Request for Proposals (RFP)

Understanding the Contributions of Chemical Mixtures to Breast Cancer Risk

California Breast Cancer Research Program
Preventing Breast Cancer: Community, Population, and Environmental Approaches

Deadline to apply:
November 9, 2023

Table of Contents

About the California Breast Cancer Research Program and the Preventing Breast Cancer Initiative

The **California Breast Cancer Research Program (CBCRP)** was established pursuant to the 1993 Breast Cancer Act (*AB 2055 (B. Friedman) [Chapter 661, Statutes of 1993]* and *AB 478 (B. Friedman) [Chapter 660, Statutes of 1993]*). The program is responsible for administering funds for breast cancer research in California.

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

- CBCRP is the largest state-funded breast cancer research effort in the nation and is administered by the University of California, Office of the President.
- CBCRP is funded through the tobacco tax, a voluntary tax check-off on personal income tax forms, and individual contributions.
- The tax check-off, included on the personal income tax form since 1993, has drawn over $13 million for breast cancer research.
- Ninety-five percent of our revenue goes directly to funding research and education efforts.
- CBCRP supports innovative breast cancer research and new approaches that other agencies may be reluctant to support.
- Since 1994, CBCRP has awarded over $290 million in 1,249 grants to institutions across the state. With continued investment, CBCRP will work to find better ways to prevent, treat and cure breast cancer.

PBC Priority Areas

CBCRP's Program Initiatives integrate expertise and experience from a range of stakeholders to identify compelling research questions and fund research projects that help find solutions to reduce suffering from breast cancer and move science closer to eliminating the disease. The Program Initiatives engage scientists, advocates, people impacted by breast cancer, and the broad community in a dialogue to frame research priorities and fund meaningful research.

In 2004, CBCRP launched its Special Research Initiatives (SRI), devoting 30% of research funds to research to environmental causes of breast cancer and the unequal burden of the disease. Under this initiative, CBCRP funded 26 awards totaling over $20.5 million. In 2010, CBCRP launched its second round of Program Initiatives, the California Breast Cancer Prevention Initiatives (CBCPI), adding population-level prevention interventions as a target area and devoting 50% of its funds to these priority areas. To date, CBCRP has funded 22 awards under CBCPI, totaling over $19 million.

In 2015, CBCRP's Council decided to build on the existing Program Initiatives by devoting 50% of CBCRP research funds between 2017 and 2021 to a third round of Program Initiatives. This new effort is titled Preventing Breast Cancer (PBC): Community, Population, and Environmental

Approaches. Approximately $20 million is being dedicated to directed, coordinated, and collaborative research to pursue the most compelling and promising approaches to:

- Identify and eliminate environmental contributors to breast cancer.
- Identify and eliminate fundamental causes of health disparities with a focus on breast cancer in California.
- Develop and test population-level prevention interventions that incorporate approaches to address the needs of the underserved and/or populations experiencing disparities in the burden of breast cancer.

In 2020, CBCRP began releasing a series of initiative based on 10 concept proposals to stimulate compelling and innovative research in all three PBC focus areas.

Understanding the Contributions of Chemical Mixtures to Breast Cancer Risk

Available Funding

The goal of this RFP is to identify chemical mixture exposures associated with risk of breast cancer and/or biomarkers of effect using either: (1) analytical chemistry applications on stored materials from (a) a breast cancer cohort or (b) women at potential risk of breast cancer (e.g., high mammographic density, atypia, occupational risk); or (2) artificial intelligence, big data methods and/or mining of existing data. Preference will be given for projects involving study populations that are diverse in terms of social and environmental exposures.

CBCRP intends to fund up to two smaller proposals for a maximum duration of 2 years at up to $350,000 maximum direct costs each and one additional laboratory-based proposal for a maximum duration of 3 years at up to $1,000,000 maximum direct costs.

Completed responses to this RFP are due by Thursday, November 9, 2023, 12 noon PST. The project start date is March 1, 2024.

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Introduction

Some individual chemicals or chemical groups (e.g., polycyclic aromatic hydrocarbons) have been reported to contribute to breast cancer risk. A few heterogeneous common-source mixtures, such as tobacco smoke and air pollution, have also been associated with breast cancer risk. However, women who develop breast cancer are exposed to a wide variety of complex chemical mixtures that may include chemicals from many sources such as consumer products, food, air, water, and their workplace. The goal of this RFP is to identify the complex mixtures of environmental chemicals that contribute to breast cancer risk using novel tools, approaches, data sets, and populations. Examples of preferred approaches include data mining, use of artificial intelligence, big data methods or novel analytical methods, including mixtures analysis and machine learning techniques that identify the environmental chemicals, exposures and subpopulations that may be at enhanced risk for breast cancer; exposome biomonitoring, fractionation of stored samples, geospatial mapping of large and diverse datasets, or further characterization of exposures via non-targeted analyses in combination with metabolomic/proteomic/transcriptomic data is envisioned. Given budget constraints, leveraging already-collected specimens and existing data from well-characterized and demographically diverse cohorts is encouraged. Unique opportunities to study highly exposed

or vulnerable groups are also welcomed. Characterization of unique mixture exposures in populations with health disparities/inequities or in occupational settings is needed.

Background/Justification

Breast cancer is the most common cancer worldwide, yet steps to prevent the disease have been slow to predominate the research field compared to treatment approaches. According to two expert panel reviews (IOM 2012; IBCERCC 2013), preventing breast cancer should be a funding priority. One of the primary goals of CBCRP is to identify chemical exposures that cause breast cancer, so that they can be targeted for reduction or elimination from our environment. Hundreds of chemicals have been identified in our everyday environment and have been measured in people. A significant number of them are suspected breast carcinogens (Rudel et al. 2007, Fenton et al. 2012, Reed and Fenton 2013, Terry et al. 2019) and animal studies have proven that many individual environmental chemicals enhance mammary tumor formation (Rudel et al. 2011). For more than two decades, it has been recognized that environmental exposures, whether accidental, occupational, or from consumer product use, may be significant contributors to breast cancer risk in women as well (Rodgers et al. 2018; Terry et al. 2019).

Environmental chemicals that contribute to breast cancer risk have been reported in animal studies and cultured breast cell lines, but translation to human health has not been established in some cases (IOM 2012; IBCERCC 2013; Rudel et al. 2011). There are likely numerous potential reasons for this:

- The need to take into account age-dependent exposure paradigms;
- The variation in dose applied vs what humans are exposed to;
- Breast to breast variability in composition;
- The simplicity of cell models and lack of predictive utility for whole organisms; and potentially
- That chemical mixtures humans are exposed to may have different effects than individual chemicals.

Additionally, the multiple environmental factors in the exposome that may alter breast cancer risk vary by person and between communities.

Further, women from marginalized groups may have increased exposure/risk burden from multiple sources (polluted neighborhoods, high exposure occupations, personal use products with high chemical content, etc.) (Nguyen et al. 2020). Non-Hispanic Black women are reported to have significantly higher mortality from breast cancer than non-Hispanic White women (Nobel et al. 2020; Yedjou et al. 2019; ACS 2019) and rates of breast cancer among women under 45 years is higher among non-Hispanic Black women compared to White women (Heer et al. 2020). Taken together, this information suggests that the mixture of environmental chemical exposures may contribute to the documented race/ethnicity-based difference in disease incidence and mortality risk and should be further interrogated.

When it comes to characterizing heterogeneous chemical mixtures that contribute to breast cancer risk in women, there are "known mixtures", those that contain chemicals that we suspect or have measured as co-occurring (come from a common source like tobacco smoke or air pollution), and "unknown mixtures", those measurable chemicals within a person's body from undefined sources in their homes, workplaces and other environments. Yet, challenges remain for more holistically characterizing complex chemical mixtures (Bessonneau and Rudel 2019). First, many chemical mixtures are not publicly or scientifically characterized, usually due to regulations and laws related to confidential business information that protect industry producers from having to disclose complete ingredient lists for their products. Second, although human chemical biomonitoring data show over 350 compounds can be measured in humans (CDC 2019), about 4,000 industrial chemicals are used or imported to the US in quantities greater than one million pounds per year (considered high production volume), and many thousands more are registered for use in smaller amounts (CompTox Dashboard 2021). Finally, it is expensive, complex, and data-intensive to analyze the mixture of chemicals in environmental media such as wildfire smoke, drinking water, dust, or air samples, and the content may be temporally/geographically variable.

