forms of breast cancer that invade neighboring tissues and grow very rapidly. In animals, elevated Myc induces various forms of cancer by deregulating specific genes. In human breast cancer, Myc has a similar deregulating effect, affecting the cellular response to hormones and altering the activity of proteins that control the cycle of cellular replication and division. The accumulated evidence on Myc activity in breast cancer indicates that Myc plays a major role both in the causation of the tumor and in the progression to an aggressive cancer. Myc is therefore an important target for therapy. Drugs that control the activity of Myc could be of great value in breast cancer therapy and in prevention.

The question(s) or central hypotheses of the research in non-technical terms:

Myc is an important genetic regulator; it changes the activity of numerous subordinate genes. However, Myc can perform this function only with the aid of the second protein, termed Max. Myc must bind to Max, and it is this pair of two proteins that can activate other genes. Without binding to Max, Myc is inactive. The central hypothesis of this proposal is that small molecules can be identified that interfere with Myc-Max binding and thus control Myc activity. These small molecules can be developed into drugs that could have a major impact on breast cancer, providing the physician with the means to control a cancer-specific protein that at present remains unchecked.

The general methodology in non-technical terms:

We have produced and purified modified versions of the Myc and Max proteins. When these proteins bind to each other, they generate a light signal that can be easily detected. If the binding is inhibited, the light signal disappears. This test allows us to screen large numbers of newly synthesized chemical compounds containing tens of thousands of individual drug-like compounds for inhibitors of Myc-Max binding. For these screens, we have available a robot that can perform several hundred of these tests simultaneously. A large collection of novel chemical compounds for these tests will be produced at The Scripps Research Institute by the laboratories of Drs. Dale Boger and Kim Janda. Both researchers are leaders in the new technology that permits simultaneous synthesis of large numbers of novel compounds.

Innovative elements of the project in non-technical terms:

Although the Myc protein is widely recognized as a highly important contributor to the causation and progression of breast cancer, there have been no serious attempts to develop small molecule drugs that affect Myc activity. There is a reason: inhibiting Myc means one must interfere with Myc binding to other proteins. Conventional

wisdom says that such protein-protein interactions are too powerful to be controlled by small molecules. All major pharmaceutical companies have therefore stayed away from this problem, considering it too risky. Yet over the past two years, we have been successful in isolating small molecule inhibitors of Myc-Max binding, providing proof of principle that small molecules can indeed affect protein-protein interactions. Some of these small molecules also inhibit tumor formation induced by Myc. Now we plan to develop these discoveries into anti-Myc drugs. We believe that these novel drugs, aimed at a neglected but important target, could be of significant benefit to breast cancer patients.

FORM 4 SCIENTIFIC ABSTRACT

Background:

Myc is a transcriptional regulator with strong oncogenic potential. It was first discovered as the key oncogene of a retrovirus, but is a cellular gene important for the control of cellular growth and survival. In roughly half of the breast cancers Myc is found elevated at the time of diagnosis, reflecting gene amplification or enhanced expression. Increased Myc activity is associated with high histologic grade, invasiveness and a raised proliferation index of the tumor. Although Myc clearly plays a major role in breast cancer, there exist no small molecule drugs that control Myc activity. Since Myc functions only when it dimerizes with its obligatory partner, Max, it is possible to regulate Myc activity by controlling their dimerization. We have been successful in isolating small molecules that interfere with Myc-Max dimerization. These inhibitors also prevent binding of Myc to DNA and Myc-dependent activation of reporter genes. Several of these molecules also prevent Myc-induced oncogenic transformation in cell culture. We plan to develop these initial discoveries into drugs that will be of benefit in breast cancer.

Hypothesis:

The basic hypothesis of this proposal is that small molecules can affect protein-protein interactions. Building on initial successes in the isolation of Myc inhibitors, we postulate that effective drugs can be developed that control Myc activity based on interference with protein-protein interactions. We further postulate that the principle of controlling protein-protein interactions with small molecules can be extended to other members of the Myc family and to other transcription factors, allowing the generation of new classes of anti-cancer drugs.

Objectives/Aims:

The following are the aims of this proposal:

(1) To isolate highly effective small molecule inhibitors of Myc. We will first develop our initial discoveries of inhibitors of Myc-Max dimerization by generating and testing analog chemical libraries based on information from our lead compounds. We will also screen a novel chemical library containing compounds that are specifically targeted at protein interaction surfaces. Complementing the search for inhibitors of dimerization, we will screen combinatorial chemical libraries for stabilizers of the Max homodimer. Such stabilizers would have an inhibitory effect on Myc.

(2) To test the inhibitors isolated in aim (1) for therapeutically significant effects on breast cancer cells. These will include determination of cell growth and differentiation, abolishing the Myc-induced resistance of breast cancer cells to anti-estrogens and the Myc-dependent regulation of cyclin E-Cdk2. We will also examine expression of endogenous and exogenous Myc target genes.

