Appendix A
Fiscal Year 2002 Tuberous Sclerosis Complex Research Program Announcement Electronic Letter of Intent

All applicants considering submission of a proposal in response to this program announcement are requested to submit an electronic Letter of Intent by May 21, 2002. This form can be found on the Congressionally Directed Medical Research Programs web site at http://cdmrp.army.mil.

Appendix B

Proposal Preparation

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Proposal Preparation

1. Who May Apply

Eligible institutions include for-profit, non-profit, public, and private organizations. Examples include universities, colleges, hospitals, laboratories, companies, and agencies of local, state, and federal governments. All individuals, regardless of ethnicity, nationality, or citizenship status, may apply as long as they are employed by, or affiliated with, an eligible institution. The U.S. Army Medical Research and Materiel Command (USAMRMC) is especially interested in receiving applications from Historically Black Colleges and Universities/Minority Institutions (HBCU/MI).

Please refer to sections on specific award mechanisms for additional eligibility criteria.

Investigators are cautioned that awards are made to institutions. Should the Principal Investigator (PI) of a funded project leave the recipient institution, both the PI and an official of the recipient institution should contact the U.S. Army Medical Research Acquisition Activity (USAMRAA) awarding office prior to the PI leaving the recipient institution to discuss options available for continued support of the research project.

Historically Black Colleges and Universities/Minority Institutions

A goal of the Department of Defense (DOD) is to allocate funds for the Congressionally Directed Medical Research Programs' (CDMRP's) peer reviewed research to fund proposals from HBCU/MI. This provision is based upon guidance from Executive Orders[1] and is intended to "advance the development of human potential, provide quality education, increase opportunities to participate in and benefit from Federal Programs and strengthen the capacity of targeted institutions." An institution's minority status is established by the Department of Education (DOEd). Proposals submitted to the DOD are assigned HBCU/MI status if they are so designated by the DOEd on the date that the program announcement is released. The DOEd list is posted on the CDMRP web site at http://cdmrp.army.mil/spp under Minority Institutions. Any individual, regardless of ethnicity, nationality, or citizenship status, may apply for funding as long as they are employed by, or affiliated with, an eligible institution.

HBCU/MI proposals will be reviewed concurrently with all others in the same research area during scientific peer review, but may be evaluated separately during programmatic review when award recommendations are determined. Consistent with the CDMRP's goal, recommendations for funding HBCU/MI submissions will be based upon scientific excellence and program relevance.

[1] Executive Orders 12876, 12900, and 13021

2. Proposal Acceptance Criteria

Please follow the compliance guidelines listed below when preparing your proposal. **Note that all proposals must be converted into an electronic PDF (Portable Document Format) file for electronic submission. Applicants unfamiliar with the preparation of PDF files are encouraged to acquire the software and learn the process before the submission deadline.**

Compliance guidelines have been designed to ensure the presentation of all proposals in an organized and easy-to-follow manner in order to assist scientific reviewers responsible for reviewing proposal merit. Scientific peer reviewers will expect to see a consistent, prescribed format for each proposal. Nonadherence to format requirements (such as font size, margins, line spacing, proposal components out of order) makes proposals difficult to read, may be perceived as an attempt to gain an unfair competitive advantage, and may result in proposal rejection or a poorer global priority score in scientific peer review. **Excess pages may result in administrative rejection prior to scientific peer review.**

For the preparation of proposals for PDF submission, it is required that the instructions in this section be followed carefully. The proposal must be clear and legible and conform to the following format, font size, spacing, margin, and printing guidelines:

- Type Font: 12 point, 10 pitch.
- Type Density: No more than 15 characters per inch. (For proportional spacing, the average for any representative section of text should not exceed either 15 characters per inch or 114 characters per line.)
- Spacing: Single-spaced between lines of text, no more than five lines of type within a vertical inch.
- Margins: Minimum of 0.5-inch top, bottom, right, and 1-inch left.
- Type Color: Black type for all graphs, diagrams, tables, and charts. The proposal should contain only material that can be photocopied. Investigators are cautioned that color graphs or photographs may not reproduce in subsequent photocopies. Therefore, submission of color figures, tables, graphs, or photographs is not recommended.
- Spell out all acronyms the first time they are used. One page following the proposal body is allocated to spell out acronyms, abbreviations, and symbols.
- Language: English.
- Print Area: 7.0 x 10.0 inches. (<u>Note to international applicants</u>: The text of the proposal must not exceed 7.0 x 10.0 inches [approximately 19 cm x 25.5 cm].)