A significant limitation of current biomonitoring methods is that they often rely on *a priori* selection of chemicals to study. While this *a priori* selection process may consider production volume, this criterion is limited due to the lack of data about where, how and the extent to which chemicals are used in production, consumer products or occupational settings, or how waste containing those chemicals is discarded. As a result, significant time and resources are expended developing analytic methods to measure chemicals that may or may not be present in biological specimens. Thus, in most epidemiological studies, the exposures linked to disease risk are typically evaluated one-by-one, and the entire exposome (defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to health; NIOSH 2014) is not determined. Moreover, even though advances in analytical chemistry allow for the identification of multiple chemicals in serum or urine samples using non-targeted high-resolution mass spectrometry, fully characterizing an individual's exposome can be cost- and time-prohibitive.

Environmental epidemiological studies are often considered critical for establishing the impact of chemical exposures on cancer risk in humans, given that they have the ability to assess relevant exposures and may take into account exposure effects during windows of susceptibility across the life cycle (Brody et al. 2007, IBCERCC 2013, Rodgers et al. 2018, Terry et al. 2019). Human biomonitoring, which measures exposures directly through analysis of biological media, is limited because for many chemicals, a spot sample only represents exposure at a snapshot in time and may not adequately characterize the level, timing or duration of exposures. In addition, because of the long latency of breast cancer, the relevant exposure(s) may have taken place decades before cancer diagnosis. Analysis of relevant biomarkers for breast cancer risk may be one option for decreasing latency to health effects related to the exposures. **Figure 1** illustrates the issue that for some studies, knowledge of

exposures, breast cancer incidence, and additional data exist, but assimilation of the exposures with the incidence or potential biomarkers may be incomplete. Knowledge from cross-disciplinary science on chemical mixtures can help decision-makers develop and prioritize exposure prevention and disease reduction strategies.

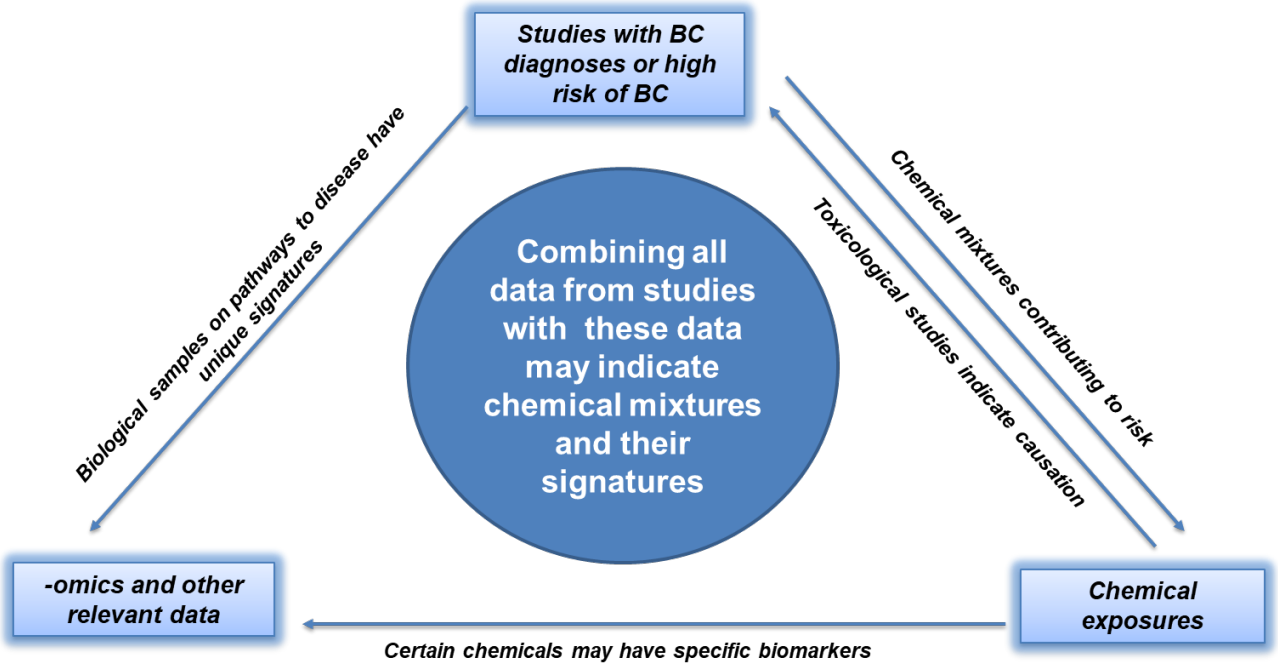

Figure 1. Knowledge generation synergies between environmental exposure data, biomarker data, and breast cancer (BC) risk data. The key for successful proposals is to integrate all the pieces of data available and use novel approaches to generate the missing pieces.

Research Questions

Human biomonitoring for chemicals that are widely present in our environment has made major contributions to understanding population exposures over time and within sensitive subpopulations. This has enabled researchers to examine the biological impact of exposure, assess potential synergies among different chemicals, and elucidate relationships between exposures and diseases, including breast cancer.

Despite important scientific progress in this realm of exposure assessment, significant challenges remain including the need to better characterize complex chemical mixture exposures and their relationship to potential effect biomarkers (determined prior to disease diagnosis) and/or breast cancer risk. To date, most studies have reported single chemical or chemical families (metabolites or alternate forms of the same chemical) and their associations with breast cancer.

Accordingly, we seek proposals to aid in **understanding the contributions of chemical mixtures to breast cancer risk** and will cover two main topic areas that are further described below. The aims of the proposed projects will be to:

1. Identify complex chemical mixture exposures associated with eventual risk of breast cancer using analytical chemistry applications on stored materials from either (a) breast cancer cohorts or (b) women at potential risk of breast cancer due to their occupation, biomarkers of effect (e.g., high mammographic density, atypia), or residential proximity to carcinogenic exposures.
2. Develop an understanding of the relationship between breast cancer risk and the complex mixture of exposures associated with it using artificial intelligence, big data methods and/or creative mining of existing data.

Priority projects will use novel approaches to identify chemical mixtures related to breast cancer risk in high (unique) exposure cohorts or particular individuals/groups that are at increased risk for environmental exposures for social reasons, such as poverty, that limit life choices. Applicants might use contemporary approaches to identify chemical mixtures most contributing to breast cancer risk or effect biomarkers of relevance to breast cancer in uniquely exposed communities. This might require characterizing socioeconomic factors and other social determinants of health along with environmental factors.

Approaches and Methods

Environmental mixtures can include metals, pesticides, endocrine disrupting compounds, persistent organic pollutants, particulate matter, volatile organic substances, and others. Each of the mixture components may activate unique key biological mechanisms/pathways for the combined effects of the chemical mixture that are associated with risk for breast cancer. These components, along with non-chemical stressors, may be eliminated from the environment or may be avoided if they can be identified, lowering the incidence of breast cancer for future generations.

For the purposes of this RFP, we seek proposals from researchers who will identify environmental chemical mixtures linked to breast cancer risk via: analytical chemistry, data mining and analysis of existing cohort data, or through artificial intelligence/big data approaches, mixtures analysis, Geographic Information System (GIS – software that lets you produce maps and other geographic displays to analyze and present information) exposure mapping, and machine learning methods. Breast cancer incidence is not required as the only end point of interest. Breast cancer risk may be inferred by characteristics including, but not limited to, early effect biomarkers of relevance to breast cancer, measures of breast density, or abnormal breast diagnoses on the pathway to cancer.

A specific area of interest to CBCRP are chemical mixtures previously identified as hormonally active or carcinogenic to the breast, which are still produced in high-volume and present in the environment or in people. We encourage careful consideration of exposure assessment and how to address inter-individual variability in exposure. A focus on vulnerable life-course time periods and historically marginalized populations is also encouraged. We expect that some of the following approaches may be proposed:

a) Use fractionated stored samples to identify the environmental chemicals (via analytical techniques) that are most abundant in populations of women that eventually developed breast cancer, compared to age-matched populations of women without the disease.

b) Use stored samples from women with exposures of interest to identify environmental chemicals and potential biomarkers of breast cancer risk; such biomarkers of risk could be genetic, metabolic, or other (e.g., breast density). Studies in this area should clearly identify why the population selected may have exposures of particular interest (e.g., exposure to wildfire smoke, pesticides, or specific occupational groups).

c) Using complex exposure data, create a realistic mixture of environmental chemicals and determine the risk for breast tumors in a relevant rodent model, making sure to understand the body burden of the chemicals (in their blood/urine) in the animal model so that comparisons can be made to humans with similar mixture exposures.

d) Holistically characterize or map the exposome associated with breast disease and effect biomarkers of relevance for breast cancer in cohorts where some individual environmental chemicals have already been identified, using further non-targeted analytic or data mining/artificial intelligence/big data techniques.

e) In breast cancer or occupational studies, characterize the content of chemical mixture profiles that may put women at higher risk.

