Program Announcement

Department of Defense Congressionally Directed Medical Research Programs

Breast Cancer Research Program

Clinical Translational Research Award

Funding Opportunity Number: W81XWH-08-BCRP-CTR

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I. HELPFUL INFORMATION

A. Contacts

1. Program announcement, proposal format, or required documentation: To view all funding opportunities offered by the Congressionally Directed Medical Research Programs (CDMRP), perform a Grants.gov basic search using the CFDA Number 12.420. Submit questions as early as possible. Response times will vary depending upon the volume of inquiries. Every effort will be made to answer questions within 5 working days.

Phone: 301-619-7079

Fax: 301-619-7792

Email: cdmrp.pa@amedd.army.mil

2. eReceipt system: Questions related to pre-application components through the CDMRP eReceipt system should be directed to the eReceipt help desk, which is available Monday through Friday from 8:00 a.m. to 5:00 p.m. Eastern time.

Phone: 301-682-5507

Website: https://cdmrp.org

Email: help@cdmrp.org

3. Grants.gov contacts: Questions related to submitting applications through the Grants.gov (http://www.grants.gov/) portal should be directed to Grants.gov help desk. Deadlines for proposal submission are 11:59 p.m. Eastern time on the deadline date. Therefore, there is an approximate 3-hour period during which the Grants.gov help desk will NOT be available. Please plan ahead accordingly, as the CDMRP help desk is not able to answer questions about Grants.gov submissions.

Phone: 800-518-4726, Monday through Friday 7:00 a.m. to 9:00 p.m. Eastern time

Email: support@grants.gov

Grants.gov will notify Principal Investigators (PIs) of changes made to this Program Announcement and/or Application Package ONLY if the PI clicks on the "send me change notification emails" link and subscribes to the mailing list on the Opportunity Synopsis Page for this announcement. If the PI does not subscribe and the Application Package is updated or changed, the original version of the Application Package may not be accepted.

B. National Technical Information Service

The technical reference facilities of the National Technical Information Service (www.ntis.gov) are available for the purpose of surveying existing knowledge and avoiding needless duplication

of scientific and engineering effort and the expenditure thereby represented. All other sources also should be consulted to the extent practical for the same purpose.

C. Commonly Made Mistakes

- Not obtaining or confirming the organization's DUNS number well before the proposal submission deadline.
- Not obtaining or confirming the organization's registration with the Central Contractor Registry (CCR) well before the proposal submission deadline.
- Failing to request "send me change notification emails" from Grants.gov.
- Not contacting HELP DESKS until just before or after deadlines.
- Not completing the pre-application submission before the mandatory pre-application deadline (pre-application remains in draft status).
- Using an incorrect Grants.gov application package to submit a proposal through Grants.gov. Each Program Announcement/Funding Opportunity requires a specific application package.
- Uploading attachments into incorrect Grants.gov forms.
- Attaching files in the wrong location on Grants.gov forms.
- Submitting attachments that are not PDF documents, except for the R&R Subaward Budget Attachment(s) Form.
- Exceeding page limitations.
- Failing to submit a proposal 48-72 hours before the deadline so that Grants.gov can provide notification of errors and allow for resubmission of application package.
- Failing to submit proposal by submission deadline.

II. FUNDING OPPORTUNITY DESCRIPTION

A. Program History and Objectives

The BCRP was established in fiscal year 1992 (FY92) to promote innovative research focused on eradicating breast cancer. Appropriations for the BCRP from FY92 through FY07 totaled $2.1 billion. The FY08 appropriation is $138.0 million (M).

The BCRP challenges the scientific community to design innovative research that will foster new directions for, address neglected issues in, and bring new investigators to the field of breast cancer research. The BCRP focuses its funding on innovative projects that have the potential to make a significant impact on breast cancer, particularly those involving multidisciplinary and/or multi-institutional collaborations and alliances. The BCRP encourages risk-taking research; however, all projects must demonstrate solid judgment and rationale.

B. Award Description

The Breast Cancer Research Program (BCRP) Clinical Translational Research (CTR) Award mechanism was first introduced in FY97. Since that time, 216 Clinical Translational Research Award proposals have been received and 40 have been recommended for funding. The CTR Award is intended to promote substantial improvements over current approaches to breast cancer chemoprevention and therapy, including predictive biomarker studies that would better align treatment options with more specific breast cancer subtypes and/or may identify a new way to treat breast cancer patients. These awards are intended to support research projects that are likely to have a major impact on breast cancer by applying promising research findings to the treatment of patients with, or populations at risk for, breast cancer.

