Request for Proposals (RFP)

Many Pathways to Cancer: Identifying Exposures Linked to the Key Characteristics of Carcinogens

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

Deadline to apply:
November 9, 2023

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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.

Many Pathways to Cancer: Identifying Exposures Linked to the Key Characteristics of Carcinogens

Available Funding

The goal of this RFP is to address the urgent need to identify chemicals and other environmental exposures that influence the development of breast cancer by (1) developing new assays to fill gaps in coverage for key characteristics of carcinogens relevant for breast cancer, (2) analyzing results from existing assays and/or (3) identifying new biomarkers relevant to the key characteristics of carcinogens that can be applied as early effect markers for breast cancer in studies in women.

CBCRP intends to fund up to three proposals for a maximum duration of three years and $560,000 maximum total direct costs each.

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

For more than two decades, researchers working to understand cancer have identified changes that occur in cells and tissues to promote carcinogenesis. Studies examining these "hallmarks of cancer" have led to the development of therapeutics to treat cancers including breast cancer. Yet, studies focusing on the features of cancer as a disease have provided few insights into the identification of environmental agents that act as carcinogens. Relatively new approaches are now asking whether there are shared characteristics of the agents that cause cancer, and whether reliable assays can be developed to define these "key characteristics" of carcinogens. This RFP aims to address three related challenges:

1) Current methods used to screen and test chemicals for carcinogenic properties do not fully encompass the diverse mechanisms by which agents may cause breast cancer;
2) Data that are already available from in vitro and short-term in vivo bioassays could be better leveraged to predict outcomes relevant to breast cancer, prioritize agents for further testing, and improve the identification of new breast carcinogens;
3) There is a need to identify biomarkers for a broader range of effects relevant to breast carcinogens and apply these biomarkers to studies of women to characterize risk in highly exposed populations.

Background/Justification

Female breast cancer has become the most commonly diagnosed cancer type in the world. Breast cancer is a deadly disease and is now the most common cause of cancer death in women globally. Understanding the causes of breast cancer is vital to understanding these alarming trends and for informing public health actions to reduce women's exposures to breast carcinogens. Yet, breast cancer-causing chemicals remain largely unidentified. Of the 121 agents classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Group 1), only six had "sufficient" evidence for risk of breast cancer in humans: alcoholic beverages, diethylstilbestrol, estrogen-progestogen contraceptives and menopausal therapy, as well as X- and gamma-radiation. A further four Group 1 carcinogens had "limited" evidence for breast cancer in humans: tobacco smoking, polychlorinated biphenyls (PCBs), ethylene oxide, and estrogen-only menopausal therapy. Among the 89 agents considered probably carcinogenic (Group 2A) and the 315 agents considered possibly carcinogenic (Group 2B), "limited" evidence for breast cancer in humans was found by IARC for night shift work (Group 2A), the organochlorine pesticide dieldrin (Group 2A), and digoxin, a medication used to treat heart failure and abnormal heart rhythms (Group 2B).

These IARC findings illustrate the important role of epidemiological studies in the identification of cancer hazards, but they also illustrate that human population studies have limitations for identifying new breast carcinogens. Breast cancer studies in women are limited in number because they are costly and take years or decades to complete. In addition, these studies may have limitations in characterizing women's breast cancer risks because of deficiencies in the size of studies (e.g., inadequate sample sizes), confounding (the distortion of the association between an exposure and health outcomes by an extraneous third variable), and limited characterization of exposures (for example, about the source of exposures or during times in the life cycle when the breast is most vulnerable).

Lifetime rodent cancer bioassays can help to fill this gap. Previous research shows that some human breast carcinogens (e.g., ethanol, diethylstilbestrol, estradiol, various forms of radiation, alteration of the light-dark schedule) also cause mammary gland tumors in experimental animals. (Rudel, Attfield, Schifano, & Brody, 2007). However, the number of *in vivo* rodent bioassays conducted using intact animals is declining in number. Only a fraction of the ~75,000 chemicals in the Toxic Substances Control Act Chemical Substance Inventory having been formally evaluated by the National Toxicology Program (NTP), and fewer than 1000 have been tested for carcinogenicity (Guyton et al., 2009). Even fewer have been examined specifically for mammary carcinogenicity. Furthermore, recent evaluations of US EPA registration documents for pesticides identified 28 pesticides that induced mammary cancers in rodent cancer bioassays, yet the EPA's risk assessment dismissed the evidence for 19 of these chemicals (Cardona & Rudel, 2020).

