Program Announcement

Department of Defense (DOD) Congressionally Directed Medical Research Programs

Peer Reviewed Orthopaedic Research Program (PRORP)

Hypothesis Development Award

Funding Opportunity Number: W81XWH-09-PRORP-HDA

Table of Contents

I. FUNDING OPPORTUNITY DESCRIPTION

A. Background Information

1. Program Objectives

The Peer Reviewed Orthopaedic Research Program (PRORP) was established in Fiscal Year 2009 (FY09) to address the leading burden of injury and loss of fitness for military duty by funding innovative, high-impact, clinically relevant research to advance treatment and rapid rehabilitation from musculoskeletal injuries sustained during combat or combat-related activities. The FY09 congressional appropriations bills, Public Law 110-329 and 111-32, provided $61 million (M) and $51M, respectively, for a total appropriation of $112M to support military-relevant, peer-reviewed orthopaedic research. The Government reserves the right to increase or decrease the PRORP funding to execute the program.

The FY09 PRORP challenges the scientific community to design innovative research that will foster new directions for and address neglected issues in the field of medical research focused on combat-relevant orthopaedic problems. Though the program emphasizes funding groundbreaking research, all projects must demonstrate appropriate judgment and sound rationale. The program highly encourages the submission of applications involving multidisciplinary collaborations among academia, industry, the military services, the Department of Veterans Affairs (VA), and other Federal Government agencies.

2. Priority Research Areas

The FY09 PRORP priority research areas relevant to musculoskeletal injury are provided below. ***Not all of the following research areas may be applicable to this Program Announcement/ Funding Opportunity;*** some areas are relevant to other mechanisms offered by the FY09 PRORP. Focus areas specific to this award mechanism are provided in Section B, Award Description. ***All applications for PRORP funding must specifically and clearly address a focus area of the specific award mechanism to which the application is being submitted.***

The FY09 PRORP priority research areas are:

- Acute Care of Battle Injuries (**Roles II and III**)
  - Enhancement of the tissue environment for healing
    - Optimal indicators of viability for soft tissue and bone
    - Methods of enhancing viability
    - Modulators of local inflammatory processes
    - Optimal indicators for limb salvage vs. amputation
    - Optimal timing and materials for vascular, nerve, and other soft tissue repair
  - Prevention of complications
    - Preventing, identifying, and treating compartment syndrome
    - Early intervention strategies for acute management of pain

        - Methods of early bone or soft tissue stabilization
        - Early prevention strategies for infection
    - Development of in vivo translational models for the acute injury environment
- Definitive Care of Battle Injuries
    - Restoration of joint function
        - Optimal materials and clinical care for joint reconstruction
        - Treatment of articular cartilage injury
        - Regeneration of bone, muscle, and cartilage
        - Development of *in vivo* translational models
    - Treatment of orthopaedic injuries (and sequelae) of the spine not related to spinal cord injury (e.g., spinal fractures, acute herniated disks, infection of the spinal column, acute instabilities)
    - Restoration of Function
        - Clinical studies of motor and sensory reinnervation
        - Development of a functional innervated muscle for soft tissue injury
    - Acceleration of healing
        - Clinical efficacy of new and existing products
        - Modulation of systemic responses to injury healing
        - Clinical care for segmental bone loss
- Rehabilitation
    - Evaluation of clinical efficacy of new technologies
        - New and novel approaches to rehabilitation, prosthetics, and orthotics
    - Evaluation of clinical outcomes of rehabilitation strategies, prosthetics, and/or orthotics
    - Evidence-based rehabilitation strategies for warriors in transition with orthopaedic-related injuries
- Prosthetics and Orthotics
    - Maintenance/enhancement of long-term socket performance/fit
        - Design and development of flexible socket suspension systems
        - Evaluation of socket performance
        - Maintenance of limb volume/mass
        - Clinical applications of new technologies
    - Solution of critical issues in osseointegration
        - Translational investigation of skin/prosthesis interface for osseointegrated sockets
        - Reduction of infection risk of osseointegrated limb interfaces

B. Award Description

The PRORP Hypothesis Development Award mechanism is being offered for the first time in FY09.