To assist applicants, the following example is included.

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3. Proposal Information

Please complete the Proposal Information as described at http://cdmrp.org/proposals. Instructions will be available through the web site by April 15, 2002. See Section 5, page ii of the Foreword or Part 20 of this Appendix (Proposal Submission) for more information regarding the complete electronic submission process.

4. Title/Referral Page – No page limit

Please complete the Title/Referral Page, which can be downloaded from the CDMRP web site at http://cdmrp.army.mil/funding/reposit Complete each section as described:

a. Proposal title (up to 160 characters).

b. Proposal log number (this will be automatically provided when a draft of the Proposal Information is completed and saved).

c. PI's full name (first, middle initial, last).

d. Award mechanism.

e. Keyword descriptive technical terms: To assist the staff in assigning proposals to the appropriate scientific peer review panel, please specify the subject area of the proposal. Also, list specific keywords and descriptive technical terms that would best describe the technical aspects of the project (e.g., signal transduction, drug development, gene therapy, clinical neurology, magnetic resonance imaging, genetic counseling, quality of life).

f. Conflicts of interest: Every effort is made to avoid real and apparent conflicts of interest during the peer review process. To assist the staff in this regard, list the names of all scientific participants in the proposal including the PI, co-investigators, research associates, research assistants, consultants, collaborators, and subcontractors. In addition, list the names of other researchers outside the scope of this proposal that may have a conflict of interest in review of this proposal. Provide the following information for each participant: name, institutional affiliation(s), and role(s) on the proposed project or perceived conflicts of interest.

Title/Referral Page

No Page Limit

a. Proposal title (up to 160 characters)

b. Proposal log number

c. PI's full name (first, middle initial, last)

d. Award mechanism

e. Keyword descriptive technical terms

f. Conflicts of interest: Include the following information (no page limit)

Name	Institutional Affiliation(s)	Role(s) on Proposed Project or Perceived Conflicts of Interest

5. Table of Contents – Start section on a new page – 1-page limit

Prepare a Table of Contents, with page numbers, using the outline provided in the Proposal Preparation section under each award mechanism. Number all pages consecutively at the bottom center, beginning with the Title/Referral Page. Provide a header on every page of the proposal that includes the PI's name (last name, first name, middle initial) and proposal log number (this will be automatically provided when a draft of the electronic Proposal Information is saved).

6. Checklist for Proposal Submission (Instructions)

The Checklist for the Fiscal Year 2002 (FY02) Tuberous Sclerosis Complex Research Program (TSCRP) Proposal Submission found on page B-7 must be completed and submitted with your PDF proposal. Place it immediately after the Table of Contents.

Complete and place this form immediately after the Table of Contents to confirm that all components are included in your application.

Checklist for the FY02 TSCRP Proposal Submission

Yes	No	
☐	☐	Proposal Information completed
☐	☐	Title/Referral Page
☐	☐	Table of Contents
☐	☐	Checklist for FY02 TSCRP Proposal Submission
☐	☐	Structured Technical Abstract (1-page limit)
☐	☐	Lay Abstract (1-page limit)
☐	☐	Statement of Work (2-page limit)
☐	☐	Proposal Relevance Statement (1-page limit)
☐	☐	Proposal Body **(adhere to page limits for the individual mechanism)**
☐	☐	Abbreviations (1-page limit)
☐	☐	References (no page limit)
☐	☐	Biographical Sketches (3-page limit per individual)
☐	☐	Principal Investigator
☐	☐	Collaborating investigators and other key personnel
☐	☐	Existing/Pending Support (no page limit)
☐	☐	Facilities/Equipment Description (no page limit)
		Administrative Documentation:
☐	☐	List of items included in this section
☐	☐	Letters of support from collaborating individuals and/or institutions (all awards)
☐	☐	Detailed Cost Estimate (no page limit)
☐	☐	Total cost estimate matches Proposal Information, item 4
☐	☐	Instruments (no page limit)
☐	☐	List of documents included in Instruments Section (all awards)
☐	☐	Publications and/or Patent Abstracts (5-document limit)
☐	☐	Certificate of Environmental Compliance
☐	☐	Principal Investigator Safety Program Assurance

