CALIFORNIA
Breast Cancer
Research Program

Request for Proposals (RFP)
Chemical Safety Testing to Reduce Breast Cancer Risk

California Breast Cancer Research Program
California Breast Cancer Prevention Initiatives

Deadline to apply
October 22, 2014

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About the California Breast Cancer Research Program and the California Breast Cancer Prevention Initiatives

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

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

- The 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
- The CBCRP is funded through the tobacco tax, 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 $8.5 million for breast cancer research.
- Ninety-five percent of our revenue goes directly to funding research and education efforts
- The CBCRP supports innovative breast cancer research and new approaches that other agencies may be reluctant to support.
- Since 1994, the CBCRP has awarded over $230 million in 939 grants to 107 institutions across the state. With continued investment, the CBCRP will work to find better ways to prevent, treat and cure breast cancer.

CBCPI Priority Areas

In 2004, the CBCRP launched its Special Research Initiatives. The CBCRP's Breast Cancer Research Council devoted 30 percent of CBCRP research funds to support coordinated, directed, and collaborative research strategies that increase knowledge about and create solutions to both the environmental causes of breast cancer and the unequal burden of the disease.

In March 2010, CBCRP's Council decided to build on the existing SRI by devoting 50 percent of CBCRP research funds between 2011 and 2015. This new effort is titled the California Breast Cancer Prevention Initiatives (CBCPI). Approximately $24 million will be dedicated to directed, coordinated, and collaborative research to pursue the most compelling and promising approaches to:

1. Identify and eliminate environmental causes of breast cancer.
2. Identify and eliminate disparities/inequities in the burden of breast cancer in California.
3. Population level interventions (including policy research) on known or suspected breast cancer risk factors and protective measures.
4. Targeted interventions for high-risk individuals, including new methods for identifying or assessing risk.

To focus these research efforts, the CBCRP issued a Request for Qualifications (RFQ) to fund a team to collaborate with the CBCRP to develop and implement the California Breast Cancer Prevention Initiatives

planning process. In 2010, the grant was awarded to Tracey Woodruff, PhD, MPH, Professor and Director of the University of California, San Francisco, Program on Reproductive Health and the Environment (PRHE).

CALIFORNIA Breast Cancer Research Program

Chemical Safety Testing to Reduce Breast Cancer Risk

Available Funding

This initiative aims to advance the science of chemical testing and the understanding of biological pathways to breast cancer with the ultimate goal of developing policies related to breast cancer prevention.

CBCRP intends to fund two types of projects:

- Up to four projects, each with a maximum direct cost budget of $900,000 and a maximum duration of 3 years that develop and test new methods for screening chemicals for their potential as breast carcinogenesis.
- One project for up to $150,000 in direct costs and a maximum duration of 3 years to identify synergies among the funded chemical testing projects and to aid in the translation of research outcomes to policy.

Completed responses to this RFP are due by the deadline: noon, October 22, 2014. Signed face pages of submitted applications must be emailed to RGPOgrants@ucop.edu by 5pm **October 29, 2014**. The project start date is March 1, 2015.

For more information and technical assistance, please contact:
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Research Questions

Lack of data on toxicity makes the task of evaluating the impacts of exposure to many chemicals on breast cancer risk unachievable. There is a need to reform chemicals policies in ways that would mandate such testing and take action on the basis of what is known. But it is also critical to create a toxicity testing strategy for breast cancer that would identify biological mechanisms that play a role in breast cancer and develop new tests to screen for activity in these mechanisms. CBCRP began funding an earlier round of improved chemical testing methods in 2011. The results of these efforts are beginning to materialize, though further investigation is needed to advance the field. Additionally, the lessons learned through the first and second phase of this research need to be interpreted for synergies and translated so the findings can be relevant to policy interventions to prevent breast cancer. *This project aims to advance the science of chemical testing and the understanding of chemical-induced*

biological pathways to breast cancer with the ultimate goal of improving policy development related to breast cancer prevention.

Two types of projects are proposed:

1. Develop new testing methods for identifying and testing chemicals for their potential to contribute to breast cancer, with the following areas of interest:

    a. Advance the understanding of chemically-induced biological pathways to breast cancer as a basis for designing chemical safety tests,
    b. Develop or improve tests targeting biological gaps in current screening/testing strategies in order to improve tools for identifying potential breast carcinogens,
    c. Test additional chemicals in existing or new tests to identify toxicants relevant to mammary carcinogenesis and development, and/or
    d. Evaluate the predictive validity of suites of tests using existing or newly generated data.

2. Identify synergies between CBCRP-funded projects (previously funded and concurrently funded chemical testing projects) and translate the outcomes for policy development relevant to breast cancer.

Background/Justification

One of the most formidable challenges to understanding the role chemical toxicants may play in breast cancer is the dearth of publicly available information on basic hazard data for the tens of thousands of chemicals now in common use in the world. Federal and state regulations do not systematically require manufacturers to generate and disclose information on chemicals to the public, government, or downstream businesses (Wilson, 2008). Indeed 95% of all chemicals have not yet undergone basic toxicity testing. Therefore, there exists a data gap on the properties of common chemicals in commerce. This lack of basic information impacts consumers, and the private and public sectors: businesses wanting to adapt greener practices are hampered by lack of basic data on the chemicals that they purchase; consumers cannot choose safer products because they have an inadequate basis for comparing them; and regulatory agencies do not have the information they need to control and prevent risks to human health and the environment. This lack of data also interferes with our ability to learn about the contribution of chemical exposure to the incidence and mortality of breast cancer.

The Toxic Substances Control Act (TSCA), which became law in 1976, is the linchpin of U.S. chemicals policy. TSCA requires little or no human health testing for the 62,000 chemicals that came onto the market before 1979 or the 20,000 chemicals introduced into commerce since then. The grandfathered chemicals still constitute the vast majority of chemicals in circulation. For example, 92 percent of the high-volume chemicals on the market today entered the marketplace prior to 1979 and thus are exempted from testing (Wilson et al., 2006). A voluntary federal program to provide just screening level hazard data for the highest volume chemicals has foundered (Dennison 2007).