This award supports the initial exploration of innovative, untested, and potentially groundbreaking concepts in the field of orthopaedic research that may lead to promising new products, pharmacologic agents (drugs or biologics), behavioral interventions, devices, clinical guidance or emerging technologies for military combat-relevant orthopaedic injuries or rehabilitative care. Innovation and novelty of concept are important aspects of this award mechanism. Results of studies conducted through this award may provide the scientific rationale upon which a new hypothesis can be based, or it should provide initial principles of an innovative hypothesis. The Hypothesis Development Award is designed to provide investigators with the opportunity to pursue serendipitous observations; it is not intended to support ongoing work. The existence of preliminary data suggests that the research project should be submitted to a different award mechanism. Successfully completed Hypothesis Development Awards are expected to lead to research endeavors that will garner funding through the Congressionally Directed Medical Research Programs (CDMRP) or other funding agencies.

PRORP Hypothesis Development Award Focus Areas: This award mechanism seeks applications from all areas of basic, preclinical, translational, and clinical research as they relate to ***all*** of the PRORP-identified priority research areas listed under Section A above. ***If the proposed project is not relevant to at least one PRORP-identified priority research area, the Government reserves the right to administratively withdraw the application***. All applications must have a direct relevance to orthopaedic injuries sustained during military combat or related activities.

Use of human subjects and human biological substances: Because these awards are designed for preliminary investigations, projects involving human subjects or specimens will not be supported unless they are either exempt under Title 32, Code of Federal Regulations, Part 219, Section 101(b)(32 CFR 219.101(b)) or eligible for expedited review (32 CFR 219.110 or 21 CFR 56.110). ***Studies that do not qualify for either exempt or expedited status will be administratively withdrawn and will not be funded.*** For studies using only commercially available unidentified specimens, a Claim of Exemption Form will be requested. Additional information regarding exempt status may be found on the USAMRMC Human Research Protection Office website (https://mrmc.amedd.army.mil/rodorphrpo.asp).

This award may not be used to conduct clinical trials. Refer to the Application Instructions & General Information, Appendix 6, for helpful information about distinguishing clinical trials and clinical research. Principal Investigators (PIs) seeking funding for a clinical trial should apply to the Clinical Trial Award mechanism.

Members of each review panel will be blinded to the identity of the PI and the PI's institution. ***Due to the blinded nature of the review process, references to the PI or the institution in the Project Narrative and/or the Military Benefit Statement are prohibited and will result in administrative rejection of the application. In addition, the use of "I," "our," "this institution," or similar phrases that refer to the PI and/or institution in the references listed will result in administrative rejection of the application.***

Encouraged DOD Collaboration and Alignment: Military relevance is a key feature of this award. Therefore, PIs are strongly encouraged to collaborate, integrate, and/or align their projects with military and/or VA research laboratories and programs. The following websites may be useful in identifying information about ongoing DOD areas of research interest:

Air Force Research Laboratory
http://www.wpafb.af.mil/afrl

Congressionally Directed Medical Research Programs
http://cdmrp.army.mil

Defense Advanced Research Projects Agency
http://www.darpa.mil/

Defense Technical Information Center
http://www.dtic.mil

Naval Health Research Center
http://www.med.navy.mil/sites/nhrc

Navy and Marine Corps Public Health Center
http://www-nmcphc.med.navy.mil/

Office of Naval Research
http://www.med.navy.mil/

Office of the Under Secretary of Defense for Acquisition, Technology and Logistics
http://www.acq.osd.mil/

U.S. Army Medical Research Acquisition Activity
http://www.usamraa.army.mil

U.S. Army Medical Research and Materiel Command
https://mrmc.amedd.army.mil

U.S. Army Research Laboratory
http://www.arl.army.mil

U.S. Naval Research Laboratory
http://www.nrl.navy.mil

U.S. Department of Veterans Affairs, Office of Research and Development
http://www.research.va.gov

Use of Human Subjects and Human Biological Substances*:* All DOD-funded research involving human subjects and human biological substances must be reviewed and approved by the USAMRMC Office of Research Protections (ORP), Human Research Protection Office (HRPO), in addition to local 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. Refer to Application Instructions & General Information, Appendix 6, for detailed information.

Use of Military Populations: Describe the military population(s) to be used for the proposed study, if applicable. Coordination of access to various military populations is described below.

1. Active Duty, National Guard, Reserve troops, and/or military patient populations (not CENTCOM Area of Responsibility): Unless the PI has already established access to a service member population, access to Active Duty, National Guard, or Reserve troops must be coordinated through the CDMRP. Collaboration with Associate Investigators in military treatment facilities is encouraged as a method for access to patient populations. ***PIs who do not have a previously established study population should not contact unit Commanders at this time or during preparation of the proposal submission. If selected***

for funding, the PI will be provided guidance on how to obtain access to the appropriate population.

2. CENTCOM Area of Responsibility military populations: Access to military populations in these areas is very limited and will be coordinated through the CDMRP as described above.