In contrast to the relative paucity of data from *in vivo* rodent bioassays, data on cancer mechanisms from human biomarker studies and *in vitro* cell culture models are increasing in both volume as well as in the number and types of endpoints examined. These mechanistic data provide an important opportunity to address the urgent need to fill gaps in knowledge concerning breast cancer causation and are the focus of this project. CBCRP has supported science to ensure that the advances in this field are specifically relevant to breast cancer. However, the knowledge gaps and failures to translate knowledge into policy remain enormous. Decision-makers need new assays that cover the many pathways to breast cancer, as well as new studies to provide evidence that *in vitro* tests are relevant to humans, so they may inform policy decisions.

Carcinogens can act through multiple mechanisms and pathways to induce cancer (Guyton et al., 2009). Although the number of ways by which cancer-causing agents induce cancer can be extensive, these mechanisms can be grouped into a limited number of categories. In 2012, two workshops organized by the IARC noted that human carcinogens often share one or more characteristics related to the multiple mechanisms by which agents cause cancer. These ten "key characteristics" of carcinogens comprise the chemical and biological properties of established human carcinogens (Smith et al., 2016). The key characteristics include a range of distinct properties of established carcinogens (See Table 1).

Table 1: Ten Key Characteristics of Carcinogens, from (Smith et al., 2016)

1	Is electrophilic or can be metabolically activated
2	Is genotoxic
3	Alters DNA repair or causes genomic instability
4	Induces epigenetic alterations
5	Induces oxidative stress
6	Induces chronic inflammation
7	Is immunosuppressive
8	Modulates receptor-mediated effects
9	Causes immortalization
10	Alters cell proliferation, cell death, or nutrient supply

Similar themes have emerged independently from other groups, creating synergies in laying the foundation to broaden consideration of how individual chemicals and more complex mixtures may cause cancer. For instance, work at the US NIEHS and US EPA described how chemicals that target multiple cancer-relevant pathways *in vitro* are more likely to be rodent carcinogens

in vivo (Kleinstreuer et al., 2013). Separately, in work initiated and supported by CBCRP, Schwarzman et al. (2015), investigated methods for identifying breast carcinogens. These authors found that a broad range of different endpoints, spanning all ten of the key characteristics of carcinogens, are relevant to consider in the identification of breast carcinogens. Importantly, these authors also noted significant gaps in coverage in federal testing approaches, including the absence of bioassays to evaluate effects such as altered mammary gland development and progesterone receptor activity, among others. These testing deficits hamper identification of breast carcinogens.

Another landmark effort was the Halifax project (Goodson et al., 2015), which assembled experts to review evidence on whether various chemical and environmental agents—acting alone or in concert, including at low exposures—can induce the "hallmarks of cancer" (Hanahan & Weinberg, 2000, 2011). While the key characteristics describe how agents (e.g., carcinogens) induce one or more cancer pathways, the hallmarks describe the biology of the cancers themselves. The hallmarks of cancer therefore include a range of distinct properties of cancer cells and tumors (Table 2).

Table 2: Ten Hallmarks of Cancer, from (Hanahan & Weinberg, 2011)

1	Sustained proliferative signaling
2	Evasion of growth suppressors
3	Avoidance of immune destruction
4	Replicative immortality
5	Tumor-promotion inflammation
6	Invasion and metastasis
7	Induction of angiogenesis
8	Genome instability and mutations
9	Resistance to cell death
10	Deregulation of cellular energetics

To date, the majority of cancer research has focused on understanding the pathways that occur within cells and tissues to promote tumorigenesis and carcinogenesis. Until recently, much less effort has been spent to identify assays that can be used to identify new carcinogens. Current and emerging assays can be used to measure the key characteristics of carcinogens and experts have recommended areas for new assay development (Smith et al., 2016). For instance, new

assays are needed to evaluate systemic immune status and to leverage methods such as mass cytometry to interrogate multiple immune cell types and functions concomitantly.

In all, these developments have opened opportunities for applying new research findings on a diversity of relevant mechanisms in identifying new cancer hazards. This is now being done at IARC (Samet et al., 2020) and by other authoritative bodies and regulatory agencies such as the National Toxicology Program Report on Carcinogens, the U.S. EPA, and the California EPA. As such, the outputs of the CBCRP-funded projects will be important for advancing the identification of breast carcinogens, with potential impacts at the state, national and international levels.