Topic 1: Apply novel approaches in analytical chemistry to understand chemical mixtures contributing to breast cancer risk

Approaches will be considered novel if they measure a chemical(s) not previously interrogated, improve on or validate an existing strategy (e.g., reliability, lower cost, more practical, measures multiple chemicals), or apply novel analytical chemistry and/or statistical methods. Examples include:

a) Fractionate stored serum or urine from women who went on to develop breast cancer or an effect biomarker, such as high mammographic density, inflammatory breast disease, atypia, etc. Determine what in their exposome profiles was associated with the increased risk.

b) Fractionate drinking water, air, or dust samples or apply spatial GIS and exposure modeling techniques to determine novel chemical mixtures or their exposure sources that are associated with breast cancer risk or presence of effect biomarkers of relevance for breast cancer (e.g., wildfires, industrial exposure sources, a drinking water "hotspot", or oil/gas extraction fenceline community, etc.).

c) Further define the exposome in studies in which stored samples are available for further nontargeted mass spectrometry (MS)/MS and where breast cancer incidence or effect biomarkers of relevance for breast cancer risk is known.

d) Develop relationships between -omics data, exposures, and breast cancer risk (incidence or effect biomarkers) to potentially identify measurable markers of a chemical mixture exposure indicating increased risk of breast cancer.

Topic 2. Data Mining/Artificial intelligence/Big data methods linking mixture exposures and breast cancer risk using existing data

A limitless number of projects are potentially possible with the right team of investigators and may include:

a) Inclusion of bioinformatics in chemical mixture exposure modeling may help discover novel exposures linked to disease. Additionally, a novel exposure discovered using artificial intelligence or other bioinformatic tools (i.e., pattern recognition or cross-species or cross-strain similarities/differences in existing datasets) could be tested for its predictive potential for breast cancer in animal or advanced cell-based studies.

b) Updating and expanding previous GIS mapping projects and combining datasets could provide novel insights into exposure mixtures effects. For example updating the California Breast Cancer Mapping Project (Breast Cancer Mapping Project --- Tracking California) and combining it with a California based update of the National Air Toxics Assessment (National Air Toxics Assessment | US EPA) may yield important insights. Other datasets could also be layered in that examine, for example, socioeconomic status, pesticide exposure, water quality etc.

If possible, these studies should be carried out with relevant female cohorts that have existing chemical exposure and other types of data. Combining multiple data sets with similar data types is encouraged. For instance, it is anticipated that some chemicals may induce a gene or metabolite signature that was discovered through transcriptomic or metabolomic analyses and may indicate mixtures of chemicals linked to effect biomarkers of potential relevance to breast cancer risk. Also, use of multiple datasets from multiple studies may elucidate mixture "hotspots" that overlap with regions or study populations with high breast cancer rates (Sister Study, All of Us, Child Health and Development Studies (CHDS), Teacher's Study, Nurses Study, etc.).

If possible, investigators can collaborate and integrate data in order to develop a proposal that can also demonstrate the relationship between a human-relevant chemical mixture and breast cancer in an animal model or in order to increase sample size of a human study population to evaluate subtypes of breast cancer. The project should propose specific and definitive outcomes, such as effect biomarkers and/or tumor development, so that subsequent studies can connect them to epidemiological studies with measured exposures and clinical breast cancer outcomes.

Projects generating predictive value for current use chemicals on breast cancer risk will be viewed more favorably than research only on persistent chemicals no longer in the marketplace.

Resources to Be Used or Considered for Use

Expertise. Laboratory-based studies (analytical chemists or toxicologists) or other expertise (bioinformaticists, geospatial engineers, GIS modelers, field analysts, or computing specialists) are expected to augment the outcome of the research. Transdisciplinary applications will receive more favorable consideration. Investigators must demonstrate that they have permission to access the data they propose to use or already be conducting studies from which data would be used to address proposed aims.

Capacity. The investigator(s) should demonstrate that they would have the equipment on hand and capabilities to conduct the proposed research. Costs to purchase access to data sets, conduct animal/cell-based studies, purchase columns for analytical studies, secure data storage space, etc., are appropriate. Purchase of large pieces of equipment to enable the work that are more than 10% of direct costs are not allowed.

Data Sets. Data resources that should be considered relevant include, but are not limited to, (1) female cohorts with biospecimens, environmental samples (e.g. drinking water, dust, or air), spatial and modeled exposure estimates, and/or chemical biomonitoring and/or -omics data that can be leveraged to examine relationships with breast cancer and/or effect biomarker outcomes; (2) animal models in which human relevant exposures (chemical mixtures or complex contemporary exposures) are delivered during susceptible life stages and followed for risk evaluation for mammary carcinogenesis; (3) advanced cell-based strategies that lead to data on risk for tumor formation or suggest biological activity in the fractions from women; (4) large datasets from published studies that include environmental exposures, -omic(s) data, and/or disease or breast condition information, or (5) occupational biomonitoring studies for which breast outcomes have not been previously interrogated and other data and/or biospecimen samples from the cohort population are available.

Exposures. Novel or complex exposure identification strategies are encouraged. Measurement of body burden (blood/urine) in animal mixture exposure studies is necessary for eventual comparison to women. Modeling of mixtures exposures and biological response outcomes along the trajectory to breast outcomes/cancer are a high priority. Contemporary mixture exposures will be reviewed more favorably. Studies utilizing data or samples from occupational cohorts as well as demographically and geographically diverse cohorts are encouraged.

Dissemination Plan

Each application should identify translational potential or transdisciplinary approaches that are pertinent, research gaps that they intend to fill, potential impact on the field/policy, and the novelty of their proposal. How the findings resulting from the proposal may be applied should be discussed.

Proposals will be favored that include plans to secure community input in formulating and conducting the planned research. This might include individual and organizational advocates,

whose input will help to ensure that the research takes community needs and contingencies into account.

Proposals must include plans for dissemination and translation of newly discovered/developed methods and results. These plans should be developed with advocate input, to ensure their success. The applicants should address the likely relevance to both future research and current policy discussions. The applications should include plans to disseminate results to breast cancer advocates, policymakers, and the larger public. Summary reports should be available in at least two languages accessible to a lay audience.

Advocacy Involvement

The involvement of a breast cancer advocate or advocacy organization is a requirement for the research funded under this initiative. Applications should include a California community advocate affiliated with an advocacy and/or community organization with an interest in the area of biomonitoring, environmental exposures and breast cancer to be actively involved in the project. The community advocate(s) should be involved in the development of the project, goals, aims, and research questions and should drive the identification and definition of community needs and health equity imperatives. Community advocates should be compensated as experts.

Applications will be evaluated on the extent to which advocates are substantively involved in the project including identification of an appropriate advocate(s) for the proposed research; a detailed description of how the advocate(s) will be involved in the project; submission of a Letter of Commitment co-signed by the research advocate(s) and the PI; and a budget line item and justification covering the advocate(s) time, effort, and expenses on the project (e.g. at least quarterly, meetings with the advocate and the investigative team). If needed, CBCRP staff can assist investigators with meeting the advocacy involvement requirement as they prepare their applications.

Budget

CBCRP intends to fund up to two smaller proposals for a maximum duration of 2 years at up to $350,000 maximum direct costs each and one additional laboratory-based proposal for a maximum duration of 3 years at up to $1,000,000 maximum direct costs. The budget may vary for different types of proposals and must be carefully justified.

In addition, if more than one grant is funded in response to this announcement, CBCRP will convene grantees to consider opportunities for synergy and integration. Proposals should include plans to attend a meeting for this purpose.

Indirect (F&A) costs are paid at the appropriate federally approved F&A rate for all institutions except for University of California campuses, which receive a maximum of 35% F&A (25% for off-campus projects). Organizations that do not have a federally approved F&A rate may request a De Minimis rate of 25%.