Research conducted using military populations in Iraq is conducted with oversight by the Multi-National Force - Iraq (MNF-I). PIs who are outside of this system and submit a research proposal designed to recruit patients within MNF-I must coordinate with the in-theatre Deployed Combat Casualty Research Team charged with facilitating an in-theater review, and be approved by the MNF-I Command and the MNF-I designated Institutional Review Board (IRB). The same is true for research conducted in Afghanistan in the US Forces - Afghanistan (USFOR-A) Area of Responsibility. PIs who are outside of this system and submit a research proposal designed to recruit patients within USFOR-A must coordinate with the in-theatre Deployed Combat Casualty Research Team charged with facilitating an in-theater review, and be approved by the USFOR-A Command and the USFOR-A -designated Institutional Review Board (IRB). If selected for funding, CDMRP will assist with guidance on how to obtain the required in-theatre approvals.

Given the constraints of wartime operations, investigators without an ongoing collaboration with an appropriate military investigator should strongly consider alternatives to conducting in-theater research. DOD-supported human subjects research can only be conducted by institutions (including those in-theater) with approved Federal Assurances of Compliance from the Human Research Protection Office. It is suggested that proposals submitted necessitating the use of this population involve civilian and non-deployed military populations as an alternative.

3. Department of Veterans Affairs (VA) Medical Centers patient populations: Access to patient populations from the VA Medical Centers or use of information from VA data systems must be coordinated by the PI. PIs who submit a research project designed to recruit patients from a VA Medical Center or use information from VA data systems and those who do not have an appointment at one of the VA Medical Centers must include a collaborator with a VA appointment. This collaborator must be willing to assume the role of PI for the VA component of the research. IRB Approval from all participating VA clinical sites will be required.

C. Eligibility

Investigators at all academic levels (or equivalent) are eligible to submit applications. Refer to the Application Instructions & General Information, Appendix 1, for general eligibility information.

D. Funding

- The maximum period of performance is **18** months.
- The maximum allowable funding for the entire period of performance is **$100,000** in direct costs.
- The applicant may request the entire maximum direct cost amount for a project that may be less than the maximum **18**-month period of performance.
- Regardless of the period of performance proposed, the applicant may not exceed the maximum direct cost. In addition to the direct costs, indirect costs may be proposed in accordance with your institution's negotiated rate agreement.

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

- Salary
- Research supplies
- Equipment
- Clinical research costs (While correlative clinical research studies are allowed under this mechanism, clinical trials are not supported.)
- Travel between collaborating institutions
- Travel to a scientific/technical meeting
- Other direct costs as described in Application Instructions & General Information, Attachment 5, Detailed Budget and Justification

In addition, travel funds must be requested for the PI to attend one DOD military research-related meeting to be determined by the Office of the Congressionally Directed Medical Research Programs (CDMRP) during the award performance period.

The CDMRP expects to allot approximately $2.2M of the $112M FY09 PRORP appropriation to fund approximately 14 Hypothesis Development Award applications, depending upon the quality and number of applications received. Funding of applications received in response to this Program Announcement/Funding Opportunity is contingent on the availability of Federal funds for this program.

E. Award Administration

Changes in PI and institution are discouraged and will be allowed only at the discretion of the USAMRMC Contracting Office**.** Refer to the Application Instructions & General Information, Appendix 5, for general award administration information.

II. TIMELINE FOR SUBMISSION AND REVIEW

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

Pre-application Submission Deadline:	**August 25, 2009, 5:00 p.m. Eastern time**
Application Submission Deadline:	**September 15, 2009, 11:59 p.m. Eastern time**
Scientific Peer Review:	**October–November 2009**
Programmatic Review:	**March 2010**

Awards will be made approximately 4 to 6 months after receiving a funding notification letter, but no later than September 30, 2010.

III. SUBMISSION PROCESS

Submission is a two-step process consisting of (1) a pre-application submission through the CDMRP eReceipt system (https://cdmrp.org/), and (2) an application submission through Grants.gov (http://www.grants.gov/).

PIs and organizations identified in the application 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 help desk at help@cdmrp.org or 301-682-5507.

The Government reserves the right to administratively withdraw duplicative applications submitted within the same program or to other CDMRP programs.

A. Step 1 – Pre-Application Components and Submission

Pre-application submission is the required first step. 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 pre-application deadline date***. Refer to the Application Instructions & General Information for detailed information.