NOTE: Exceeding page limits may result in proposal rejection prior to peer review. Submit only materials specifically requested or required in this program announcement. Submission of additional materials may be construed as an attempt to gain an unfair advantage.

7. Proposal Abstracts – Start each abstract on a new page – 1 page each

Both a 1-page structured technical abstract and a 1-page lay (nontechnical) abstract are required. Each proposal abstract page should contain the title of the proposal and the name of the PI. Abstracts must be submitted as part of the proposal. **Do not include figures or tables in either abstract.**

These abstracts are vitally important to the review of the proposal. **Programmatic review is based upon the Integration Panel's review of these two abstracts as part of the peer review summary statements; therefore, it is paramount that the investigator submits abstracts that fully describe the proposed work.** Sample abstracts are included in Appendix D of this program announcement.

The structured technical abstract should provide a clear and concise overview of the proposed work, including the background, objective or hypothesis and its supporting rationale, significance of the proposed work to the program's goals, specific aims of the study, and study design.

Please use the outline below for preparing the structured technical abstract.

a. Background: Provide a brief statement of the ideas and reasoning behind the proposed work.

b. Objective/Hypothesis: State the objective/hypothesis to be tested. Provide evidence or rationale that supports the objective/hypothesis.

c. Specific Aims: State concisely the specific aims of the study.

d. Study Design: Briefly describe the study design.

e. Relevance: Provide a brief statement explaining the potential relevance of the proposed work to the program's goals. For example, how the study will prevent or improve the detection or treatment of the disease.

The lay abstract is intended to communicate the purpose of, and rationale for, the study to the non-scientific community. It should be composed in a way to make the scientific objectives and rationale for the proposal understandable to non-scientifically trained readers. The lay abstract should not duplicate the technical abstract.

Abstracts of all funded proposals will be posted on the CDMRP web site at http://cdmrp.army.mil. Thus, proprietary or confidential information should not be included in the abstract.

8. Statement of Work – Start section on a new page – 2-page limit

The Statement of Work (SOW) is a concise restatement of the research proposal that outlines and establishes the PI performance expectations and timeline for which the USAMRMC will provide financial support. Although some allowance is made for problems encountered and uncertainties that are part of research, the PI is expected to meet the provisions and milestones in the SOW.

The SOW should be a series of relatively short statements that outline, step-by-step, how each of the major goals or objectives of the proposed research/services will be accomplished. As appropriate, the SOW should:

a. Describe the work to be accomplished as tasks (tasks may relate to specific aims),

b. Identify the timeline and milestones for the work over the period of the proposed effort,

c. Indicate the numbers of research subjects (animal or human) for each task,

d. Identify methods, and

e. Identify products/deliverables for each phase of the project.

The SOW must not exceed 2 pages of single-spaced typing. Several sample SOWs are included in Appendix D of this program announcement.

9. Proposal Relevance Statement – Start section on a new page – 1-page limit

In the Proposal Relevance Statement, the investigator should describe how the proposed research/services are pertinent to one or more critical issues of the disease.

10. Proposal Body – Start section on a new page

Each award mechanism has specific instructions for the description of the project and page limits. Investigators should refer to the specific evaluation criteria listed under the award mechanism to which they are applying to ensure that the necessary information is included.

11. Abbreviations – Start section on a new page – 1-page limit

Provide a glossary of all acronyms, abbreviations, and symbols used.