Supplemental funding is available for funded projects to support promising high school students, undergraduate students and/or community members from groups underrepresented in breast cancer research and/or those who wish to pursue careers focused on questions affecting underrepresented communities to breast cancer research. Applications for these supplements will be accepted during the prefunding stage of the award and will start March 1, 2024. Visit https://cabreastcancer.org/files/cbcrp-diversity-supplement.pdf to learn more.

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How We Evaluate RFPs

CBCRP uses a two-tier evaluation process: peer review and programmatic review. It is a combination of (i) the peer review rating, (ii) the programmatic rating, and (iii) available funding that determines a decision to recommend funding.

Peer Review

All applications are evaluated by a peer-review committee of individuals from outside of California. The committee is composed of scientists from relevant disciplines and breast cancer advocates and other community representatives. Applications are rated using:

- **Innovation.** Extent to which the project explores novel approaches to study chemical mixtures (contemporary mixtures encouraged) and their effects on breast cancer risk. Are the concepts and hypotheses speculative and exploratory. Are the methods novel and original?
- **Impact.** Potential for the project, if successful to develop, improve or refine methods to characterize complex chemical mixture exposures and their relationship to Breast cancer risk or intermediate biomarkers. Does the research address relevant mechanisms, methods and/or models for testing mixtures of chemicals.
- **Approach.** The quality, organization, and presentation of the research plan, including methods and analysis plan. Will the research planned answer the research questions? Are the design, methods and analyses well-developed, integrated and appropriate to the aims and stated milestones of the project? Does the application demonstrate an understanding of the research question and aims? How well developed is the dissemination plan?
- **Feasibility.** The extent to which the aims are realistic for the scope and duration of the project; adequacy of investigator's expertise and experience, and institutional resources; whether a transdisciplinary team is involved; and availability of additional expertise and integration of multiple disciplines. Does the investigator (and do co-investigators) have demonstrated expertise and experience working in the topic area? Can the project be completed as proposed given the available funding, time frame and the staff knowledge, skills, experience, and institutional resources?

Programmatic Review

This review is conducted by the California Breast Cancer Research Council and involves reviewing and scoring applications with sufficient scores from the peer review process based on the criteria listed below. 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 evaluates **only a portion of the application materials** (exact forms are underlined). Pay careful attention to the instructions for each form. The Programmatic criteria include:

- **Responsiveness.** How responsive are the project and co-PIs to the stated intent of the selected Initiative? Compare the PI's statements on the Program Responsiveness form and the content of the Lay and Scientific Abstracts to the PBC topic area. Is the dissemination plan adequate?
- **Critical path/Translation:** The degree to which the applicant's statements on Critical Path and Focus on Underserved Populations form provides a convincing argument that the proposed research fits into and advances a critical path for translation and impact on breast cancer. What barriers must be overcome to take the project to the next level, and what plans are provided for to address these barriers?
- **Quality of the lay abstract.** Does the Lay Abstract clearly explain in non-technical terms the research background, questions, hypotheses, and goals of the project? Is the relevance to the research initiative understandable?
- **Addressing the needs of the underserved.** Do the project and the PI's statements on Critical Path and Focus on Underserved Populations template demonstrate how this research will contribute to health equity by addressing breast cancer issues that disproportionally affect communities who have been historically underserved by research and/or health systems? Does the project address inequities and/or the specific needs of communities who are underserved as they bear a disproportionally high burden of health-related problems due to factors related to race, ethnicity, socioeconomic status, geographic location, sexual orientation, physical or cognitive limitations, age, occupation and/or other factors?
- **Advocacy involvement.** Are the named advocate(s) and advocacy organization appropriate for the proposed research project? Will the advocate provide a perspective that is historically underrepresented in breast cancer research? Were they engaged in the application development process? Are meetings and other communications sufficient for substantive engagement? Are the roles and responsibilities of the PI and the advocate(s) clearly outlined and is the agreement for advocate compensation and reimbursement clear? [The Advisory Council will examine the PI's statements on the Lay and Scientific Abstracts and Advocacy Involvement forms.]

Application Instructions

Application materials will be available through RGPO's SmartSimple application and grant management system beginning on September 1, 2023. Please review the SmartSimple Application Instructions for the technical instructions for accessing and completing your application. This supplemental programmatic instruction document provides guidance for the content of your application.

Application Components

Section 1: Title Page

- **Project Title:** Enter a title that describes the project in lay-friendly language. (Max 100 characters).
- **Project Duration:** Select a duration of 2 or 3 years.
- **Proposed Project Start Date:** Enter a project start date of March 1, 2024.
- **Proposed Project End Date:** Enter a project end date of February 28, 2026 for a 2-year award or February 28, 2027 for a 3-year award

Section 2: Applicant/PI

A required field entitled "ORCID ID" is editable on the Profile page. ORCID provides a persistent digital identifier that distinguishes you from every other researcher and, through integration in key research workflows such as manuscript and grant submission, supports automated linkages between you and your professional activities ensuring that your work is recognized. If you have not already obtain an ORCID ID number, you may do so at http://orcid.org/ Once you have done so, please enter your 16-digit identifier in the space provided on your profile page in the following format: xxxx-xxxx-xxxx-xxxx.

Section 3: Project Information

Please use the following guidelines to differentiate between Lay and Scientific Abstracts:

Lay Abstract (Max 2400 characters)**:** This item is evaluated mainly in the programmatic review. The Lay Abstract must include the following sections:

- A **non-technical introduction** to the research topics
- The **question(s) or central hypotheses** of the research in lay terms
- The **general methodology** in lay terms
- **Innovative elements and potential impact** of the project in lay terms

The abstract should be written using a style and language comprehensible to the general public. Avoid the use of acronyms and technical terms. The scientific level should be comparable to either a local newspaper or magazine article. Avoid the use of technical terms and jargon not a part of general usage. Place much less emphasis on the technical aspects of the background, approach, and methodology. Ask your advocate partner to read this abstract and provide feedback.

Scientific Abstract (Max 2400 characters)**:** This item is evaluated mainly in the peer review. The Scientific Abstract should include:

- A short introductory paragraph indicating the **background** and overall topic(s) addressed by the research project
- The **central hypothesis** or **questions to be addressed** in the project
- A listing of the **objectives or specific aims** in the research plan
- The major research **methods and approaches** used to address the specific aims
- A brief statement of the **impact** that the project will have on breast cancer

Provide the critical information that will integrate the research topic, its relevance to breast cancer, the specific aims, the methodology, and the direction of the research in a manner that will allow a scientist to extract the maximum level of information. Make the abstract understandable without a need to reference the detailed research plan.

Additional information: Applicants must respond to the following categories and discussion points using the online fields provided:

- **Specific aims** (Max 2400 characters/approx. 350 words). List the proposed aims of the project.
- **CBCRP Research Priorities.** Select "Etiology and Prevention" as the CBCRP priority issue that the research addresses.
- **CSO Research Type(s) and Sub-Type(s).** Select the CSO Type and Sub-Type that best represent your project.
- **Subject Area(s).** See SmartSimple submission instructions for more details.
- **Focus Areas(s).** See SmartSimple submission instructions for more details.
- **Research Demographics.** See SmartSimple submission instructions for more details.
- **Milestones.** Add significant milestones that are described in your research plan to this table along with anticipated completion dates and arrange them in chronological order.

Section 4: Project Contacts

Project Personnel. Provide contact information and effort for Key Personnel and Other Significant Contributors on your project including the Applicant Principal Investigator, Co-Investigator, Advocate, Trainee, Consultant, and support personnel, as necessary. Upload biosketches to each of your Key Personnel members in this section, as shown in the SmartSimple instructions. A 10% minimum effort (1.2 months per year) is required for the Applicant PI.

Section 5: Budget

This section contains several sub-tabs: Institution Contacts, Budget Summary, Budget Details, and Subcontract Budget Details. Complete the information in the Institutional Contacts, Budget Summary, Budget Detail and, if applicable, Subcontract Budget Details tab as described in the SmartSimple Application Instructions.

For smaller proposals, the duration is 2 years, and the direct costs budget cap is $350,000; for larger, lab-based proposals, maximum duration is 3 years and the direct costs budget cap is $1,000,000.

Note: The amount of a subcontracted partner's F&A costs can be added to the direct costs cap. Thus, the direct costs portion of the grant to the recipient institution may exceed the award type cap by the amount of the F&A costs to the subcontracted partner's institution.