Currently, available toxicology data on new chemicals must be reviewed by the EPA. However

chemical companies are not required to provide any toxicology data to EPA when they begin marketing their new chemicals and in practice provide very little such information. Nor does the EPA conduct such testing itself. Rather, the EPA relies on modeling to predict potential toxicity. The U.S. General Accounting Agency has found EPA's protocols under TSCA insufficient to predict public health consequences (GAO, 2005). Accordingly, most new chemicals reach the market with no actual publically available toxicity data. TSCA compels manufacturers to provide toxicity and exposure data only after the EPA demonstrates that a risk exists, yet the EPA cannot demonstrate risk without toxicity and exposure data; U.S. chemicals policy is held in the grip of logical paralysis (Wilson and Schwartzman 2008).

The National Research Council's *Toxicity Testing in the 21st Century: A Vision and a Strategy* (National Academies Press, 2007), calls for development of new chemicals screening technologies to replace existing ones, and the US EPA and the National Toxicology Program have announced an initiative to develop new, more cost-effective screening methodologies. In this initiative, they specifically requested collaborators to contribute information to improve relevance of the target-organ specific testing, for example the mammary gland. Thus, this new program should provide an important opportunity to improve the relevance of chemicals testing programs to the identification and understanding of environmental breast cancer risk. However, this opportunity will only be realized if new research fosters the development and validation of tests targeting indicators relevant to the induction and formation of breast cancer.

Reliable tests are needed for *all* the known and suspected mechanisms by which chemicals can contribute to breast cancer: tumor promotion, tumor initiation, tumor enabling and developmental disruption. The first category, tumor initiation, is well-established, and there are many assays available that are synergistically informative in that they can test for different mechanisms of initiation. In contrast, the tumor promotion category is more undefined, and, while representing an accepted general mechanism(s) of carcinogenesis, it requires a battery of non-redundant assays such as those for estrogenic activity and other breast cell proliferating agents. Tumor enabling and developmental disruption categories have solid theoretical and clinical underpinnings, but have not traditionally been addressed for evaluating potential environmental carcinogens; and therefore lack established high throughput assays.

Chemical hazard identification needs to incorporate breast cancer-relevant screening and testing, including high throughput *in vitro* methods. Various efforts, including EPA's ToxCast^{TM} and NTP's High Throughput Screening Initiative (Tox21), are underway to develop and evaluate *in vitro* screening tests, but these efforts are not focused on breast cancer. In addition, improvements are needed in tests for chemicals that alter mammary gland development or susceptibility to cancer using *in vivo* or *in vitro* methods.

In 2009 CBCRP funded the Breast Cancer and Chemicals Policy project. The project sought to assess both existing toxicological tests and gaps in the availability of testing measures that could be used to prioritize which chemicals are of most concern for their links to breast cancer. This work resulted in the publication of *Pathways to Breast Cancer: A Case Study for Innovation in Chemical Safety Evaluation* (Schwarzman, 2010). This report was based on the outcomes obtained from convening a multidisciplinary panel of experts to:

a) Identify biological pathways relevant to breast cancer.

b) Identify tests that will pick up chemicals that have effects on these pathways and can differentiate active versus not active chemicals on a relevant pathway.

c) Identify a set of tests that discriminates potential breast carcinogens from non-carcinogens as determined in animal and human studies.

Results of this project highlight the need for additional work in all three of these areas. The project identified gaps in breast cancer-relevant tests and indicated the need to continue to develop new approaches (step "b"). Currently, tests are lacking for important pathways to breast cancer, including tests relevant to HER2, ER beta, various hallmarks of cancer such as limitless replication, expression of breast cancer relevant genes (CYP1B1 - enzyme in the metabolism of estrogen in the breast, CYP19/aromatase, other CYP enzymes, ER, HER2, PR, Notch, P53, Wnt, cyclin B1, CDK 1, b-catenin), and models of mammary gland developmental endpoints that affect susceptibility (Schwarzman et al 2010).

Importantly, many breast cancer-relevant chemicals have not yet been tested in existing tests; therefore tests may be made more relevant by using more realistic mammary gland tissue models. The development of a battery of toxicologically relevant and informative tests is inter-related with the need for a better understanding of biological pathways to breast cancer (step "a"). In addition, computational toxicology approaches are needed to identify sets of assays that predict potential breast carcinogens (step "c"). EPA's ToxCast™ program has published on approaches for liver tumors, cancer hallmarks, reproductive toxicity, and other endpoints, but this approach has not yet been extended to focus on breast cancer.

In 2011 CBCRP funded 5 projects to advance the science, which include (see *CBCRP Special Research Initiatives* funded projects at www.cabreastcancer.org/priorities/sri/research-underway.html for additional details):

1. Biologically Relevant Screening of Endocrine Disruptors
2. Xenoestrogen-Specific Perturbations in the Human Breast
3. Cell Bioassays for Detection of Aromatase Gene Activators
4. Biomarkers for Environmental Exposures in Breast Cancer
5. Building on National Initiatives for New Chemicals Screening

While important progress is being made with these efforts, there remains a great need to strengthen chemical testing methods, especially those methods that can be used to identify chemicals that are more likely increase breast cancer risk and/or alter endocrine signaling and/or mammary gland development and carcinogenesis.

Approaches (Methods)

Successful applicants should adhere to the following approaches/methods in developing their response to this RFP:

1) Applicants should construct their research plans to address two or more areas listed under Project Type I. Additionally, applicants may apply to address the need listed in Project Type 2

(one award expected, preferably in conjunction with an award under Project Type 1).

Project Type 1: Develop new testing methods for identifying and testing chemicals for their potential to contribute to breast cancer, with the following areas of interest:

A. Advance the understanding of chemically-induced biological pathways to breast cancer as a basis for designing chemical safety tests

The ability to identify potential breast carcinogens would be improved by research that better characterizes the biological processes that, when altered by chemical exposures, increase the development or progression of, or susceptibility to breast cancer. This includes identifying early events in a chemically-induced biological pathway—such as altered development of the mammary gland—that occur well "upstream" of tumor formation.