12. References – Start section on a new page – No page limit

List all relevant references using a standard reference format that includes the full citation (i.e., author(s), year published, title of reference, source of reference, volume, chapter, page numbers, and publisher, as appropriate).

13. Biographical Sketches – 3-page limit per investigator

Biographical sketches should be included for each of the key personnel listed on the budget page, including collaborating investigators and support staff. Each biographical sketch must not exceed 3 pages. The Biographical Sketch form can be found in Appendix E or downloaded from the CDMRP web site at http://cdmrp.army.mil/funding/default

14. Existing/Pending Support – No page limit

List on a separate page, the titles, time commitments, supporting agencies, durations, and levels of funding for all existing and pending research projects involving the PI and key personnel. Proposals submitted under this program announcement should not duplicate other funded research projects. If no support exists, state "none."

15. Facilities/Equipment Description – No page limit

Describe the facilities available for performance of the proposed research/services. Describe the institutional commitment, including any additional facilities or equipment proposed for acquisition or available for use at no cost to the USAMRMC. Indicate if government-owned facilities or equipment are proposed for use.

16. Administrative Documentation – No page limit

The first item in this section must be a list of all the items in the Administrative Documentation section.

Provide letter(s) from proposed collaborating individuals or institutions confirming collaborative efforts that are necessary for the project's success. Other support documentation also may be required within specific award categories. Please follow specific instructions in each award mechanism.

Note: This section is not for additional data, figures, or other similar information. Support documentation **will not** be accepted separately from the electronic proposal submission.

All administrative documentation must be incorporated into the electronic PDF version of your proposal. All documents or letters requiring signatures must be signed and then scanned into the proposal prior to submission. Help lines will be available by May 7, 2002 to answer specific questions regarding the preparation of proposals for electronic submission, or the process of electronic submission. The help line phone numbers will be provided on two web sites: the CDMRP web site (http://cdmrp.army.mil) and the proposal submission web site (http://cdmrp.org/proposals). Alternately, help can be obtained by e-mail, at help-proposals-cdmrp@cdmrp.org

17. Detailed Cost Estimate – No page limit

Budget is a key consideration in both scientific peer and programmatic review; applicants are cautioned to use discretion in budget requests. In addition, budgets will also be reviewed during award negotiations. Use the Detailed Cost Estimate form to prepare a detailed cost estimate of the proposed research/services. This form can be found in Appendix F or downloaded from the CDMRP web site at http://cdmrp.army.mil/funding/default. The cost of preparing proposals in response to this program announcement is not considered an allowable direct charge to any resultant award.

For all DOD-funded research involving human subjects, medical care for research-related injuries must be provided at no cost to the subject. Many institutions and states provide for this medical care as part of their liability insurance. If not, investigators should plan on budgeting for such costs. The institution business office can assist applicants with budgeting for this requirement. See part 7 of Appendix F (Detailed Cost Estimate) for more details.

18. Instruments – No page limit

Include an appropriately titled page listing the documents you have in this section. Questionnaires, survey instruments, or clinical protocols that apply to the proposal should be included in this section.

19. Publications and/or Patent Abstracts – 5-document limit

Include up to five relevant publication reprints and/or patent abstracts. A patent abstract should provide a non-proprietary description of the patent application. If more than five such items are included in the submission, **the extra items will not be peer reviewed. Submit only material specifically requested or required in this program announcement. Submission of unrequested material may be construed as an attempt to gain a competitive advantage and will be removed.**

These documents must be incorporated into the electronic PDF version of your proposal. Help lines will be available by May 7, 2002 to answer specific questions regarding the preparation of proposals for electronic submission, or the process of electronic submission. The help line phone numbers will be provided on two web sites: the CDMRP web site (http://cdmrp.army.mil) and the proposal submission web site (http://cdmrp.org/proposals). Alternately, help can be obtained by e-mail, at help-proposals-cdmrp@cdmrp.org

20. Proposal Submission

Electronic submission is required. No paper copy submissions will be accepted.