Research Gaps to Address

There are several major challenges ahead:

a) **The available screening and testing methods do not fully encompass the diverse mechanisms by which agents may cause breast cancer.** The known or suspected breast carcinogens identified by IARC from epidemiological studies exhibit a range of key characteristics of carcinogens. Many are endocrine disrupting compounds that predominantly modulate estrogen receptor-mediated effects. Others are predominantly genotoxic (e.g., ethylene oxide). Still other potential and known breast carcinogens exhibit many of the key characteristics of carcinogens (radiation, tobacco smoking, alcoholic beverages). There are numerous methods for evaluating some characteristics of carcinogens (e.g., those that induce genotoxicity), but poor methods available for evaluating others (e.g., the effect of chemicals on mammary gland development and maturation). There are validated methods for identifying chemicals that bind to and activate estrogen receptors, but methods are lacking for identifying chemicals that interfere with other relevant hormone receptor systems such as the progesterone receptor; methods are also needed to identify chemicals that increase the synthesis of estradiol or progesterone or affect their degradation. Importantly, addressing these gaps requires concerted efforts to discover which key characteristics of carcinogens are most relevant to breast cancer causation. Ultimately, it is essential to develop low-cost, reproducible, accurate and high-throughput methods to identify breast carcinogens. Addressing this knowledge gap will make it possible to quickly and cost-effectively screen large numbers of chemicals for effects on the breast.

b) **The results of *in vitro* and short-term *in vivo* screening tests have not been fully leveraged to 1) predict *in vivo* outcomes relevant to breast cancer, 2) prioritize agents for further testing and assessment and 3) advance identification of new breast carcinogens.** Carcinogenesis is a disease of tissues, and thus involves complex biological processes that occur *in vivo*, including several that require the whole animal to evaluate. However, chronic *in vivo* cancer bioassays are low-throughput and there can be challenges in interpreting the findings obtained from these approaches. As *in vivo* carcinogenesis assays decline in number in favor of *in vitro* and short-term *in vivo* screening tests, demonstrating whether such screening tools can predict human effects

is paramount. There are substantial efforts to develop a broader range of simplified and rapid methods to screen suspected carcinogens *in vitro*. However, there are gaps in the methods to interpret and apply these data (other than on genotoxicity) in prioritization exercises and to support decision-making. Importantly, some current methods directly relevant to identifying breast carcinogens (including validated methods to evaluate chemicals that bind to estrogen receptors) have not been used for risk assessment purposes. For example, tools from ToxCast (the high-throughput screening methods developed by the EPA to evaluate dozens of biological pathways with hundreds of *in vitro* assays) have been used to predict a set of chemicals that have estrogen receptor agonist properties. Yet, ToxCast data have not been applied in hazard and risk characterizations for these compounds. Although some work has focused on approaches to translate *in vitro* findings to *in vivo* outcomes for estrogen receptor binding assays (Casey et al., 2018), for the key characteristics of carcinogens, this remains another important research need. The potential to immediately inform policy by applying the "key characteristics of carcinogens" framework to existing data is illustrated by the recent study that reviewed pesticide registration documents that found 28 were linked to mammary gland tumors (Cardona & Rudel, 2020). For the majority of these chemicals, the evidence of carcinogenicity was ignored, most likely because the chemicals act via endocrine disruption rather than mutagenesis. The decision to ignore endocrine-mediated effects of these pesticides is in spite of the 8th key characteristic of carcinogens, e.g., chemicals that modulate receptor-mediated effects. Five of the breast cancer promoting chemicals are widely used - IPBC, triclopyr, malathion, atrazine and propylene oxide -- showing the potential for immediate translational relevance of analyses following this model.

c) **Important avenues to identify breast carcinogens in exposed women, and to characterize risk in highly exposed populations, remain under-explored.** Data from molecular biomarker studies in humans are especially influential in decision-making by health agencies including the California EPA, the US EPA, and the IARC. For example, micronuclei frequency in peripheral lymphocytes has been shown to be predictive of overall cancer risk (Bonassi et al., 2007), and these data have been influential in classification of breast carcinogens such as ethylene oxide. The National Academy of Sciences has promoted the development of biomarkers that can be applied in studies of humans. There is a particular need to expand the development of biomarkers to address a broader range of effects relevant to breast carcinogens, and to apply them in studies of women addressing a wider set of potential exposures. Short-term studies in women exposed to suspected carcinogens (for example, in women working in occupations with likely high exposures such as hairdressing and home or commercial cleaning, building on CBCRP-funded work on women firefighters) can be conducted using biomarkers that are specific to breast cancer, and that are relevant to key characteristics of the agents that cause this disease. In these same studies, exposure biomarkers can be incorporated to clarify associations of effects with specific suspected carcinogens. These studies have

the potential to become powerful tools for providing evidence in exposed women that can be directly applied in hazard and risk characterization of breast carcinogens.