Principal Investigators (PIs) may have originated projects in their laboratories that will form the basis for translational research leading to clinical trials to be conducted during this award period. Alternatively, PIs may leverage partnerships with industry (if the ability to conduct the required translational research and early phase clinical trial can be demonstrated).

Proposals must include preliminary data and a solid rationale to support the feasibility of innovative translational research leading to a prospective clinical trial or study during the course of the award. Proposals also must include a clear experimental plan and a properly powered statistical plan to perform a prospective clinical trial. Investigators must demonstrate availability of and access to an appropriate patient population that will support a meaningful outcome for the study. Proposals addressing predictive biomarker studies must be supported by a previous, retrospective study and must include data validating the methods for the collection, storage, annotation, and analysis of human biological substances.

Investigators must provide a detailed plan for how they will meet the requirements for obtaining Investigational New Drug (IND) or Investigational Device Exemption (IDE) status (or other approvals required by the US Food and Drug Administration [FDA]) early in the lifetime of the award to further investigate chemoprevention or therapeutic interventions developed through the CTR Award. Participating institutions must be willing to resolve potential intellectual and material property issues and remove institutional barriers to achieving high levels of cooperation. If the proposals involve multiple institutions, an intellectual and material property plan agreed to by all participating institutions is required in the proposal's supporting documentation. Further, investigators must demonstrate how they plan to move findings or interventions into the breast cancer community.

Please note that all DOD-funded research involving human subjects and human biological substances must be reviewed and approved by the USAMRMC Office of Research Protections, Human Research Protection Office (HRPO) in addition to local institutional review boards (IRBs). The HRPO is mandated to comply with specific laws and directives governing all research involving human subjects that is conducted or supported by the DOD. These laws and directives are rigorous and detailed and will require information in addition to that supplied to the local review board. Allow a minimum of 6 months for regulatory review and approval processes for studies involving human subjects.

C. Eligibility

Investigators at all academic levels (or equivalent) are eligible to submit proposals.

Refer to Application Instructions, Appendix 1, for general eligibility information.

D. Funding

These awards have no dollar amount restrictions; however, research should be completed within 5 years. No more than $5M in total direct and indirect costs will be granted in any single year during the lifetime of the award. Funding will be disbursed in installments, which will be contingent upon the successful completion of specific milestones. Milestones from the approved Statement of Work will be determined during award negotiation. If the clinical trial will not be completed during the award performance period, evidence that sufficient funds and resources will be available to complete the clinical trial must be provided prior to the release of funds for the initiation of the clinical trial. ***Failure to complete each milestone may result in forfeiture of the subsequent installment of CTR Award funding.***

Within the guidelines provided in the Application Instructions, funds can cover:

- salary
- research supplies
- equipment
- clinical costs
- travel to scientific/technical meetings
- travel between collaborating institutions

The CDMRP requires attendance at the biennially scheduled 3½-day DOD BCRP Era of Hope meeting, which is held to disseminate the results of BCRP-sponsored research.

From the $138M FY08 BCRP appropriation, the CDMRP expects to fund approximately 3-4 Clinical Translational Research Award proposals, depending on the quality and number of proposals received. Funding of proposals received in response to this program announcement is contingent on the availability of Federal funds for this program.

E. Award Administration

No change in institution will be permitted after the clinical trial commences.

Refer to the Application Instructions, Appendix 5, for general award administration information.

III. TIMELINE FOR SUBMISSION AND REVIEW

Proposal submission is a two-step process consisting of (1) pre-application submission and (2) proposal submission. ***Pre-application submission is a required first step***.

- **Pre-application Submission Deadline: 5:00 p.m. Eastern time, March 27, 2008**
- **Invitation to Submit Proposal April 25, 2008**
- **Confidential Letters of Recommendation 5:00 p.m. Eastern time, June 19, 2008**
- **Proposal Submission Deadline: 11:59 p.m. Eastern time, June 19, 2008**
- **Peer Review: August 2008**
- **Programmatic Review: September 2008**

Awards will be made approximately 4 to 6 months after receiving the funding notification letter, but no later than September 30, 2009.

IV. SUBMISSION PROCESS

Proposal submission is a two-step process consisting of (1) a pre-application submission through the CDMRP eReceipt system (https://cdmrp.org/) and (2) a proposal submission (***requires a letter of invitation***) through Grants.gov (http://www.grants.gov/).

Submission of the same research project to different award mechanisms within the same program or to other CDMRP programs is discouraged. The Government reserves the right to reject duplicative proposals.