Better characterization of the relationships between chemical exposure, biological alterations, and the ultimate progression to breast cancer will improve the predictive value of any observed changes. More investigation is needed to identify pathways through which chemicals lead to breast cancer that are not yet identified as well as improving our understanding of pathways that have already been identified.

Mammary gland (MG) development is one area where research has been done, but much more is needed. Research is needed to develop experimental approaches to learn how MG development is disrupted and influences cancer susceptibility. How do chemicals alter MG development? What biological pathways are involved? How do these disruptions alter susceptibility to carcinogenesis? (Rudel 2011). Specific areas for research include:

- Develop models for evaluating and quantifying altered susceptibility to carcinogens, and determine the features of altered MG development that are influential.
- Develop sensitive exposure measures for hormones and growth factors that regulate MG development, including total steroid hormone (estrogen and progesterone) levels/activity, tissue-specific (liver, ovary, MG) endogenous steroid hormone (estrogen and progesterone) levels/activity; and, use these tools to explore the link between MG developmental disruption and subsequent mammary cancer.
- Identify early biomarkers of MG cancer effects (e.g., hyperplasia, immuno-histochemical markers, MG-specific gene markers, presence of nodules and bridging, changes in hormone levels, changes in hormone receptor levels, receptor sensitivity, effects on stromal-epithelial interactions) by utilizing banked MG tissue blocks, serum samples, and other stored tissues from longer term studies that observed MG tumors.
- Evaluate epigenetic changes in mammary epithelium and stroma following prenatal exposures to better understand early life programming and its connection to subsequent mammary cancer
- Characterize the role of epigenetic changes in mammary carcinogenesis.

Researchers proposing projects should explain the relevance of the pathway they propose to focus on to understanding how exposure to chemicals may influence breast cancer development; what type of high throughput test might come out of it; and, what in vivo indicator, biological effect and/or outcome they would hope to predict.

B. Develop or improve tests targeting biological gaps in current screening/testing strategies in order to improve tools for identifying potential breast carcinogens

The following are examples of needs for improving testing of potential breast carcinogens:

- Adapt existing assays to improve their relevance to breast cancer;
- Develop and validate new assays to evaluate biological processes important in chemically-induced breast cancer—both known and novel;
- Develop and validate higher throughput screening (HTS) methods with increased relevance to breast tissue and carcinogenesis; and,
- Develop models of normal breast tissue that can be used for *in vitro* testing.
- Develop rapid quantitative methods for systematic evaluation of mammary gland growth and development in juvenile rodents, so that altered mammary gland development can be more easily included as an outcome to evaluate in standard toxicology studies.

Potential focus for relevant testing improvements may include key biological targets in breast tissue related to mammary development, HER2 activation, progesterone receptor/activity, aromatase promoter regulation, prolactin effects or estrogen receptor β activity.

Researchers proposing projects should explain the relevance of pathway they propose to focus on to understanding how exposure to chemicals may influence breast cancer development; how the specific targeted biological key event, protein, or other cellular target improves over current testing/screening methods; what type of high throughput test might come out of it; and, what in vivo indicator, biological effect and/or intermediate outcome they would hope to predict as it relates to breast carcinogenesis.

C. Test additional chemicals in existing or new tests to identify toxicants relevant to mammary carcinogenesis and development

In order to expand the understanding of chemicals associated with breast carcinogenesis, mammary gland development and other breast cancer pathways, and to evaluate the relative ability of *in vitro* and other shorter-term testing models to identify these effects, chemicals need to be tested in both existing and new test systems. Assessment of existing tests and new and developing assays may clarify data gaps that are important to understand carcinogenic pathways which may be relevant in the mammary gland.

Potential work to inform this aim may include:

- Identifying targeted *in vitro* tests to measure chemical influence on specific mechanistic data gaps known or suspected to be associated with mammary gland carcinogenesis or altered development.

- Identifying and prioritizing a list of chemicals based on their known or potential relevance to breast cancer/development. These considerations may be based on some of the following criteria, and defined by the investigator:

    - Known or suspected rodent mammary carcinogens, mammary developmental toxicants, or endocrine-disruptors based on previous *in vivo*, *in vitro* or in silico/QSAR analyses;

    - Known or hypothesized biological effect at mechanistic or other cellular indicators relevant to the mammary gland or postulated cell targets (e.g. specific hormone, transcriptional or protein binding regions);

    - Relative potential for high-exposure in the general public and/or in susceptible populations based on identified characteristics such as type/relevant exposure route, for example, endocrine disrupting chemicals reported in drinking water, or consumer or food products; chemicals that are biologically persistent, or chemicals that have been detected in significant portions of the population through biomonitoring studies.

The work conducted under this aim is meant to demonstrate how new and current *in vitro* assays can effectively integrate to capture biochemical and molecular responses reflective of toxic pathways within *in vivo* tissue with adequate coverage of toxic pathways related to breast carcinogenesis.

Researchers should explain how their proposed assay(s), chemicals to be tested, and type of toxicity/biological indicator (i.e. protein, receptor, cell type), improves the ability to identify toxicants relevant to mammary carcinogenesis and development. Also, please explain/justify how the proposed work will differ and/or build on selected other work on chemical testing programs and research, such as ToxCast™ and earlier CBCRP Special Research Initiatives.

D. Evaluate the predictive validity of suites of tests using existing or newly generated data

As described previously, a major goal of high throughput screening (HTS) and other *in vitro* testing initiatives is to create the ability to screen and prioritize chemicals for assessment and to enable a quicker, standardized, proactive response to hazard and risk prediction. In addition, such testing schemes aim to provide a rapid survey of molecular and other initiating events along the toxicity pathway for chemicals. The ability of a given suite of *in vitro* assays to predict the relative likelihood or risk of an adverse health outcome remains an important constraint prior to the adoption of *in vitro* methods in the public health and regulatory community.

To date, mixed results have been reported on how well HTS and other *in vitro* data predicts actual *in vivo* hazard relative to genotoxic and non-genotoxic animal carcinogens as well as developmental and other toxic endpoints (Knight et a. 2009; Kleinstreuer et al. 2013; Kleinstreuer et al. 2011; Martin et al. 2011; Thomas et al. 2012; Wetmore et al. 2013).