Filling these gaps will substantially improve understanding of the etiology of breast cancer and immediately enhance methods and data for risk assessment and decision-making to reduce exposures relevant to breast cancer.

Approaches and Methods

A variety of possible approaches are described here, including new experiments and analysis of existing data.

1. Development of new *in silico*, *in vitro*, and/or short-term *in vivo* assays to fill gaps in coverage of the assays for key characteristics of carcinogens relevant for breast cancer causation. As background, expert groups have recently published compilations of the assays relevant to the key characteristics of carcinogens (Smith et al., 2020) and the key characteristics of endocrine disruptors (La Merrill et al., 2020) and identified important opportunities for future assay development, targeted to breast carcinogenesis. Assays for measuring some of the key characteristics have already been well advanced (e.g., estrogen receptor agonism) and thus are low priority for this initiative. Others (e.g., progesterone receptor agonism, steroidogenesis) are high priority for the development of low-cost, reproducible, accurate and high-throughput methods, including methods that can be used *in vitro* to screen chemicals and mixtures, or *in vivo* methods for use in toxicology and epidemiology. **The ultimate goal is to develop highly predictive methods to identify potential breast carcinogens that can be prioritized for further testing and/or hazard identification and classification.** The agents that are known to cause breast cancer in humans and/or mammary carcinogenesis in experimental animals may be valuable to apply in assay development and screening efforts. Further, testing results on agents that have already been prioritized for future evaluation by IARC (IARC Monographs Priorities Group, 2019), national or state agencies could be an important output of this effort.

2. Compile published and publicly available results from *in silico*, *in vitro* and short-term *in vivo* assays that are relevant to key characteristics of carcinogens and specifically to breast carcinogenesis. **The overall aim is to advance the use of data from these new approach toxicology methods to 1) predict *in vivo* outcomes relevant to breast cancer, 2) prioritize agents for further testing and assessment, 3) aid identification of new breast carcinogens, and 4) inform the integration of these data into policy.** The agents that are known to cause breast cancer in humans and/or induce mammary carcinogenesis in experimental animals can be used as important benchmarks in this effort. Further, testing results for agents that have already been prioritized for upcoming evaluations by IARC (i.e., (IARC Monographs Priorities Group, 2019)), national or state agencies could be compiled as an important aspect of the effort. These projects should specify how regulatory toxicology testing could add mammary-relevant endpoints to capture relevant effects. Specific options for projects include:

a. Compile and review published data to 1) identify *in vivo* endpoints that are linked to breast cancer; 2) determine the degree to which these are predicted by *in vitro* screening data; and 3) based on the results, develop a list of prioritized agents for further screening, testing and/or hazard identification. For example, estrogen receptor binding assays have been evaluated for their predictiveness of responsiveness in the uterotrophic assay (Casey et al., 2018); how predictive are such assays for mammary carcinogenesis?

b. Evaluate whether prediction can be improved by incorporating results from multiple test systems (e.g., from predictive models for receptor binding, related tests, or from assays on different types endpoints relevant to other key characteristics of carcinogens).

c. Develop *in silico* methods to predict chemicals of concern for breast cancer based on structural and other available chemical features, using established human breast carcinogens and/or mammary carcinogens to develop and validate the prediction model. Apply the approach to agents of unknown carcinogenicity. From this, develop a list of prioritized agents for further screening, testing and/or hazard identification.

3. **Identify new biomarkers of endpoints** relevant to the key characteristics of carcinogens **that can be applied in short-term studies of suspected breast carcinogens in women**. These biomarkers would focus on biological endpoints of carcinogenic effects, rather than biomarkers of exposure. Successful projects might plan to evaluate such biomarkers in priority populations, e.g., occupational settings where women are exposed to suspected breast carcinogens, including complex mixtures, such as in firefighting or hairdressing.

Resources to Be Used or Considered for Use

The resources that will be required for applicants to respond to this proposal will differ based on whether applicants choose to address gap a, b, or c described above.

For gap a (the development of low-cost, reproducible, accurate and precise methods to identify breast carcinogens), applicants will need access to laboratory facilities.

For gap b (leveraging the results of in vitro and short-term in vivo screening tests), applicants should include experts in chemical prioritization methods.

For gap c (identification of biomarkers that are specific to breast cancer), applicants should have access to biological materials collected from cohorts including women with breast cancer.

Dissemination Plan

Each application should identify how methods and results will be disseminated and translated into action to reduce the risk of breast cancer. Clearly describe the novelty and potential application of results.