Additional budget guidelines:

- **Equipment** purchases should not be more than 10% of Direct Costs. Only include individual items >$5,000. Any items less than $5,000 must be purchased under the "supplies" budget category.
- **Other Project Expenses:** Include other project costs such as supplies or **Advocate(s) expenses** (any travel, meeting, and consultation costs/fees associated with advocates) here.
- **Travel**: A minimum of $400 must be budgeted in year 1 for travel to the **CBCRP symposium**. Include in the budget travel to the potential CBCRP convening of initiative grantees (minimum $400). **Scientific meeting travel** is capped at $2,000/yr.
- **Indirect (F&A) costs**. Non-UC institutions are entitled to full F&A of the Modified Total Direct Cost base (MTDC); UC institutional F&A is capped at 35% MTDC*, or 25% MTDC for off-campus investigators (not retroactive to prior grants).

**Allowable expenditures in the MTDC base calculation include salaries, fringe benefits, materials and supplies, services, travel, and up to the first $25,000 of each subgrant or subcontract (regardless of the period covered by the subgrant or subcontract). Equipment, capital expenditures, charges for patient care and tuition remission, rental costs, scholarships, and fellowships as well as the portion of each subgrant and subcontract in excess of $25,000 shall be excluded from the modified total direct cost base calculation. If a grantee or subcontractor does not have a federally negotiated F&A rate at the time of the proposal submission, the grantee and/or subcontractor may request a "De Minimis" F&A rate of 25% MTDC.*

Additional budget guidelines can be found in Appendix A.

Section 6: Assurances

Enter assurance information. If available, enter your institutional Federal Wide Assurance (FWA) code or equivalent for Human Subjects, an IACUC Animal Welfare Assurance code for Vertebrate Animals, and equivalent for Biohazard ad DEA Controlled Substance approvals.

Section 7: Documentation

Complete and upload all required items. All uploads must be in PDF format. Listed below are the forms and templates you download from SmartSimple, enter text, convert to PDF, and, unless instructed otherwise, re-upload to your application in this section.

Upload Item (Template/Form)	Page limit	Required or optional	Peer Review?	Programmatic Review?
Research Plan	**10**	**Required**	**Yes**	**No**
Program Responsiveness	**2**	**Required**	**Yes**	**Yes**
Critical Path & Underserved	**2**	**Required**	**Yes**	**Yes**
Advocacy Involvement	**1**	**Required**	**Yes**	**Yes**
Letter of Commitment	**2**	**Required**	**Yes**	**Yes**
Biosketches (All Personnel listed on Key Personnel form)	**5 (each biosketch)**	**Required** *(upload to Project Personnel section)*	**Yes**	**Yes (PI only)**
Facilities	**1 per institution**	**Required**	**Yes**	**No**
Human Subjects	**No Limit**	**Required**	**Yes**	**No**
Vertebrate Animals	**No Limit**	**Optional**	**Yes**	**No**
Appendix list and uploads	**30**	**Optional**	**Yes**	**No**

Detailed Description of Proposal Templates

Research Plan (required)

This section is the **most important** for the peer review. Note carefully the page limits, format requirements, and suggested format. **Limit the text to ten pages.**

Format issues: Begin this section of the application using the download template. Subsequent pages of the Research Plan and References should include the principal investigator's name (last, first, middle initial) placed in the upper right corner of each continuation page.

The Research Plan and all continuation pages must conform to the following four format requirements:

1. The height of the letters must not be smaller than 11 point; Times New Roman or Arial 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 0.75 inches.

Use the appendix to supplement information in the Research Plan, not as a way to circumvent the page limit.

We ask that applicants describe the proposed research project in sufficient detail for reviewers to evaluate its scientific merit and collaboration elements, as described below. If you don't use

all the pages to describe your research plan, it might be best to review what you have written and explain in more detail anything not fully explained. **However, note that a concise, focused research plan of less than the maximum number of pages is preferable to one less concise and made longer by overly elaborate or unimportant details.**

Supporting materials (such as questionnaires, consent forms, interview questions, letters of collaboration) that are directly relevant to the proposal may be included in the Appendix. **The research plan must be self-contained and understandable without having to refer extensively to supporting materials.**

Suggested outline:

Introduction and Hypotheses: Provide a brief introduction to the topic of the research and the hypotheses/questions to be addressed by the specific aims and research plan. The relationship of the project to the specific PBC Project Type and expectations outlined within the RFP should be clear.

Specific Aims: List the specific aims, which are the steps or increments deemed necessary to address the central hypothesis of the research. The subsequent research plan will detail and provide the approach to achieving each of these aims.

Background and Significance: Make a case for your project in the context of the current body of relevant knowledge and the potential contribution of the research.

Preliminary Results: Describe the recent work relevant to the proposed project. Emphasize work by the PI and data specific to breast cancer.

Research Design and Methods: Provide an overview of the experimental design, the methods to be used, and how data are to be collected and analyzed. Describe the exact tasks related to the Specific Aims above. Provide a description of the work to be conducted during the award period, exactly how it will be done, and by whom. Include a letter of commitment if the applicant PI will be using a data set that they do not control/own. Recognition of potential pitfalls and possible alternative approaches is recommended. How will technical problems be overcome or mitigated? Cover all the specific aims of the project in sufficient detail. Identify the portions of the project to be performed by any collaborators. Match the amount of work to be performed with the budget/duration requested. A description of the milestones and timeline will demonstrate how the aims are interrelated, prioritized, and feasible.

Program Responsiveness (required)

This item is evaluated in the peer review and programmatic review. **Limit the text to two pages**. The CBCRP Council (who conducts the programmatic review) will NOT see your Research Plan. The information on this template allows the CBCRP Research Council to rate the application for adherence to the objectives of the PBC research area as outlined in the specific RFP.

PBC Focus (Responsiveness): Provide a clear, brief summary for the CBCRP Council (1 or 2 paragraphs) of how your proposed research addresses the specific RFP topic area, by increasing or building on specific scientific knowledge; by pointing to additional solutions to identify and eliminate environmental causes, and or disparities in, breast cancer; and/or, by helping identify or translate into potential prevention strategies.

Dissemination and Translation Potential: Describe how research findings will be shared with various stakeholder audiences (i.e., policymakers, community members, breast cancer advocates, other researchers/agencies, health care providers, funders etc.). Describe the potential for how the research findings will be translated into policy and/or other practice.

Critical Path & Focus on Underserved Populations (required)
This item is critical to the programmatic and peer reviews. **Limit the text to two pages**.

A. Critical Path

Review the background and rationale described for Program Initiatives at Appendix B and follow the instructions on the template.

B. Focus on Underserved Populations.

Describe the potential for your project to understand and reduce disparities and health inequities in breast cancer risk, incidence, and treatment/prognosis at the individual and community levels. Underserved is defined as communities or individuals who bear a disproportionally high burden of health-related problems due to factors related to race, ethnicity, socioeconomic status, geographic location, sexual orientation, physical or cognitive limitations, age, occupation and/or other factors.

Advocacy Involvement (required)
Follow the instructions on the form, and be sure to address the requested three items (Advocacy Organization/Advocate(s) Selection and Engagement to Date, Advocate(s) Role in Proposed Research and Meeting and Payment Plans). **Limit the text to one page**.

Discuss what involvement, if any, advocates had in the development of this proposal and will have in the project, if funded. Explain how this proposal shows awareness and inclusion of breast cancer advocacy concerns involved in the proposed research.

Letter of Commitment (required)
This item is evaluated in the peer review and in the programmatic review. Please use the template as a basis for commitment letters from the advocate, scientific and/or subcontracting individuals/institutions. **Limit the text to two pages**.

Biographical Sketch (required)
This item is evaluated in the peer review and the programmatic review. **Use the NIH form (version 2015 or later) for each key person and attach it in the Project Personnel section. Limit the length of each biosketch to *no more than* five (5) pages**.

Facilities (required)
This item is evaluated in the peer review. **Limit the text to one page per institution**. Follow the instructions on the template.

Human Subjects (required)
This item is evaluated in the peer review. **This form is required to be completed for applications that use Human Subjects, including those in the "Exempt" category. Applications that do not utilize Human Subjects should state "N/A" on the form and upload, as well.** Use additional pages, if necessary.