Generally, such work has focused on different statistical methods for comparing *in vitro* HTS results from ToxCast™ phase I and *in vivo* 2-year rodent bioassays. In response, some groups have offered various frameworks for incorporating HTS and other technologies, including transcriptomic studies, into a more extensive stepwise framework involving *in vitro* HTS as one in a series of components (Thomas et al 2013; Patlewicz et al 2013). However, in regards to the available test systems and data generated, the *in vitro*-to-*in vivo* predictive capability in general remains unclear, and specifically for breast carcinogenesis is unknown.

Therefore, this aim requests proposals for work to help demonstrate the relative applicability of *in vitro* testing, improved shorter term *in vivo* test systems, or a combination of both (or with other methods), for detecting a defined endpoint(s) or indicator(s) on a relevant pathway for mammary gland carcinogenesis, toxicity or development. This work is meant to demonstrate the relative predictive ability of current and new tests for use in screening, prioritizing/scoring schemes or ultimately providing a quantified potential or other measure for breast cancer risk for use in scientific and regulatory decision making.

This area of work may involve a range of quantitative methodology for integrating testing results within and across platforms; however, the goal is to provide an innovative focus on mammary carcinogenesis and related mammary endpoints. As such, the ability to frame a predictive analysis on a transparent strategy, be it a prospective adverse outcome pathway (AOP), toxicity pathway, or other theoretical biological scaffolding accounting for intermediate/key events/model genes and pathways in mammary gland development or carcinogenesis could be crucial in building a pathway based understanding for groups or classes of chemicals relevant to breast cancer.

Researchers proposing projects should explain how the testing suites and biological end points will be selected for comparison, including their relationship to breast carcinogenesis; how the data integration and statistical analyses improves on methods examined to date; and, how the quantitative outcomes may improve the ability to identify, comparatively weigh or otherwise selectively screen and/or assess risk for chemicals at increased likelihood to induce or enhance the risk of breast cancer.

Project Type 2: Identify synergies between CBCRP-funded projects (previously funded and concurrently funded chemical testing projects) and translate the outcomes for policy development relevant to breast cancer.

One research grant will be awarded to synthesize the findings of CBCRP's funded efforts to develop and validate chemical testing methods (including the five grants funded in 2011 and all grants funded in this current round). The grant can be awarded independently or in conjunction with a grant associated with Project Type 1.

The *convener/integrator* would be responsible for organizing at least 2 meetings, one in California and, ideally, one in North Carolina to facilitate participation by researchers and agencies associated with ToxCast™ and other Tox21 partners. This would include integration work before the meeting, developing a draft summary document to be discussed at the meeting and a paper written after. The goals of the convener/integrator are to:

- Promote synergy from having all the teams interact,
- Help people outside the breast cancer research world better understand the progress being made in the field of testing for breast carcinogens, and
- Translate data and findings into specific policy recommendations that are relevant to breast cancer. This would include:
    - An evaluation of the strengths and weaknesses of the current and proposed testing protocols to identify breast carcinogens (both completed and ongoing);
    - Recommendations for how to improve toxicity testing to improve ability to identify potential mammary carcinogens;
    - A case study to evaluate how data from these *in vitro* tests could be used in risk and regulatory assessments for breast cancer (for example, how would data from a genotoxicity test be used to identify a potential breast carcinogen and used in a regulatory assessment);
    - Identification of best practices for evaluating information and data from toxicity testing;
    - Other ways that better testing methods can strengthen regulatory and policy decisions.

2) The most competitive proposals will involve researchers from multiple disciplines with demonstrated expertise in mammary gland biology, toxicology, cancer biology and chemical regulations. In order to ensure study designs that will be useful in regulatory chemicals testing, proposals should include collaborations with regulatory toxicologists such as scientists at California Environmental Protection Agency's Department of Toxic Substances Control and/or Office of Environmental Health Hazard Assessment, or at federal agencies such as Environmental Protection Agency, Centers for Disease Control and Prevention, and/or National Toxicology Program.

3) Applicants should be prepared to work with the other investigators funded under this initiative. At a minimum, this will include presenting ideas, approaches and findings at an annual meeting, and offering feedback to other researchers on their work. Investigators from other CBCRP-funded projects and outside experts may also participate in these meetings. Thus, all awardees from Project Type 1 must attend up to three meetings organized by the convener identified in Project Type 2, with the goal of integrating findings and translating the information to be relevant to policy development.

References

Dennison RA. *High Hopes, Low Marks: A Final Report Card on the High Production Volume Chemical Challenge* (Environmental Defense Fund, August 2007). Available at http://www.edf.org/sites/default/files/6653_HighHopesLowMarks.pdf

Knight AW, Little S, Houck K, Dix D, Judson R, Richard A, McCarroll N, Akerman G, et al. (2009) Regulatory Toxicology and Pharmacology. 55:188-199.

Kleinstreuer NC, Judson RS, Reif DM, Sipes NS, Singh AV, Chandler KJ, Dewoskin R, Dix DJ, Kavlock RJ, Knudsen TB. (2011) Environmental impact on vascular development predicted by high-throughput screening. Environmental Health Perspectives 119:1596-1603.

Kleinstreuer NC, Dix DJ, Houck KA, Kavlock RJ, Knudsen TB, Martin MT, Paul KB, Reif DM, Crofton KM, Hamilton K, Hunter R, Shah I, Judson RS. (2013) *In vitro* perturbations of targets in cancer hallmark processes predict rodent chemical carcinogenesis. Toxicological Sciences 131(1):40-55.

Martin MT, Knudsen TB, Reif DM, Houck KA, Judson RS, Kavlock RJ, Dix DJ. (2011) Predictive model of rat reproductive toxicity from ToxCast high throughput screening. Biology of Reproduction 85(2):327-39.

National Research Council. *Toxicity Testing in the 21st Century: A Vision and a Strategy* (National Academies Press, 2007).