- Proposal Information
- Proposal Contacts
- Collaborators and Conflicts of Interest (COI)
- Letter of Intent (LOI) Narrative

B. Step 2 – Application Components and Submission

Applications will not be accepted unless the pre-application process is completed by the pre-application deadline date. Applications must be submitted electronically by the Authorized Organizational Representative (AOR) through Grants.gov (www.grants.gov).

Each application must include the completed application package of forms and attachments identified in www.grants.gov for the US Army Medical Research Acquisition Activity (USAMRAA) Program Announcement/Funding Opportunity. In addition to the specific instructions below, please refer to the Application Instructions & General Information for detailed requirements of each component.

The package includes:

1. **SF-424 (R&R) Application for Federal Assistance Form**

2. **Attachments Form**

   Members of each review panel will be blinded to the identity of the PI and the PI's institution. ***Due to the blinded nature of the review process, identifying or making references to the PI or the institution in the Project Narrative or Military Benefit Statement is prohibited and will result in administrative rejection of the application. In addition, the use of "I," "our," "this institution," or similar phrases that refer to the PI and/or institution in the references listed will result in administrative rejection of the application.***

   - **Attachment 1: Project Narrative (two-page limit)**

     Describe the proposed project in detail using the following outline:

     - **Innovation:** Innovation should be the primary feature of the proposed study.
     - **Rationale/Purpose:** State the rationale for the proposed research. Identify the PRORP research priority area(s) with which the proposed project aligns.
     - **Objectives:** State concisely the specific aims and research strategy of the study. Do not request funding as part of a larger study.
     - **Methods:** Describe the experimental design and methodology. If the methodology is new or unusual, describe it in sufficient detail for evaluation. ***This award may not be used to conduct clinical trials or studies that are not exempt under 32 CFR 219.101(b) or eligible for expedited review (32 CFR 219.110 or 21 CFR 56.110).***

   - **Attachment 2: Supporting Documentation**
     - References Cited (one-page limit)
     - Acronyms and Symbol Definitions
   - **Attachment 3: Statement of Work (SOW; two-page limit)**
   - **Attachment 4: Military Benefit Statement (one-page limit)**

The PI and institution must not be identified in the Military Benefit Statement.

Describe how the proposed work, if successful, may lead to a positive impact on the lives of individuals recovering from combat-relevant orthopaedic injuries, orthopaedic research, and/or treatment outcomes. Describe how the expected results of the proposed work will contribute to the goals of decreasing the clinical impact of these injuries.

Demonstrate how the proposed study is responsive to the health care needs of the Armed Forces and/or the U.S. veteran population. If active duty military or veteran population(s) will be used in the proposed research project, describe the population(s), the appropriateness of the population(s) for the proposed study, and the feasibility of using the population. If a non-military population will be used for the proposed research project, explain how the population simulates the targeted population (i.e., Armed Forces and/or the U.S. veteran population). Show how the proposed study complements ongoing DOD areas of orthopaedic research interest. Describe how the study design will replicate field conditions, if applicable.

- **Attachment 5: Detailed Budget and Justification**
- **Attachment 6: Federal Agency Financial Plan (if applicable)**
- **Attachments 7–15: Subaward Detailed Budget and Justification (if applicable)**

3. Research & Related Senior/Key Person Profile (Expanded Form)

Although requested, Biographical Sketches and Current/Pending Support documentation will not be forwarded for review due to the blinded nature of each level of review for this award. These documents will be used for administrative purposes only.

- 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 Project/Performance Site Location(s) Form

IV. INFORMATION FOR APPLICATION REVIEW

A. Application Review and Selection Overview

Reviewers will be blinded to the identity of the PI and the PI's institution. Due to the blinded nature of the review process, identifying or making references to the PI or the institution within the Project Narrative or Military Benefit Statement is prohibited and will result in administrative rejection of the application. In addition, the use of "I," "our," "this institution," or similar phrases that refer to the PI and/or institution in the references listed will result in administrative rejection of the application.

All applications are evaluated by scientists, clinicians, and consumer advocates using a two-tier review process. The first tier is a scientific peer review of applications against established criteria for determining scientific merit. The second tier is a programmatic review that compares submissions to each other and recommends applications for funding based on scientific merit, the overall goals of the program, and the specific intent of the award mechanism. 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 programmatic review processes are conducted confidentially to maintain the integrity of the merit-based selection process. Each tier of review requires panelists to sign a non-disclosure statement attesting that application and evaluation information will not be disclosed outside the panel. Violations of the non-disclosure statement can result in the dissolving of a panel(s) and other corrective actions. Institutional personnel and PIs are prohibited from contacting persons involved in the application review process to gain protected evaluation information or to influence the evaluation process. Violations of these prohibitions will result in the administrative withdrawal of the institution's application. Violations by panelists or PIs that compromise the confidentiality of the peer review and programmatic review processes may also result in suspension or debarment of their employing institutions from Federal awards. Furthermore, it is a crime for Federal officials to disclose confidential information of one party to another third party (Title 18 United States Code 1905).