For applications requesting "Exemption" from regular Institutional Review Board (IRB) review and approval. Provide sufficient information in response to item #1 below to confirm there has been a determination that the designated exemptions are appropriate. The final approval of exemption from DHHS regulations must be made by an approved IRB. Documentation must be provided before an award is made. Research designated exempt is discussed in the NIH PHS Grant Application #398 http://grants2.nih.gov/grants/peer/tree_glossary.pdf. Most research projects funded by the CBCRP fall into Exemption category #4. Although a grant application is exempt from these regulations, it must, nevertheless, *indicate the parameters of the subject population* as requested on the form.

For applications needing full IRB approval: If you have answered **"YES"** on the Organization Assurances section of the application and designated no exemptions from the regulations, the following **seven points** must be addressed. In addition, when research involving human subjects will take place at collaborating site(s) or other performance site(s), provide this information before discussing the seven points. Although no specific page limitation applies to this section, be succinct.

1. Provide a detailed description of the proposed involvement of human subjects in the project.

2. Describe the characteristics of the subject population, including its anticipated number, age range, and health status. It is the policy of the State of California, the University of California, and the CBCRP that research involving human subjects must include members of underserved groups in study populations. Applicants must describe how minorities will be included and define the criteria for inclusion or exclusion of any sub-population. If this requirement is not satisfied, the rationale must be clearly explained and justified. Also explain the rationale for the involvement of special classes of subjects, if any, such as fetuses, pregnant women, children, prisoners, other institutionalized individuals, or others who are likely to be vulnerable. Applications without such documentation are ineligible for funding and will not be evaluated.

3. Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data. Indicate whether the

material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.

4. Describe the plans for recruiting subjects and the consent procedures to be followed, including: the circumstances under which consent will be sought and obtained, who will seek it; the nature of the information to be provided to the prospective subjects; and the method of documenting consent.

5. Describe any potential risks —physical, psychological, social, legal, or other. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.

6. Describe the procedures for protecting against, or minimizing, any potential risks (including risks to confidentiality), and assess their likely effectiveness. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects on the subjects. Also, where appropriate, describe the provision for monitoring the data collected to ensure the safety of subjects.

7. Discuss why the risks are reasonable in relation to the anticipated benefits to subjects, and in relation to the importance of knowledge that may be reasonably expected to result.

Documentation of Assurances for Human Subjects

In the Assurances tab, if available at the time of submission, include official documentation of the approval by the IRB, showing the title of this application, the principal investigator's name, and the approval date. Do not include supporting protocols. Approvals that are obtained under a different title, investigator or organization are *not* acceptable, unless they cross-reference the proposed project. Even if there is no applicant institution (i.e., an individual PI is the responsible applicant) and there is no institutional performance site, an USPHS-approved IRB must provide the assurance. If review is pending, final assurance should be forwarded to the CBCRP as soon as possible. Funds will not be released until all assurances are received by the CBCRP. If the research organization(s) where the work with human subjects will take place is different than the applicant organization, then approvals from the boards of each will be required.

Data and Safety Monitoring Boards (DSMB)

Applications that include Phase I-III clinical trials may be required to provide a data and safety monitoring board (DSMB) as described in the NICI policy release, http://grants.nih.gov/grants/guide/notice-files/not98-084.html. This ensures patient safety, confidentiality, and guidelines for continuing or canceling a clinical trial based on data collected in the course of the studies. The CBCRP may require documentation that a DSMB is in place or planned prior to the onset of the trial.

Vertebrate Animals (optional)
This form is required ONLY for applications involving vertebrate animals.

If your application involves vertebrate animals the following five points must be addressed. When research involving vertebrate animals will take place at collaborating site(s) or other performance site(s), provide this information before discussing the five points. Although no specific page limitation applies to this section of the application, be succinct.

1. Provide a detailed description of the proposed use of the animals in the work outlined in the research plan. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.

2. Justify the use of animals, the choice of species, and the numbers used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.

3. Provide information on the veterinary care of the animals involved.

4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.

5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If it is not, present a justification for not following the recommendations.

Documentation of Assurances for Vertebrate Animals

Grants will not be awarded for research involving vertebrate animals unless the program for animal care and welfare meets the standards of the AAALAC or the institution has a U.S. Public Health Service assurance. In the appendix, if available at the time of submission, include official documentation of institutional review committee approval showing the title of this application, the principal investigator's name, and the inclusive approval dates; do not include supporting protocols. Approvals obtained under a different title, investigator, or institution are not acceptable unless they cross-reference the proposed project. If review is pending, final assurances should be forwarded to the CBCRP as soon as possible. Funds will not be released until all assurances are received by the CBCRP.

Appendix (optional)
Follow the instructions and items list on the template. **The appendix may not be more than 30 pages in length.**

Note that the *research plan must be self-contained* and understandable without having to refer to the appendix. Only those materials necessary to facilitate the evaluation of the research plan

or renewal report may be included; the appendix is not to be used to circumvent page limitations of the application.

Appendix A: Cost and Expense Guidelines

For all budget categories, clearly label all costs associated with research dissemination activities in the budget justification.

1) Personnel

- The Budget Summary line item for Personnel should reflect the total cost of all individuals identified as supported by the grant and their level of effort. In the personnel section of the application, be sure to name all individuals to be supported by the grant and provide their percent effort (months devoted to the project). All paid individuals must also be listed on the budget.

- Follow the NIH Guidelines and Calculation scheme for determining Months Devoted to Project, available at the links below:
    - NIH Guidelines:
    - http://grants.nih.gov/grants/policy/person_months_faqs.htm
    - NIH Calculation Scheme: http://grants.nih.gov/grants/policy/person_months_conversion_chart.xls

- When computing salary for key personnel, use only the base salary at the applicant organization, excluding any supplementary income (e.g., clinical or consulting incomes). CBCRP does not enforce a salary cap, as long as the overall budget adheres to the costs & expenses guidelines and the amount requested stays within the allowable costs.

2) Student Tuition Fees, Graduate Student Stipends

- For non-fellowship awards: Graduate students may be paid as personnel and may also receive tuition remission. Tuition remission, however, will be considered compensation. The total compensation (salary plus fringe benefits plus tuition listed in this category) may not exceed $30,000 per project year. A maximum of $16,000 per year is allowed for the combined costs of tuition/enrollment fee remission, fringe benefits, and health insurance. Stipend may be budgeted as salary (and included in the MTDC cost calculation) if the institution pays these expenses through a personnel line item.

3) Other Project Expenses

- Include expected costs for supplies and other research expenses not itemized elsewhere.
- Pooled expenses may be allowed as a direct cost at the discretion of the Program with certification of the following: 1) the project will be directly supported by the pooled expenses, 2) the pooled expenses have been specifically excluded from the indirect cost rate negotiation, and 3) the pooled expenses have been allocated consistently over time within the organization. Please explain any requested pooled expense requests in the budget justification.

- Advocate (s) Expenses. Include any travel, meeting, and consultation costs/fees associated with advocate engagement.

4) Equipment (Unit Cost over $5,000)

- Each requested equipment item must be >$5,000 and explain in budget justification.

5) Travel

- **Travel – CBCRP Meeting:** CBCRP may organize an event requiring your travel within the funded grant period. All applicants should budget a one-time minimum expense of $400 under year 1 in the travel budget line labeled: "Travel - CBCRP Meeting".
- **Travel - Project Related:** Project-related travel expenses are allowable only for travel directly related to the execution of the proposed research activities. Label such expenses as "Travel – Project Related." These expenses must be fully justified in the budget justification.
- **Travel - Scientific Meetings:** Scientific conference travel is limited to $2,000 per year (excluding a mandatory allocation of $400 in one year of the project for travel to the CBCRP Conference under Travel - CBCRP Meeting). Label such expenses as "Travel-Scientific Meetings" and explain in budget justification.

6) Service Contracts and Consultants

- Both categories require additional description (Budget Justification).

7) Subcontracts

- In the case of University of California applicants, subcontracts need to be categorized and broken out as one of two types, University of California-to-University of California (UC to UC) sub agreements or transfers; or, Other. A subcontract is not allowed to have another subcontract. Requires additional description (Budget Justification).