Patlewicz G, Simon T, Goyak K, Phillips RD, Rowlands JC, Seidel SD, Becker RA. (2013) Use and validation of HT/HC assays to support 21st century toxicity evaluations. Regulatory Toxicology and Pharmacology 65:259-268.

Rudel RA, Fenton SE, Ackerman JM, Euling SY, Makris SL. (2011) Environmental Exposures and Mammary Gland Development: State of the Science, Public Health Implications, and Research Recommendations. Environmental Health Perspectives 119(8):1053–1061.

Schwarzman M, Janssen S. *Pathways to Breast Cancer: A Case Study for Innovation in Chemical Safety Evaluation*. 2010. A report of the Breast Cancer and Chemicals Policy Project (University of California, Berkeley and the Natural Resources Defense Council, with funding from the California Breast Cancer Research Program, University of California Office of the President). Available at http://coeh.berkeley.edu/greenchemistry/cbcrpdocs/executive_summary.pdf

Thomas RS, Black MB, Lili L, Healy E, Chu TM, Bao W, Andersen ME, Wolfinger RD. (2012) A comprehensive statistical analysis of predicting *in vivo* hazard using high-throughput *in vitro* screening. Toxicological Sciences 128(2):398-417.

Thomas RS, Philbert MA, Auerbach SS, Wetmore BA, Devito MJ, Cote I, Rowlands JC, et al. (2013) Incorporating new technologies into toxicity testing and risk assessment: moving from 21st century vision to a data-driven framework. Toxicological Sciences 136(1):4-18.

United States Government Accountability Office, *Chemical Regulation: Options Exist to Improve EPA's Ability to Assess Health Risks and Manage Its Chemical Review Program* (U.S. GAO, June 2005). http://www.gao.gov/cgi-bin/getrpt?GAO-05-458

Wetmore BA, Wambaugh JF, Ferguson SS, Li L, Clewell HJ 3rd, Judson RS, Freeman K, Bao W, Sochaski MA, Chu TM, Black MB, Healy E, Allen B, Andersen ME, Wolfinger RD, Thomas RS. (2013) Relative impact of incorporating pharmacokinetics on predicting *in vivo* hazard and mode of action from high-throughput *in vitro* toxicity assays. Toxicological Sciences 132(2):327-46.

Wilson MP, Chia DA, Ehlers BC. Green Chemistry in California: A Framework for Leadership in Chemicals Policy and Innovation (University of California, California Policy Research Center,

2006).

Wilson MP, Schwartzman MR. *Green Chemistry: Cornerstone to a Sustainable California* (University of California, Centers for Occupational and Environmental Health, January 2008). http://www.coeh.ucla.edu/Greenchemistry.pdf

Budget

It is anticipated that up to $3,750,000 in direct costs is available for this initiative. 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 25% F&A.

Project Type 1: Up to four awards expected at $300,000/year for up to three years (total $900,000 direct per award) plus indirect costs. Application must propose work applicable to more than one category (A through D).

Project Type 2: One award preferably awarded in conjunction with one Project Type 1 award for up to $150,000 total direct plus indirect costs.

Applicants should consider the following elements when constructing their budgets:

Expertise: Proposals must involve researchers with proficiency in breast cancer biology, toxicology and include a translational/policy expert

Capacity: Applicants should demonstrate possession of or access to appropriate tools and technologies (e.g. laboratory facilities and equipment, animal facilities, etc.)

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 comprised of scientists from relevant disciplines and breast cancer advocates and other community representatives.

- **Innovation** Extent to which the project explores new and potentially useful tests for biologically relevant effects of chemicals on breast tissues and development. Are the concepts and hypotheses speculative and exploratory? Are methods novel and original? Has(ve) the investigator(s) thought creatively about possible mechanisms, pathways and/or addressing multiple factors relevant to breast cancer?

- **Impact:** Potential for the project, if successful, to refine or generate biologically relevant assay(s) that will improve current testing modalities for setting chemicals policy. Does the research address relevant mechanisms, methods and/or models for testing chemicals? Are there plans to validate the new assay in a biological system. Will the data yielded by the assays be to sufficient to inform policy? Can the assays be designed to be financially realistic?

- **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?

- **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 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 PI to the stated intent of the selected Initiative? Compare the PI's statements on the Program Responsiveness template and the content of the Lay and Scientific abstracts to the CBCPI topic area. (A score of "0" for Responsiveness is an automatic disqualification.)

- **Dissemination and translation potential.** The degree to which the applicant's statements on the Additional Criteria template provides a convincing argument that the proposed research has the potential to inform the development and/or implementation of California chemicals policy.

- **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?

- **Advocacy Involvement.** Are the named advocate(s) and advocacy organization appropriate for the proposed research project? 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 Additional Criteria forms.]

Application Process and Instructions

Submission Deadline: Applications must be submitted through proposalCENTRAL (https://proposalcentral.altum.com/) by **Wednesday October 22, 2014** at 12 noon Pacific Standard Time.

Signed face pages of submitted applications must be emailed to RGPOgrants@ucop.edu by 5pm **October 29, 2014**.

The application materials will be available on proposalCENTRAL by September 2, 2014.

proposalCENTRAL Online Submission Instructions

Formatting Instructions

All submissions must be in **English**.

Follow these format requirements for written text (consistent with NIH/PHS 398 form):

- The height of the letters must not be smaller than 11 point. Times New Roman or Arial are the suggested fonts.
- Type density must be no more than 15 characters per inch (cpi).
- Page margins, in all directions, must be at least 1/2 inch.
- PI(s) last names and first initials must be in a header, on each page, flush right.

Deviations from the page format, font size, specifications and page limitations are grounds for the CBCRP to reject and return the submission without peer review.

Online Application (Proposal) Management

The CBCRP requires applications be submitted via an online system: proposalCentral. Following are instructions on how to register and how to submit your response to the RFP. The submission deadline is 12 noon Pacific Time **Wednesday October 22, 2014.** *Note*: the proposalCENTRAL site shows East Coast times. Do NOT wait until the deadline to submit your application; if you miss the deadline, the system will not allow you to submit.

If you have any problems using proposalCENTRAL, please contact the proposalCENTRAL help line at (800) 875-2562.