Projects should include plans to inform stakeholders about the research early on and to include stakeholders in designing dissemination and translation plans so that they are tailored to reach intended audiences via effective methods. Proposals should specify skills and resources for these purposes. Dissemination and translation plans should address the research community, policy-makers at multiple levels, cancer-focused organizations, breast cancer and community advocates, and the public. Important stakeholders for this project include California EPA's Office of Health Hazard Assessment, as well as advocacy groups and the public interested in identifying breast carcinogens. Summary reports in at least two languages, accessible to laypersons and to policy makers will be required.

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 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 three proposals for a maximum duration of three years and $560,000 maximum total direct costs each. 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 the following criteria:

- **Innovation.** Extent to which the project will (1) develop highly predictive methods to identify potential breast carcinogens that can be prioritized for further testing and/or hazard identification and classification; (2) advance the use of data from new approach toxicology methods to accomplish the aims of the RFP; or (3) identify new biomarker endpoints that map onto the aims of this initiative. Are the concepts and hypotheses appropriately speculative and exploratory. Are the methods novel and original?
- **Impact.** Potential for the project, if successful to develop novel methods that can impact current testing modalities, hazard identification, and/or classification for breast cancer relevant chemicals. Does the research address relevant mechanisms, methods and/or models for testing chemicals at state, national or international levels. Will the project identify new biomarker endpoints that can be applied in short-term studies of suspected breast carcinogens. Will the dissemination plan be effective in sharing the findings of the project.
- **Approach.** The quality, organization, and presentation of the research plan, including methods and analysis plan. Does the project plan clearly identify the research gap it aims to address? 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? Do the research questions map directly to the research gaps that are the focus of the application? 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; 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 up to 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, 2027 for a three year project.

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.

The maximum duration is 3 years, and the direct costs budget cap is $560,000.

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,

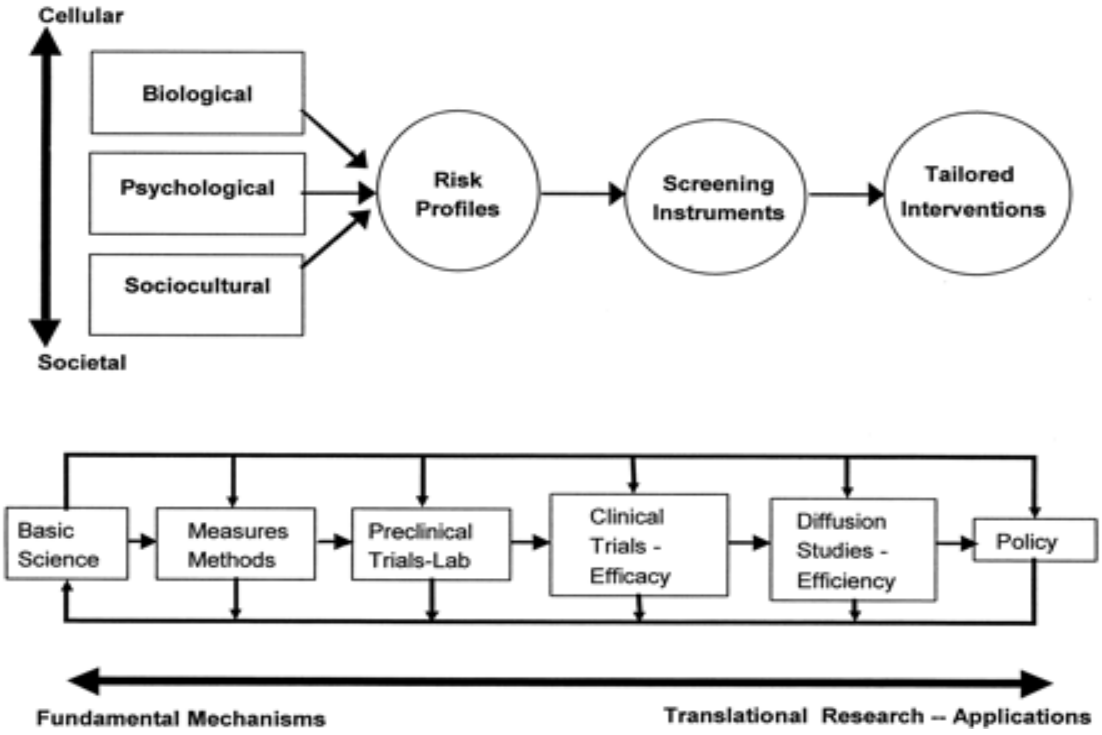
Dimension/Level	Definitions	Examples of activities
		psychological, sociocultural or policy concepts. o Conceptualizing possible interventions. o Planning culturally appropriate, acceptable, and feasible delivery approaches for new community-based interventions and prevention strategies. o Identifying 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.