8) INDIRECT (F&A) COSTS

- **Indirect cost policy:** Indirect costs are NOT allowed for Conference Awards. For other awards, non-UC institutions are entitled to full F&A of the Modified Total Direct Cost base (MTDC); UC institutional F&A is capped at 35% MTDC (25% for off-campus projects).
- **Modified Total Direct Costs (MTDC)** include salaries and wages, fringe benefits, materials and supplies, services, travel, and up to the first $25,000 of each subgrant or subcontract (regardless of the period covered by the subgrant or subcontract) to an outside institution. MTDC does not include (indirect costs are not allowed on): capital expenditures, charges for patient care, scholarships and fellowships (including postdoctoral stipends), tuition remission and graduate student stipends, rental costs of space, equipment purchases more than $5,000 per item, the portion of each sub grant

and subcontract in excess of the first $25,000, and the total cost of any subcontract from one UC to another UC campus. On a non-fellowship award, you may apply indirect costs to graduate student salary (under salary only, not as stipend) but not to tuition & fees.

- For all eligible projects that allow grantees to recover the full amount of their federally negotiated indirect cost rate agreement, grantees must also accept the full federally recognized F&A rate for all award subcontractors (except for subcontracts to another UC institution, where F&A is not allowed). If a grantee or subcontractor does not have a federally negotiated F&A rate at the time of the proposal submission, the grantee and/or subcontractor may request a "De Minimis" F&A rate of 25% MTDC. A higher indirect rate that has been accepted for state or local government contract or other California grantmaker contract may be approved at the discretion of the Program Director and the Research Grants Program Office Executive Director.
- **INDIRECT COSTS ON SUBCONTRACTS**
  - The award recipient institution will pay indirect costs to the subcontractor.
  - For non-UC subcontracted partners, CBCRP will allow full F&A of the Modified Total Direct Cost (MTDC), as defined above.
  - F&A costs are not allowed for one UC institution's management of a subcontract to another UC institution.
  - The amount of the subcontracted partner's F&A costs can be added to the direct costs cap of any award type. Thus, the direct costs portion of the grant to the recipient institution may exceed the award type cap by the amount of the F&A costs to the subcontracted partner's institution.

Appendix B: Critical Path for CBCRP Program Initiatives

Purpose: The point of asking for the "critical path" is to have the PI place the project on a research continuum (i.e., temporal trajectory) that begins with an idea or hypothesis and continues through development leading to a defined result of practical value (e.g., in the clinic or community). First, ask yourself the question: How will my project and its research goals/milestones lead to a measurable impact on the prevention, detection, diagnosis and treatment, reduction in community and social burden, or improved patient quality of life for breast cancer?

Background: Breast cancer research funding has been successful in the creation of new knowledge. However, the useful application of this knowledge to prevent and detect the disease, and increase survival and quality of life for breast cancer patients could be improved. If funding agencies and researchers are to be accountable to stakeholders, more emphasis needs to be placed on the "critical path" from research-to-practice.

In 2003 Best et al. (*Cancer Epidemiology Biomarkers & Prevention*,12:705-712) distinguished two pathways to practical application of research, "…. it is important to view "translational research" to encompass not only the pervasive view of transfer of basic science discoveries into clinical applications ("bench to bedside"), but also its transfer into effective interventions at the population level with active community participation in the process ("bench to trench"). Collaboration between research producers and research consumers in this translational approach is critical to reduce the cancer burden at the population level, the ultimate measure of benefit to all people."

An early conceptualization and model for a "critical path" between research and action, developed in the context of smoking/tobacco, was advanced in 1985 by Peter Greenwald and Joseph Cullen (*J. Natl. Cancer Inst*., 74:543-551) who distinguished phases of cancer control research:

Basic Research & Epidemiology
↓
Phase I: Hypothesis development
Phase II: Methods development
Phase III: Controlled intervention trials
Phase IV: Defined population studies
Phase V: Demonstration and implementation
↓
Nationwide prevention and health services programs

In addition, Phases I-V incorporate "feedback loops", so new hypotheses and methods can be generated in concert with novel intervention efforts. The "take home message" from this

model is that the CBCRP expects researchers to actively consider where and how their results might find practical applications at the end of the "critical path." Thus, your research decision making and innovative approach should incorporate these elements when planning projects: (i) an awareness of the social (i.e., human and community) needs and environmental determinants of health and disease, (ii) limitations of current prevention, detection, prognosis, and treatment strategies, (iii) the state of the existing science for the topic being addressed, (iv) an understanding of the limitations and barriers that block translation to a higher level, and (v) a framework for visualizing the desired research outcome and potential benefit (practical uses).

Overview and conceptual framework: The CBCRP believes that each grant should be capable of advancing the topic under investigation along the "critical path." To provide an outline to get you started, we have developed the following chart, which derived and greatly expanded from Table 1 in the FDA's "Challenge and Opportunity on the Critical Path to New Medical Products" (http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html). For the "critical path" dimensions/levels we have added definitions and provided examples of activities relevant to both the "basic science/clinical" and the "public health/community/population/social science" disciplines.

Dimension/Level	**Definitions**	**Examples of activities**
Concept & hypothesis development	Discovery and exploration The links between the hypothesis and a research problem in breast cancer Considering problems from novel perspectives Initial tests in basic systems Establishing the basis for scientist-community interactions	Basic science/clinical track: ○ Assessing background information in breast cancer, other cancer types, and cell/biological models. ○ Developing new information on breast cancer through data collection. ○ Establishing relationships to breast cancer. ○ "Mining" basic science for new treatment, detection, and prognosis concepts. ○ Pilot testing of new compounds and detection/prognosis strategies. Community/population/intervention track: ○ Considering social needs, disparities, and community issues from new perspectives. ○ "Mining" basic science for new epidemiological, behavioral,

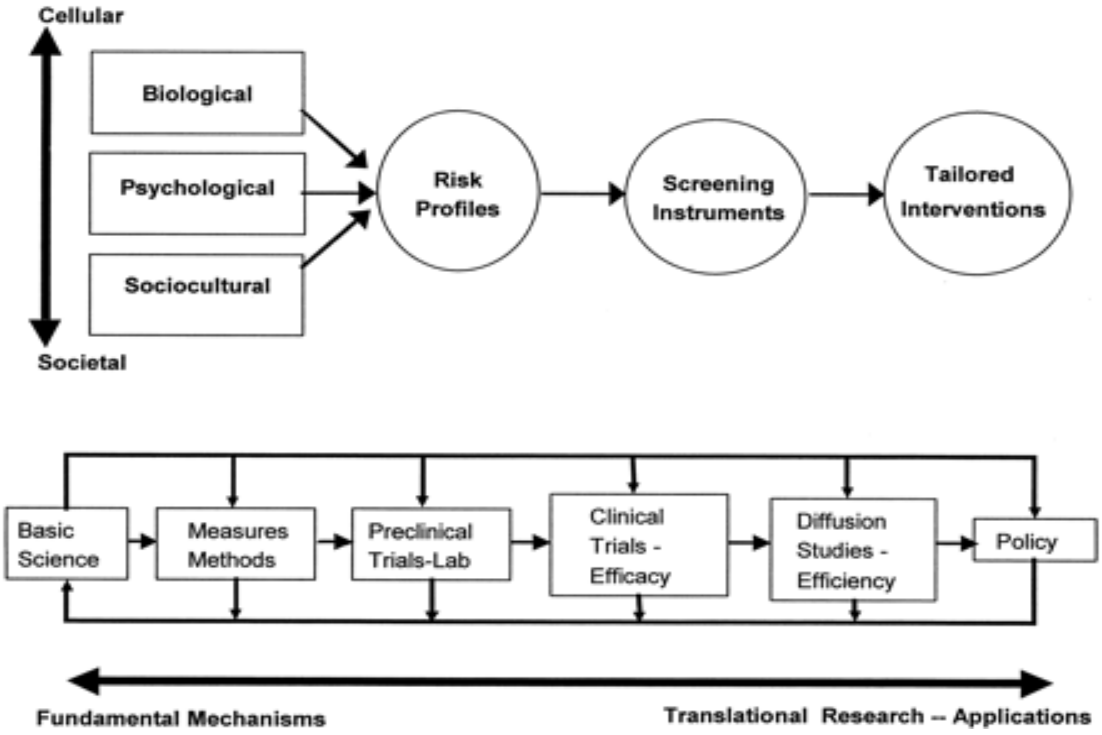
Dimension/Level	Definitions	Examples of activities
		psychological, sociocultural or policy concepts. o Conceptualizing possible interventions. o Planning culturally appropriate, acceptable, and feasible delivery approaches for new community-based interventions and prevention strategies. o Identifying target populations and establishing new collaborations. o Demonstrating or gaining trust and acceptance by the community. o Pilot data collection and field methodology developed. (Cancer control phase I --Cullen & Greenwald model)
Methods development and establishing "proof-of-principle"	Obtaining significant data to substantially support the hypothesis and point the direction for future work Establishing direct relevance to breast cancer in the basic science, clinical, or community settings Active scientist-community "partnering" in the research "Multi-disciplinary" collaborations (researchers in different disciplines work <u>independently</u> or	<u>Basic science/clinical track:</u> o Studies in model systems. o Integration into and challenging existing information on breast cancer. Publication. o Early pre-clinical phases (e.g., rational drug design, validate lead compounds). o Showing the potential to challenge and improve upon existing therapies and detection/prognosis standards. <u>Community/population/intervention track</u>: o Refine prevention strategies and collaborative networks. o Preliminary field tests of epidemiological hypotheses, policies or intervention methods and delivery systems. o Determination of outcome and process variables. o Development of measurement tools and data collection procedures. [Cancer Control Phases II and III (small trials) —Cullen & Greenwald model]