Online Registration

The PI as well as the institution's signing official, contracts & grants manager and fiscal contact must be registered in proposalCENTRAL: https://proposalcentral.altum.com/. Start with "Click here to register". Fill out all the necessary fields on the registration page: First Name, Last Name, Email Address, User ID (can be your name), Password (case-sensitive), Challenge Question, and Answer.

Click BOTH BOXES on the bottom of the page to confirm your agreement with their "Terms of Service" and "Acceptable Use Policy." Click on the "Register" button. ProposalCENTRAL will send you an email with your username, password and a confirmation number. Once confirmed, you can login and the first time you enter the system, it will ask you to enter the confirmation number. You won't need that number again.

Online Forms and Fields

Once logged on, select the "Grant Opportunities" (gray) tab on the top of the page. Open up the filter and scroll down to California Breast Cancer Research Program. Sort the available funding by CBCRP and all of the funding opportunities for CBCRP will be showing. Choose the SRI-Chemicals Testing Initiative and click on "Apply Now" at the far right of the line.

Portions of the application are prepared using pre-formatted web pages in proposalCENTRAL (Proposal Sections 1 and 3-8). To move from section to section you can click the "Next" button to both save your work and go to the next section, or click "Save" and then click on the next section.

Proposal Section 2 allows you to download the Templates and Instructions for the CBCRP forms. After completing the forms on your computer, Proposal Section 9 allows you upload each one as PDF to attach it to your application.

❒ Title Page

On the "Title Page" enter the Project Title in the space provided (do not exceed 60 characters). Enter the total budget amount requested for the project, including indirect costs, if eligible. The projected start date for this project is March 1, 2014. Enter the end date of the project (up to 3 years).

❒ Download Templates & Instructions

This section includes these instructions as well as the relevant application forms. You will need these forms in order to respond to this RFP.

❒ Enable Other Users to Access this Proposal

Note: A person must be registered in proposalCentral before s/he can be given access.
Read the instructions on this page thoroughly to understand the different levels of access. At the bottom of that page, in "Proposal Access User Selection," type in the email address of other individuals who will be working on the RFP, then click "Find User." Select the desired level of access and Click "Accept Changes" to save.

❒ Applicant/PI

Click on "Applicant/PI" and make sure that all required fields (identified with a red asterisk) are complete. (Click "Edit Professional Profile" to enter any missing data.)

Click "Return to Proposal" after entering missing data. Enter the % effort that the PI will devote to this project. The minimum effort for Project 1 is 10% FTE and for Project 2 is 5% FTE. Click "Save."

❒ Institution & Contacts

On the "Institution & Contacts" page, make sure that all required fields (identified with a red asterisk) are complete, including the Signing Official, Contracts and Grants Official, and Fiscal (Accounting)

Contact for the applicant institution. To complete these fields select the name or enter the email address of the individual in each of those roles and click “Add.”

If you add someone, the “Contact Screen - Applicant Institution” screen will open. Make sure that all required fields (identified with a red asterisk) are completed.
Click “Save”, then click “Close Window”.
Then click “Save” on the Institution & Contacts page.

- ❒ **Abstracts**

Copy each the Lay Abstract and the Scientific Abstract from the CBCRP templates into the appropriate boxes on the proposalCENTRAL page. ***Note***: symbols or other special text will not copy.

On this page you should also select and add CSO codes. At www.cancerportfolio.org/cso.jsp you will find the seven major CSO categories, each with 4-9 sub-categories. Choose a major heading for your research and read the subcategory description. Choose the one that most closely fits. If your project fits under more than one CSO category, add a second code. The second code should represent a different, but integral, part of the research and about half of the total effort.

- ❒ **Budget**

Provide the total costs for the entire funding request for each grant year on this page. Make sure the budget numbers are exactly the same as those in the provided Excel Budget Summary form that you upload.

- ❒ **Organization Assurances**

Provide any required information for Human Subjects. If assurances will be required and have not yet been received, mark “pending” and enter the (proposed) date of submission in the “Approved or Pending Date”.

- ❒ **Upload RESEARCH PLAN and Other Attachments**

This page contains a duplicate list of the forms and instructions that are in Download Templates and Instructions (above and Proposal Section 2). This is where you will upload the CBCRP forms and any other attachments to your proposal; the required items are listed.

To upload attachments, fill in the fields at the top of the page:

- **Describe Attachment:** Provide a meaningful description, such as Jones CV.
- **Select Attachment Type:** From the drop down menu, select the type of form that is being attached.
- **Allowable File Type:** Only Adobe PDF document may be uploaded. Do not Password Protect your documents. Help on converting files to PDF can be found on the proposalCentral site at https://proposalcentral.altum.com/FAQ/FrequentlyAskedQuestions.asp.
- **Select File From Your Computer to attach:** The Browse button allows you to search for the PDF on your computer; click Open to select the file.

Note: Explicit instructions on the content of the documents to be uploaded follow in the “Instructions for CBCRP Forms” section.

❒ **Validate**

This function allows you to check whether all required items have been completed and attached. Don't wait until the last minute to check! Validate often during the course of completing your application so you have time to address missing items. Clicking the "Validate" button will either result in a link to missing items so you can easily go to the page and complete them, or a message at the top of the page "Has been validated and is ready to submit."

❒ **Print Face Page When Application Complete**

Applicants must print application's Face Page and obtain the necessary PI and institutional signing official signatures within a week of the electronic submission (see below).

❒ **Submit**

Submission is only possible when all required items have been completed and all required forms have been attached. Once an applicant hits "Submit," the application cannot be recalled.

❒ **Email Face Page Submission**

The PI, institution's signing official, Contract and Grants official and Fiscal (or Accounting) official all must sign the printed Face Page. Scan the signed form as a PDF and email to RGPOGrants@ucop.edu before 5 pm (Pacific Time) by **Wednesday, October 29, 2014.**

CBCRP Uploaded Form Instructions

Lay Abstract (REQUIRED)

This item is evaluated mainly in the programmatic review. The Lay Abstract is limited to one page and 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 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 you advocate partner to read this abstract and provide feedback.