A. Step 1 – Pre-Application Components and Submission

The pre-application consists of the components discussed below. All pre-application components must be submitted electronically through the CDMRP eReceipt system by ***5:00 p.m. Eastern time on the deadline***. The PI and Organization identified in the proposal submitted through Grants.gov should be the same as those identified in the pre-application. If there is a change in PI or Organization after submission of the pre-application, the PI must contact the eReceipt helpdesk at help@cdmrp.org or 301-682-5507. In addition to the specific instructions below, refer to the Application Instructions for detailed information.

1. Proposal Information
2. Proposal Contacts
3. Collaborators and Conflicts of Interest (COI)
4. Preproposal Narrative (four-page limit)

   The investigator is responsible for articulating clearly how the proposed research addresses each of the following:

- Describe in detail how the proposed project applies innovative, yet well-founded observational data, laboratory, or other preclinical insights that justify the progression of the project into a clinical trial.
- Explain how the results of this project have the potential to revolutionize the chemoprevention and/or therapy of breast cancer.
- Outline a plan for the translational experiments and/or biomarker validation studies to be conducted through this award in order to move the project into clinical trials.
- Outline the experimental plan for a prospective human clinical study or trial that will be conducted.
- Provide evidence supporting access to patients and the ability to accrue sufficient study subjects in the proposed prospective trial.
- Describe the appropriateness of the patient population to be targeted for the clinical trial.
- Describe the expertise available for conducting the translational and clinical research.

5. Preproposal Supporting Documentation
   - References (one-page limit)
   - Biographical Sketches (four-page limit per individual)
   - Resources Access
     - Materials Access: Provide signed letters from collaborating individuals or institutions documenting the availability of, access to, and quality control for all critical reagents. Include information regarding the resources available to aid in the development of sufficient quantities of the reagent under Good Manufacturing Practice (GMP), if applicable. If the reagent is to be provided from industrial sources, evidence of a cost-sharing plan also must be provided.
     - Patient Access: Provide letters from collaborating individuals or institutions documenting the availability of and access to the patient population and evidence that the accrual rate can be achieved within the performance period of the award.

Preproposal Screening: Preproposals will be reviewed by the BCRP Integration Panel, which is composed of scientists, clinicians, and consumer advocates. PIs whose preproposals meet the intent of the award mechanism will be invited to submit proposals. Each PI will be notified as to whether they have been invited to submit a proposal.

B. Step 2 – Proposal Components and Submission

Proposal submission will not be accepted unless the PI has been invited. Do not submit a proposal unless a letter of invitation has been received. Proposals must be submitted electronically by the AOR (Authorized Organizational Representative) through Grants.gov (www.grants.gov). No paper copies will be accepted.

Each proposal submission must include the completed Grants.gov application package of forms and attachments identified in www.grants.gov for the US Army Medical Research Acquisition Activity (USAMRAA) program announcement. The PI and Organization identified in the proposal submitted through Grants.gov should be the same as those identified in the pre-application. If there is a change in PI or Organization after submission of the pre-application, the PI must contact the eReceipt helpdesk at help@cdmrp.org or 301-682-5507. In addition to the specific instructions below, refer to the Application Instructions for detailed requirements of each component.

The package includes:

1. SF-424 (R&R) Application for Federal Assistance Form
2. Attachments Form
    - Attachment 1: Project Narrative (15-page limit)

      CTR Award proposals must include promising preliminary preclinical data relevant to the proposed project. In addition, the PI is responsible for clearly articulating the ways in which the proposed research will have a significant impact on the prevention and/or treatment of breast cancer.

      Describe the overall project using the following outline.

      - Background**:** Provide a brief statement of the ideas and reasoning on which the proposed work is based. Explain why and how the proposed work would proceed to a clinical trial for the chemoprevention or treatment of breast cancer. Describe previous experience most pertinent to the proposal. Cite relevant literature references that support the hypothesis to be tested.
      - Purpose: State the hypothesis to be tested and the expected results.
      - Objectives: State concisely the study's specific aims and research strategy.
      - Preliminary Data: Provide sufficient preliminary data to support the feasibility of the translational or clinical work proposed.
      - Proposed Research and Methods: Describe the experimental design and methodology, including reagents, assay validation, statistical analysis, potential pitfalls, and alternative approaches. Provide a well-developed, well-integrated research strategy that supports the translational feasibility and promise of the approach. If the methodology is new or unusual, provide sufficient details for evaluation. Describe the translational studies that will be performed through this award and ***clearly link*** the laboratory and other preclinical findings to the prospective clinical trial. If preliminary studies are not focused on breast cancer, explain how the preliminary work will support the proposed research on breast cancer. As appropriate, outline a plan for applying for and obtaining IND/IDE status (or other FDA approvals).
      - Clinical Trial: Discuss plans for initiating the prospective human clinical trial or study during the course of this award. Provide a properly powered statistical plan to perform a prospective clinical trial and information demonstrating that a

sufficient number of participants will be accrued to the proposed clinical trial during the award period. The investigator must demonstrate appropriate expertise in conducting clinical trials. (Evidence of expertise may include that of collaborating investigator and highly trained support staff.)