Methods:

We have constructed fusion proteins of the Myc and the Max basic helix-loop-helix and leucine zipper regions (the DNA binding and dimerization domains) linked to yellow fluorescent and cyan fluorescent protein, respectively. These constructs are expressed in bacteria and purified. They dimerize in vitro, generating fluorescence resonance energy transfer (FRET), a readily detectable signal. This FRET assay is used in the robot-driven high throughput screen of combinatorial chemical libraries for the identification of Myc dimerization inhibitors. Hits are confirmed by electrophoretic mobility shift assay and by reporter assays for Myc-dependent transcription. The structure of the hits and of closely related inactive compounds guides the design of analog libraries that are then tested in a reiterative process, aiming at the isolation of even more effective Myc inhibitors. Highly effective inhibitors will be

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tested in breast cancer cell lines for their effect on (1) anchorage-dependent and independent growth, (2) resistance to antiestrogens and to other drugs used in the treatment of breast cancer, and (3) levels of cyclinE-cdc2 and p21.

Impact on breast cancer:

We are attempting to develop an entirely new class of therapeutic compounds: drugs that will control protein-protein interactions. Our primary targets are Myc and Max, two proteins that play important roles in breast cancer. These new drugs would complement currently available therapeutic modalities for breast cancer.

FORM 5**1. Explain the application's responsiveness to the Priority Issue.**

This application is tied mainly to CBCRP's Innovative Treatments priority issue. The principal aim of the proposal is to develop inhibitors of Myc-Max dimerization, identified in preliminary studies, into a novel class of anti-cancer drugs that will be beneficial in breast cancer. However, the proposed studies are also relevant to the CBCRP priority issue of Prevention and Risk Reduction. For instance, post-menopausal hormone replacement therapy (HRT) is associated with a significant increase in the risk of breast cancer. Estrogen, which is a component of HRT, enhances the expression of the Myc protein. Controlling Myc activity could eliminate the increased risk of breast cancer associated with HRT. Control of Myc activity may also effect risk reduction for other patient categories that show increased risk for breast cancer.

2. Explain the application's responsiveness to the Award Type.

The STEP Award type was chosen for this application for the following reasons:

The principal aim to develop a novel class of anti-breast cancer drugs constitutes admittedly a high-risk project. Our preliminary work suggests, however, that the project may be successful, and the pay-off generated by anti-Myc drugs would clearly be high. The proposal is hypothesis driven, the basic idea being that small molecules can affect protein-protein interactions. Small molecules could either bind to critical protein residues or induce a conformational change that alters the binding surfaces. Our initial results offer proof of principle for an effect of small molecules on protein dimerization. The work challenges the existing paradigm that states protein-protein interactions cannot be affected by small molecules because the interacting surfaces are too large. Pharmaceutical companies, after some unsuccessful attempts to influence protein-protein interaction with small molecules, have stayed away from this area.

The proposal involves the interaction of chemists and biologists. The combinatorial libraries that will be used are novel and not available elsewhere. The technique of using fluorescence resonance energy transfer in high-throughput tests is not widely applied in breast cancer research.

There is abundant evidence in the scientific literature for an important role of Myc in breast cancer, justifying the choice of the STEP award type for this application.

In our preliminary studies we have shown a growth-inhibitory effect of one of our lead compounds on MCF-7 cells. This compound does not affect the growth of normal human cells. In the active portfolio of the CBCRP no projects were identified that target Myc for the development of novel drugs. Conceptually closest to the current proposal is a year 2000 award for a postdoctoral fellowship to Thomas A. Robertson (University of California, San Francisco). The grant is entitled "A New Class of Drugs to Treat Breast Cancer". The aim of this research is to isolate inhibitors of the interaction between the estrogen receptor and its co-activator. The underlying hypothesis is similar to the one of the current proposal: small organic molecules should affect protein-protein interactions. The Robertson proposal also places protein-protein interactions in the center of new drug design, and it is a good example of the fact that there exist very many protein-protein interactions that can be considered promising drug targets. Besides this similarity of the basic idea to select a protein-protein interaction for drug development, there is no overlap between the current proposal and the project funded for Thomas A. Robertson. The CBCRP grant portfolio contains a few projects that combine the approaches of modern synthetic chemistry with targets identified

by molecular biology. An example is the 2002 IDEA to Vito Quaranta of the Scripps Research Institute. He will collaborate with chemists at the Scripps Institute using click chemistry to develop novel inhibitors of MMPs.