Dimension/Level	Definitions	Examples of activities
	sequentially on a common problem) Testing in small populations & initial data gathering	
Developmental and testing phase	Formulating a strategy for practical application Stimulate interest in other researchers and "interdisciplinary" collaborations (researchers working jointly to address a common problem) Generation of derivative concepts (feedback loop) Demonstrating efficacy or utility in a human	Basic science/clinical track: o Significant findings showing a clear connection to the disease. o Formulation and testing in animal models. o Publication and dissemination. o Late pre-clinical studies and early (Phase I & II) clinical trials. o Analysis of target groups and cost effectiveness. o Definitive links to target populations for detection, prognosis, treatment strategy. Community/population/intervention track: o Larger scale testing of epidemiological hypotheses, policies, or interventions in a well-defined populations enabling

Dimension/Level	Definitions	Examples of activities
	detection, prognosis, or therapeutic setting. Researchers and community groups "partner" and reach common goals	generalization to ultimate target populations (efficacy trial). o Systematic testing of epidemiological hypotheses, policy proposals, or community-based intervention in a larger population under "real-world" conditions (effectiveness trial). o Publication and dissemination. [Cancer Control Phases III (larger trials) & IV—Cullen & Greenwald model]
Implementation & translation	Wide acceptance of concept Improvements for detection, diagnosis, prognosis, and treatment Tangible social benefit New public health policies evolve from community-driven needs and researcher-driven outcomes to decrease disparities in detection, treatment, and disease burden Prevention and lowering risk for breast cancer	<u>Basic science/clinical track:</u> o Final basic research studies to validate a new clinical approach. o Feedback loop to stimulate new concepts to be tested (level #1) o Phase III & IV clinical trials. o Application of new therapies and chemoprevention approaches. o Advancing the standard of care. <u>Community/population/intervention track</u>: o Demonstration and implementation on a large scale. o Diffusion studies to other populations and communities. o Integration into cancer control health policy. o Interventions to lower disease incidence and mortality. (Cancer Control Phase V—Cullen & Greenwald model)

Finally, a major "critical path" limitation is the absence of cross-talk between disciplines. "Basic/clinical" and "public health/social/population/community" researchers often work apart. Thus, the CBCRP is asking researchers to <u>consider and explore avenues of research communication and common interest that allow the different disciplines to become integrated and lead to practical applications directed at breast cancer.</u> This approach was recently

presented by Best et al. (*Cancer Epidemiology Biomarkers & Prevention*,12:705-712),who proposed the term "transdisciplinary research." "*Transdisciplinarity* is a process by which researchers work jointly using a shared conceptual framework that draws together discipline-specific theories into a new synthesis of concepts, methods, measures, and approaches to address a common problem."



Final thoughts: Provide a brief, thoughtful discussion of how your research project would advance along a "critical path" to take your topic from one level to the next and provide practical applications. How might your innovative research "make a significant difference" and provide "transdisciplinary links" between the basic science, clinical, and public health/social/population/community research landscapes?

Appendix C: Other CBCRP Application Policies and Guidelines

Eligibility and Award Limits

1. **Any individual or organization in California may submit an application**. The research must be conducted primarily in California by Principal Investigators who are resident 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. **Applicants at California-based Nonprofit Institutions**: CBCRP will accept applicants from PIs at non-profit organizations or institutions, provided that the organization can manage the grant and demonstrate financial health. The organization must also meet our liability insurance requirements. If the application is recommended for funding, the University will collect additional information, such as tax ID numbers and financial reports, to review the organization during the pre-funding process to ensure all financial management and project management eligibility criteria can be met.
2. **We encourage researchers new to breast cancer to apply.** Applicants who have limited experience in breast cancer research should collaborate with established breast cancer researchers.
3. **Multiple applications and grant limits for PIs.** A PI may submit more than one application, but each must have unique specific aims. For Cycle 30 applicants are limited to a maximum of two (2) grants either as PI or co-PI, and these must be in different award types. The Program and Policy Initiative grants are not included in this limit. A PI may have more than one Program and Policy Initiative grant in a year.
4. **University of California Campus Employees:** 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 on Applications from PIs with Delinquent Grant Reports

PIs with current RGPO 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 an application to 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 CBCRP to allow an extension of any report deadlines.

Confidentiality

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 CBCRP makes public, (i) the title, principal investigator(s), the name of the organization, and award amount in a "Compendium of Awards" for each funding cycle, (ii) the costs (both direct and indirect) in CBCRP's annual report, (iii) the project abstract and progress report abstracts on the CBCRP website. 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.

Award Decisions

Applicants will be notified of their funding status by February 1, 2024. The written application critique from the review committee, the merit score average, component scores, and programmatic evaluation are provided at a later time. Some applications could be placed on a 'waiting list' for possible later funding.

Appeals of Funding Decisions

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). The **period open for the appeal process is within 30 days of receipt of the application evaluation** from the Program office. Before submitting appeals, applicants are encouraged to talk about their concerns informally with the appropriate program officer or the CBCRP program director.

Final decisions on application funding appeals will be made by the Vice President for Research & Innovation, University of California, Office of the President. 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.

The full appeals policy can be found in the online the University of California, Office of the President, "RGPO Grant Administration Manual – Section 5: Dispute Resolution":

https://www.ucop.edu/research-grants-program/_files/documents/srp_forms/srp_gam.pdf

Pre-funding Requirements

Following notification by 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:

1. Supply approved indirect (F&A) rate agreements as of the grant's start date and any derived budget calculations.
2. Supply any missing application forms or materials, including detailed budgets and justifications for any subcontract(s).
3. IRB applications or approvals pertaining to the award.
4. Resolution of any scientific overlap issues with other grants or pending applications.
5. Resolution of any Review Committee and Program recommendations, including specific aims, award budget, or duration.
6. Modify the title and lay abstract, if requested.

Publications Acknowledgement

All scientific publications and other products from a RGPO-funded research project must acknowledge the funding support from UC Office of the President, with reference to the specific CBCRP funding program and the assigned grant ID number.

Open Access Policy

As a recipient of a California Breast Cancer Research Program (CBCRP) grant award, you will be required to make all resulting research findings publicly available in accordance with the terms of the *Open Access Policy* of the Research Grants Program Office (RGPO) of the University of California, Office of the President (UCOP). This policy, which went into effect on April 22, 2014, is available here: https://www.ucop.edu/research-grants-program/grant-administration/rgpo-open-access-policy.html.

Grant Management Procedures and Policies

All CBCRP grant recipients must abide by other pre- and post-award requirements pertaining to Cost Share, Indirect Cost Rates, Monitoring & Payment of Subcontracts, Conflict of Interest, Disclosure of Violations, Return of Interest, Equipment and Residual Supplies, Records Retention, Open Access, and Reporting. Details concerning the requirements for grant recipients are available in a separate publication, the University of California, Office of the President, "***RGPO Grant Administration Manual***." The latest version of the Manual and programmatic updates can be obtained from the Program's office or viewed on our website: http://www.ucop.edu/research-grants-program/_files/documents/srp_forms/srp_gam.pdf

Contact Information

Technical support and questions about application instructions and forms should be addressed to the Research Grant Programs Office Contracts and Grants Unit:
RGPOGrants@ucop.edu

For scientific or research inquiries, please contact:
Sharima Rasanayagam, PhD
Environmental Health & Health Policy Program Officer, CBCRP
sharima.rasanayagam@ucop.edu
(510) 987-9216

The California Breast Cancer Research Program is part of the Research Grants Program Office of the University of California, Office of the President.