- Strategic Plan: Provide an overall strategic plan for completing the clinical trial. If the entire trial will not be completed during the performance period of the award, provide evidence that sufficient funds and resources will be available to complete the trial. Address long-term goals of the study including how the findings will be distributed throughout the breast cancer community.

- Attachment 2: Supporting Documentation
  - References Cited
  - Acronyms and Symbol Definitions
  - Facilities & Other Resources
  - Description of Existing Equipment
  - Publications and/or Patent Abstracts (five-document limit)
  - Letters of Institutional Support
  - Letters of Collaboration (if applicable) (two-page limit per letter)

    Provide a signed letter from each collaborating individual or institution that will demonstrate that the PI has the resources necessary for the proposed work, including but not limited to:

    1. Availability of, access to, and quality control for all critical reagents. If applicable, include information regarding the resources available to aid in the development of sufficient quantities of the reagent under Good Manufacturing Practice. If the reagent is to be provided from industrial sources, evidence of a cost-sharing plan must also be provided.
    2. Availability of and access to breast cancer patients.
  - Intellectual and Material Property Plan (if applicable)
- Attachment 3: Technical and Public Abstracts
- Attachment 4: Statement of Work (SOW)

  Include in addition to other requirements for the SOW:

  Establish milestones for the following upon which release of funds will be contingent:

  - Completion of toxicity and pharmacokinetic studies
  - Strategic meeting with the FDA prior to applying for IND/IDE or other required approval (as appropriate)
  - Achievement of the necessary regulatory approvals (IRB, RAC, FDA)
  - Patient accrual goals relevant to the clinical trial

- Adequate funding support obtained for clinical trial completion if the trial will not be completed within the award performance period

- Attachment 5: Impact Statement

  Describe how the proposed work, if successful, will have a significant impact on breast cancer research or patient care. Describe how the proposed work could make advancements in the chemoprevention and/or therapy of breast cancer.

- Attachment 6: Translatability Statement

  Clearly describe how the project is expected to translate promising research findings into novel prevention strategies or treatments for breast cancer.

- Attachment 7: Federal Agency Financial Plan (if applicable)

3. Research & Related Senior/Key Person Profile (Expanded Form)
   - PI Biographical Sketch (four-page limit)
   - PI Current/Pending Support
   - Key Personnel Biographical Sketches (four-page limit each)
   - Key Personnel Current/Pending Support
4. Research & Related Budget Form
   - Budget Justification
5. Research & Related Project/Performance Site Location(s) Form
6. R&R Subaward Budget Attachment(s) Form (if applicable)

V. INFORMATION FOR PROPOSAL REVIEW

A. Proposal Review and Selection Overview

All proposals are evaluated by scientists, clinicians, and consumer advocates using a two-tier review process. The first tier is a scientific peer review of proposals against established criteria for determining scientific merit. The second tier is a programmatic review that compares submissions to each other and recommends proposals for funding based on scientific merit and overall goals of the program. Additional information about the two-tier review process used by the CDMRP may be found at http://cdmrp.army.mil/fundingprocess

The peer review and program review processes are conducted confidentially and anonymously to maintain the integrity of the merit-based selection process. Each tier of review requires panelists to sign a non-disclosure statement attesting that proposal and evaluation information will not be disclosed outside the panel. Violations of the nondisclosure statement can result in the dissolving of a panel(s) and other correcting actions. Correspondingly, institutional personnel and PIs are prohibited from contacting persons involved in the proposal review process to gain protected evaluation information or to influence the evaluation process. Violations of this prohibition will result in the

administrative withdrawal of the institution's proposal. Violations by panelists or PIs that compromise the confidentiality or anonymity of the peer review and programmatic review processes may also result in suspension or debarment of their employing institutions from Federal awards.

The Government reserves the right to review all proposals based on one or more of the required attachments or supporting documentation (e.g., Impact Statement or Translatability Statement).