Scientific Abstract (REQUIRED)

This item is evaluated mainly in the peer review. The Scientific Abstract is limited to one page and 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.

Other Review Criteria (REQUIRED)

This item is evaluated in the 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 CBCPI research area as outlined in the specific RFP and by the CBCRP Council/SRI Steering Committee (see www.cabreastcancer.org/funding-opportunities/sri/index.html).

CBCPI Focus: 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 indentify or translate into potential prevention strategies.

Advocacy-sensitivity and Inclusion: 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.

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.

Advocacy Involvement (REQUIRED)

Follow the instructions on the form, and 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.

Letter(s) of Commitment (REQUIRED)

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.

Budget Summary (REQUIRED)

Please enter the budget for the presented categories by year into the summary sheet (Excel format). Additional instructions are presented on the form.

The maximum duration and direct costs may not exceed the following for the RFP *Chemical Safety Testing to Reduce Breast Cancer Risk*:

Project Type 1:	3 Years & $900,000
Project Type 2:	3 Years & $150,000

Note: The amount of the 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 cap by the amount of the F&A costs to the subcontracted partner's institution.

Personnel. List the PI for the application and "individuals who contribute in a substantive way to the scientific development or execution of the project, whether or not salaries are requested." (NIH definition). Include those at the level of postdoctoral fellow and higher. Upload a NIH "Biographical Sketch and Other Support" form for each individual listed. The minimum "Months Devoted to Project" required for each Project 1 PI is 1.2 months (= 10% FTE) and .6 months (= 5% FTE) for Project 2.

Other Project Expenses. Enter the costs associated with each category presented on the template (description to be provided in Budget Justification).

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

Equipment. Purchases up to $10,000 are allowed. Only include individual items >$5,000. Any items less than $5,000 must be purchased under the "supplies" budget category above.

Travel Expenses. Requested travel costs must be broken down and justified as Project-related, Annual meeting (third year only) or Scientific meeting (PI only capped at $2,000 per year).

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. Both categories require additional description (Budget Justification) and documentation (Appendix).

Service Agreements and Consultants. Both categories require additional description (Budget Justification) and documentation (Appendix).

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 25% MTDC*

**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.

Please see the RFP under **Allowable Indirect (F&A) Costs** for more information.

Budget Justification & Facilities (REQUIRED)

This item is evaluated in the peer review. Limit the text to two pages. Follow the instructions on the template. The minimum "Months Devoted to Project" required for each Project 1 PI is 1.2 months (= 10% FTE) and .6 months (= 5% FTE) for Project 2.

Key Personnel (REQUIRED)

This item is evaluated in the peer review. Limit the text to one page. Follow the instructions on the template.

Biographical Sketch & Other Support (REQUIRED)

This item is evaluated in the peer review. Use the NIH form. Limit the length of each biosketch to *no more than* four (4) pages.

Research Plan (REQUIRED)

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

Page limit: **10 pages - Project 1**
5 pages - Project 2
An additional 3 pages is allowed for References.

Format issues: Begin this section of the application using the 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 at least ½ inch.

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

Applicants should be clear in describing how their proposed research project adheres to, and/or builds on, approaches/methods described in the RFP including the expectations at the end of each Project Type 1 area of interest (A through D). A proposed research project may include to one or more of these interest areas.

Suggested content:

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 CBCPI 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 is 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 timeline at the end will demonstrate how the aims are interrelated, prioritized, and feasible. Explain the use of human subjects and vertebrate animals and show their relationship to the specific aims.

Resources and Facilities: Describe the resources and facilities to be used (e.g., laboratory space, core facilities, major equipment, access to populations, statistical resources, animal care, and clinical resources) and indicate their capacities, relative proximity and extent of availability. Include an explanation of any consortium/ contractual arrangements with other organizations regarding use of these resources or facilities. Describe resources supplied by subcontractors and those that are external to the institution. Make sure all of the research needs described in the research plan are addressed in this section.

Human Subjects (OPTIONAL)

This item is evaluated in the peer review. **This form is required only for applications that use Human Subjects, including those in the "Exempt" category. Use additional pages, if necessary. For applications requesting "Exemption"** from regular IRB review and approval please 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 Institutional Review Board (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 falls 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 CBCPI Application Face Page 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 appendix, 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 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, but **no later than January 1, 2015**. 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 item is evaluated in the peer review. **This form is required only for applications that use Vertebrate Animals. Limit the text to two pages**.

If you have answered **"YES"** to the Vertebrate Animals item on the Organizations Assurances section of the CBCPI Application Face Page, then 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.

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 methods 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 institutions 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, but **no later than January 1, 2015**. Funds will not be released until all assurances are received by the CBCRP.

Appendix List (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.

General Funding Policies

Who May Apply

Any individual or organization in California may submit an application. The research must be conducted primarily in California. We welcome investigators from community organizations, public or privately-owned corporations and other businesses, volunteer health organizations, health maintenance organizations, hospitals, laboratories, research institutions, colleges, and universities.

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

Pre-funding Requirements

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

- Up-to-date human IRB and animal assurance documents from a federally licensed review board must be on file for each grant.
- Modify the title and lay abstract, if requested.
- Agree to any changes in specific aims, award budget, or duration as recommended by the Review Committee and Program.
- Resolve overlap with other grant support and any issues with PI percent effort.
- Supply any missing application forms or materials.
- Supply up-to-date documentation for approved indirect rate (F&A costs) agreements as of the grant's start date and any derived calculations, if applicable.

Conditions of Awards

Details concerning the requirements for funding recipients are available in a separate Program publication, the University of California, Office of the President, "***Grant Administration Manual 2011-2012***." It is sent to every funding recipient principal investigator, contracts and grants official, and the accounting contact. The Manual can be obtained from the Program's office or viewed on our Web site: www.ucop.edu/research-grants-program/_files/documents/srp_forms/srp_gam.pdf.

Awardees are expected to account for the expenditure of funds and for the performance of work as agreed upon in a timely manner, so that the CBCRP may file reports and answer inquiries from the legislature and the public. They are also expected to adhere to the stated goals of the legislation, which include the systematic dissemination of research results to the public and to the healthcare community and the facilitation of translation of research results into commercial, alternate technological and other

applications. The Institutional Official's and Principal Investigator's **signatures on the Face Page of the application signify that the individuals are aware of the conditions for receiving funding** from the Program.