The Government reserves the right to review all applications based on one or more of the required attachments or supporting documentation.

B. Review Criteria

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

- **Innovation**
  - The degree to which the proposed concept is innovative.
  - Whether the concept is untested (existence of preliminary data is inconsistent with the intent of the mechanism).
- **Military Benefit**
  - How well the proposed work aligns with PRORP research priority areas and addresses a critical problem in orthopaedic research or clinical practice for combat-relevant musculoskeletal injuries.
- **Research Strategy and Feasibility**
  - Whether the research strategy is appropriate to accomplish the objectives.
  - How the concept will give rise to a testable hypothesis, if successful.

2. Programmatic Review: The following criteria are used by programmatic reviewers to make funding recommendations that maintain the program's broad portfolio:

- Adherence to the intent of the award mechanism
- Programmatic relevance
- Ratings and evaluations of the peer reviewers
- Relative innovation and military benefit
- Program portfolio balance

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

V. ADMINISTRATIVE ACTIONS

After receipt of applications from Grants.gov, the following administrative actions may occur:

A. Rejection

The following will result in administrative rejection of the application:

- Project Narrative exceeds page limit.
- Project Narrative is missing.
- Military Benefit Statement is missing.
- PI's name or institution is included in the Project Narrative or Military Benefit Statement.
- Use of "I," "our," "this institution," or similar phrases in the Project Narrative and Military Benefit Statement that refer to the PI and/or institution in the references listed.
- Budget is missing.
- Page size is larger than 8.5 inches x 11.0 inches (approximately 21.59 cm x 27.94 cm).

B. Modifications

- Pages exceeding the specified limits will be removed for all documents other than the Project Narrative.
- Documents not requested will be removed.
- Following the application deadline, you may be contacted by the CDMRP via email with a request to provide certain missing supporting documents (excluding those listed directly above in Section A, Rejection). The missing documents must be provided by 5:00 p.m. Eastern time on the second full business day following the date the email was sent. Otherwise, the application will be peer reviewed without the missing documents.

C. Withdrawal

The following may result in administrative withdrawal of the application:

- FY09 IP member(s) is found to be involved in the pre-application or application processes including, but not limited to, concept design, application development, budget preparation, and the development of any supporting document. A list of the FY09 IP members may be found at http://cdmrp.army.mil/09prorppanel
- The application includes a clinical trial.
- Submission of the same research project to different award mechanisms within the same program or to other CDMRP programs.
- The PI does not meet the eligibility criteria as described in this Program Announcement/Funding Opportunity.
- The application does not conform to this Program Announcement/Funding Opportunity description to an extent that precludes appropriate scientific peer and programmatic review.
- Direct costs as shown on the Detailed Budget and Justification form exceed the maximum allowed by the award mechanism.
- Inclusion of URLs, with the exception of links to published references.
- Inclusion of studies that do not qualify for either exempt status under Title 32, Code of Federal Regulations, Part 219, Section 101(b) (32 CFR 219.101[b]) or expedited review (32 CFR 219.110 or 21 CFR 56.110).
- The proposed project is not relevant to at least one of the award mechanism-specific focus areas.

D. Withhold

Applications that appear to involve research misconduct will be administratively withheld from further consideration pending institutional investigation. The institution will be requested to provide the findings of the investigation to the USAMRAA Contracting/Grants Officer for a determination of the final disposition of the application.

VI. CONTACT INFORMATION

A. Program Announcement/Funding Opportunity, application format, or required documentation: To view all funding opportunities offered by the 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

B. 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

C. Grants.gov contacts: Questions related to application submission through the Grants.gov (http://www.grants.gov/) portal should be directed to the Grants.gov help desk, which is available Monday through Friday, 7:00 a.m. to 9:00 p.m. Eastern time. Deadlines for application submission are 11:59 p.m. Eastern time on the deadline date. Please note that the CDMRP help desk is unable to answer questions about Grants.gov submissions.

Phone: 800-518-4726
Email: support@grants.gov

Grants.gov will notify PIs of changes made to this Program Announcement/Funding Opportunity and/or application package ONLY if the PI subscribes to the mailing list by clicking on the "send me change notification emails" link 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.