FORM 6 ADDITIONAL CRITERIA

Multidisciplinary Approach: (incorporation of researchers and methods from several fields)

This proposal is based on collaborations between biologists and chemists. There will be continuous interaction between the two disciplines; the chemists will not merely supply combinatorial chemical libraries but will design analog libraries based on information obtained from biological tests. This is a reiterative process; it involves regular joint meetings that occur at bi-weekly intervals. Previous experience has shown that this constant “give and take” between chemists and biologists is essential for optimizing leads obtained in biological testing. The Scripps Research Institute is one of very few academic institutions that provides a physical proximity between chemists and biologists and that has a record of productive collaboration between these two disciplines.

Translational Potential: (potential to be used for direct and immediate impact on breast cancer)

Inhibitors of the oncogenic activities of Myc have obvious potential as drug candidates. In this project we plan to identify potent inhibitors and carry out cellular tests that will mark compounds showing the most promising activities for breast cancer. The next step will be animal model systems for which we expect to be ready after completing the current two-year STEP proposal. We plan to do pharmacological and toxicological studies at the same time as the animal studies. Clinical testing will most likely require the resources of a pharmaceutical company; the Scripps Cancer Center will also be prominently involved in this phase of the work. This is to say that it is our goal to translate basic science studies into the creation of valuable anti-cancer drugs.

Focus On Underserved Populations: (potential to reduce racial/ethnic differences in incidence and treatment)

There are great differences in the extent and quality of medical insurance coverage in different segments of the U.S. population. The costs of cancer therapies are high, limiting available options for many patients. The small molecule Myc inhibitors we have identified in preliminary work are relatively inexpensive to produce and, once developed into drugs, they should represent one of the more affordable therapies available.

Advocacy Involvement in the Research: (advocacy participation or how the project addresses human needs and concerns related to breast cancer)

Inhibitors of Myc could fill a conspicuous gap in our therapeutic armament against breast cancer. For breast cancer patients and their families and for women at high risks of developing breast cancer these novel drugs would be a welcome and encouraging addition to presently available options in therapy. Advocates welcome new approaches for chemoprevention, and the development of Myc inhibitors could lead in this direction.

FORM 16 DISTINCTION FROM OTHER FUNDING

My laboratory has traditionally focused on retroviruses and on oncogenes. Our earlier work contributed decisively to discovery of the first oncogene, src. During the same period, a collaboration with molecular biologists at the University of California in Berkeley on the genome of two retroviruses led to the discovery of the Myc oncogene. More recent highlights have been the discovery of the Jun oncogene and its identification as a component of the AP-1 transcription factor complex and the discovery of the p3k oncogene, a homolog of PI 3-kinase. Again, these were studies with oncogenic retroviruses. The current research in my laboratory continues on the mechanisms of action of oncogenic transcription factors (notably Jun, as well as members of the winged helix family, e.g., brain factor 1 and PAX3-FKHR). Work on P3k and its downstream effector, Akt, has lead us to the TOR kinase and to the control points for protein synthesis and its role in the transformation of normal cells into cancer cells.

My laboratory at The Scripps Research Institute is located in the Arnold and Mabel Beckman Center for Chemical Sciences. My scientific neighbors in all directions are chemists, so it was only natural to start collaborations with chemist colleagues. Five years ago, we (3 chemists and 2 biologists) responded to an RFA of the National Cancer Institute and formalized some of these collaborations in a Program Project proposal that joins modern combinatorial

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chemistry and cancer biology in an effort to identify novel tumor targets and develop drugs for these targets. This program project was funded in 1997. With support of this grant we have identified several lead compounds. The chemist-biologist interactions have proven extremely stimulating and fruitful. I have therefore made a firm commitment to devote at least half of my laboratory and of my effort to translational research. The molecular genetics of cancer has provided us with an abundance of promising targets. Combinatorial chemistry has given us powerful tools to go after these targets. Myc is one of the cancer targets. It is particularly relevant in breast cancer where it acts as one of the driving forces that correlate with and probably determine rapid growth and invasiveness of the tumor. We have had initial success in the isolation of Myc inhibitors and want to develop these leads into drugs that will be effective and beneficial in breast cancer. This is the translational part of the work on Myc. It is admittedly "high-risk", but the pay-off in the form of a novel class of drugs could be very high as well.

The current proposal is distinct from the P01 grant entitled "Combinatorial Chemistry and Cancer." P-01 funding will terminate in May, 2003. The revised renewal application will have three projects: Dr. Boger will generate combinatorial chemical libraries, Dr. Cheresch will continue research on angiogenesis inhibitors isolated from these libraries, and I will work on basic mechanisms of small molecules that affect protein:protein interactions. Support from the P01 grant was the prerequisite for the current proposal; it not only produced the first inhibitors of Myc-Max dimerization, it also provided the substantial outlays for equipment such as the robot and spectrometer that will be essential in the present proposal. So, although the P01 has represented the background for the current proposal, there is no overlap between this applications and my other grant support.