To ensure the proper management of these public funds, a prospective funding recipient must satisfy the **following standard requirements** before an award will be made:

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

Individuals who are to be awarded funds may meet these requirements directly or by making arrangements with a research organization that does. A funding recipient may satisfy modified requirements, if this is determined to be appropriate upon review by the University of California's Office of Research Administration, Office of Risk Management and General Counsel.

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

Grant awardees must agree to:

- Use award funds only as approved by the CBCRP. The Program must approve changes in the specific aims of an initiative.
- Maintain accounts, records and other evidence pertaining to work performed and costs incurred.
- A final scientific report and any interim reports as specified in this announcement.
- File annual fiscal reports and a final fiscal report.
- Participate in CBCRP sponsored activities to disseminate research results as able and as requested.
- Ensure the timely translation of research results into commercial applications, public policy, and public communications as appropriate and/or required by this announcement.
- Attend CBCRP research symposiums, if scheduled during the award period, or forfeit budget amounts assigned to this item.

Award Period and Indirect (F&A) Costs

If a multiple year award, continuation funding for additional years is released upon receipt of an Annual Progress Report showing research effort/progress, no overlap with other support, maintenance of sufficient FTE percentage by the PI, continuing approval of Human and Animal subjects use, submission of publication copies, and reporting any changes in Key Personnel. If funding is delayed, or if all funds are not expended in the normal award period, then the investigator(s) may request a no-cost time extension for a maximum of one year in order to complete the work.

The CBCRP encumbers the funds for all approved years of an award from the appropriation in the year the funds are awarded; thus full funding of a multi-year initiative is assured, dependent only on timely submission of the required reports. Funds will be disbursed annually, contingent on receipt of required progress and fiscal reports.

For one-year initiatives, and for the final budget year of multiyear initiatives, 20% of the approved budget is withheld (except for UC institutions) and paid in arrears upon receipt and acceptance by the Program of all required final reports.

Direct Costs

CBCRP award funds may be used only for expenditures necessary to carry out the approved initiative, as specified in the approved budget. Significant changes in proposed expenditures must be approved in advance by a CBCRP Research Administrator. Please follow the policies in the "SRP Grant Administration Manual" regarding allowable changes in expenditures and the guidelines for submitting a formal request form to change initiative budgets.

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

Cost Base for Determining Indirect Cost Allocations for UCOP RGPO Awards

The "cost base" for determining the indirect cost (IDC)[1] recovery for RGPO awards will consist of: salaries and wages, fringe benefits, materials and supplies, services, travel, and sub grants and subcontracts to an outside institution up to the first $25,000 of the initial sub-award budget (excluding renewals or extensions). This base is called the Modified Total Direct Cost, or MDTC base. Equipment or other capital expenditures, charges for patient care, scholarships and fellowships (including postdoctoral stipends), tuition remission and graduate student stipends, rental costs of space, as well as 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, are **excluded** from this MTDC base. Any questions about interpretation of the MTDC base can be directed to the CBCRP Program Officer, and/or the RGPO Contracts and Grants Analyst assigned to an awarded grant.

Allowable Indirect (F&A) Costs

[1] IDC is also commonly referred to as Overhead or Facilities and Administrative costs, or F&A.

For primary grantees the following conditions apply regarding recovery of indirect costs:

- For awards to UC Campuses, a cap of no more than 25% MTDC is allowable on grant awards. See below for additional discussion on indirect on subcontracts.
- For awards to Non-UC institutions, the CBCRP awards allow F&A cost recovery utilizing the MTDC base, at the applicable federally approved F&A rate for the Non-UC Institution. (The rate approved by a federal cognizant agency must be used if available). In the absence of a federally negotiated rate agreement, an equivalently documented F&A rate for the institution may be used (upon approval of UCOP RGPO).

For indirect costs for award subcontracts the following conditions apply:

- For subcontracts to UC Campuses, a cap of no more than 25% MTDC is allowable on subcontracts related to CBCRP awards.
- For awards to Non-UC institutions, the subcontractor F&A costs recovery utilizing the MTDC base is allowed at the appropriate federally approved F&A rate for the Non-UC Institution. (An approved Department of Health and Human Services (DHHS) rate must be used if available). In the absence of a federally negotiated rate agreement, an equivalently documented F&A rate for the institution may be used (upon approval of UCOP RGPO).
- For subcontracts awards to UC-managed National Labs (LBNL, LANL, LLNL) please contact the CBCRP Program Officer.

Individuals without an institutional affiliation will not be eligible for indirect costs.

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

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

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

University of California Campuses

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 applications and 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.

Fraud and Scientific Misconduct

Policy Regarding Scientific Misconduct

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

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

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

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

Fraud or Misuse of CBCRP Funds

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

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). Details concerning the appeals procedure may be obtained from the appropriate Research Administrator (with whom the applicant is encouraged to discuss his/her concerns), the CBCRP Director, or by contacting us through the CBCRP Web site: www.cabreastcancer.org/. The period open for the appeal process is within 30 days of receipt of the application evaluation from the Program office. Contact the CBCRP to obtain full information on the appeals process.

Final decisions on application funding appeals will be made by the UCOP Research Grant Program Office (RGPO) Executive Director Dr. Mary Croughan. 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.

Confidentiality

The CBCRP maintains confidentiality for all submitted applications with respect to the identity of applicants and applicant organizations, all contents of every application, and the outcome of reviews. For those applications that are funded the CBCRP makes public, (i) the title, principal investigator(s), the name of the organization, the costs (both direct and indirect), the initiative abstracts, and progress report abstracts. CBCRP uses a variety of media to communicate this information including (i) the "Compendium of research" for each funding cycle, (ii) CBCRP's "Advances" annual report, (iii) CBCRP's e-news, web site, and social media, and (iv) other special communication tools such as press releases. If the Program receives a request for additional information on a funded initiative, 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 application 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.