B. Review Criteria

1. Peer Review: All proposals will be evaluated according to the following criteria, in decreasing order of importance.

- **Impact**
  - How the study addresses an important problem related to the chemoprevention and/or therapy of human breast cancer.
  - Whether the aims of the application, if achieved, are likely to have a ***substantial clinical impact***.
  - How the project will ***revolutionize*** the field of breast cancer, if successful.
- **Translational/Clinical Strategy**
  - How the project will translate promising, well-founded research findings for the treatment or chemoprevention of breast cancer.
  - Whether the PI demonstrates the ability to accrue a sufficient number of subjects.
  - Whether the research design, methods, and analysis plan meet the requirements for applying for and obtaining IND/IDE status (or other FDA approvals), if appropriate.
- **Research Strategy and Feasibility**
  - How the scientific rationale supports the project and its feasibility as demonstrated by a critical review and analysis of the literature, preliminary data, and logical reasoning.
  - How well the hypotheses, objectives, aims, experimental design, methods, and analyses are developed.
  - How well the PI acknowledges potential problems and addresses alternative approaches.
  - Whether there is documented availability of, access to, and quality control for all critical reagents.
  - Whether there are resources available for the development of sufficient quantities of critical reagents under GMP.
  - Whether there are a sufficient number of patients available for the study to achieve accrual goals.

- **Statistical Plan**
  - Whether an appropriate statistical plan is provided, including power analysis.
  - Whether the design of the clinical trial is sufficiently developed to support the statistical power required to lead to meaningful results.
- **Personnel**
  - How the research team's background and expertise are appropriate to accomplish the proposed work (e.g., PI, statistician, clinical coordinator, etc.).
  - The appropriateness of the levels of effort for successful conduct of the proposed work.
- **Environment**
  - How the scientific/clinical environment is appropriate for the proposed research.
  - Whether the proposed translational and clinical research is adequately supported by the scientific environment, necessary resources, and collaborative arrangements.
  - How the quality and extent of institutional support are appropriate, to include support for conducting human subjects research, as applicable.
  - Appropriateness of plans to resolve intellectual and material property issues among participating institutions.
- **Budget**
  - How the budget is appropriate for the proposed research.
  - Whether there is evidence of a cost-sharing plan, if critical reagents are to be provided from industrial sources.

2. Programmatic Review: Criteria used by programmatic reviewers to make funding recommendations that maintain the program's broad portfolio include:

- Ratings and evaluations of the peer reviewers,
- Programmatic relevance,
- Relative impact,
- Program portfolio balance, and
- Adherence to the intent of the award mechanism.

Scientifically sound proposals that best fulfill the above criteria and most effectively address the unique focus and goals of the program will be identified by Integration Panel members and recommended for funding to the Commanding General, USAMRMC.

VI. COMPLIANCE GUIDELINES

Compliance guidelines have been designed to ensure the presentation of all pre-applications and proposals in an organized and easy-to-follow manner. Peer reviewers expect to see a consistent, prescribed format. Failure to adhere to formatting guidelines makes documents difficult to read, may be perceived as an attempt to gain an unfair competitive advantage, and may result in pre-application or proposal rejection. ***Pre-applications or proposals missing required components as specified in the Program Announcement/Funding Opportunity may be administratively rejected.***

The following will result in administrative rejection of the pre-application:

- Preproposal Narrative exceeds page limit.
- Preproposal Narrative is missing.
- Margins are less than specified in the formatting guidelines.
- Print Area exceeds that specified in the formatting guidelines.
- Spacing is less than specified in the formatting guidelines.
- FY08 Integration Panel (IP) members are included in any capacity in the pre-application process and/or any supporting document. A list of the FY08 IP members may be found at http://cdmrp.army.mil.

The following will result in administrative rejection of the entire proposal:

- Project Narrative exceeds page limit.
- Project Narrative is missing.
- Margins are less than specified in the formatting guidelines.
- Print Area exceeds that specified in the formatting guidelines.
- Spacing is less than specified in the formatting guidelines.
- Budget and/or budget justification are missing.
- FY08 Integration Panel (IP) members are included in any capacity in the pre-application process, the proposal, budgets, and any supporting document. A list of the FY08 IP members may be found at http://cdmrp.army.mil.

For any other sections of the pre-application or proposal with a defined page limit, pages exceeding the specified limit will be removed and not forwarded for peer review. Material submitted after the submission deadline, unless specifically requested by the Government, will not be forwarded for peer review.

Proposals that appear to include plagiarized information will be administratively withheld from further consideration pending institutional investigation. The institution will be requested to perform the investigation and provide those findings to the Grants Officer for a determination of the final disposition of the application.