Proposals will be submitted electronically at http://cdmrp.org/proposals. The web site will be available for proposal submission by May 7, 2002. One electronic PDF proposal of the proposal is required and will count as the official proposal submission. The electronic PDF proposal must

be uploaded/submitted through the Internet by an authorized Administrative Representative from the Sponsored Programs Office (or equivalent) of your organization no later than 11:59 p.m. (applicant's local time) on June 4, 2002 and must be accompanied by the Proposal Information, as described below. Consult the timelines located in the Foreword (page ii) or specific award mechanism sections for the exact deadline date of electronic proposal submission.

Several steps are critical for successful electronic submission of your proposal.

1. The applicant is required to submit Proposal Information online at http://cdmrp.org/proposals, to include the e-mail address of an Administrative Representative from the Sponsored Programs Office who is authorized to conduct negotiations on the applicant's behalf. **The Proposal Information must be submitted prior to submission of the proposal. We encourage applicants to begin this part of the submission process at least 2 weeks prior to the submission deadline.**

2. Once the applicant has submitted the Proposal Information, the Administrative Representative from the Sponsored Programs Office will receive an e-mail notification that the Proposal Information is ready for his or her review.

3. Applicants will need to provide the Administrative Representative with an electronic copy of the proposal. Applicants are encouraged to coordinate early with their Sponsored Programs Office.

4. The Administrative Representative is required to provide final approval of the Proposal Information and then to upload/submit the proposal file in PDF. Please note that the web site does not allow applicants to upload/submit their proposals directly. **Proposals may ONLY be uploaded/submitted by the Administrative Representative from the Sponsored Programs Office and this can be done ONLY after he or she has approved the Proposal Information.**

Please note that all proposals must be submitted electronically to this program; printed supplemental materials will not be accepted. Any supporting documentation that the applicant wishes to include with the proposal must be scanned and incorporated into the PDF file prior to upload/submission. Proposal Information must be completed online and the PDF version of the proposal uploaded/submitted through the CDMRP web site no later than **11:59 p.m. (applicant's local time) on June 4, 2002.** Detailed instructions for electronic submissions will be available at http://cdmrp.org/proposals.

21. Submission Deadlines

The submission deadline for all proposals requested in this program announcement is 11:59 p.m. (applicant's local time) on June 4, 2002. The electronic PDF version of your proposal must be sent through the Internet by the sponsored programs office (or equivalent) of your organization by that time.

If your proposal is submitted electronically after 11:59 p.m. (applicant's local time) on

June 4, 2002, it may not be considered for review.

22. Regulatory Compliance and Quality Requirements

Please complete and sign the Certificate of Environmental Compliance found on pages B-14 to B-15 of this Appendix. Also, please complete and sign the Principal Investigator Safety Program Assurance form found on page B-16 of this Appendix.

The other Regulatory Compliance and Quality documents (Research Involving Human Subjects, and/or Anatomical Substances, Research Involving Animals, and Safety Program Plan) should not be included with the submitted proposal; instead, these documents should only be provided by the PI to the USAMRMC upon request. These documents should be available on the CDMRP web site by April 2002.

Certificate of Environmental Compliance

The Certificate of Environmental Compliance should be executed by the institution's official responsible for environmental compliance.

The Council on Environmental Quality (CEQ) regulations (40 CFR 1500-1508[1]) that implement the National Environmental Policy Act (Public Law 91-190, as amended) require all federal agencies to examine possible environmental consequences of their proposed and ongoing actions.

The U.S. Army Medical Research and Materiel Command (USAMRMC) examines all medical research and development projects, whether inside or outside the United States, for their potential environmental impacts. In most cases, awardees conducting research in established laboratories that are in compliance with environmental laws and regulations, or are already covered by existing environmental documentation, will not be required to provide additional information about the environmental impact of their proposed research. Such projects will receive a "categorical exclusion" according to the Army regulations that implement the CEQ regulations (Army Regulation 200-2). After a proposal has been selected for award, the USAMRMC will determine if a categorical exclusion is warranted. If there are any extraordinary circumstances surrounding the research (e.g., research that involves the transfer of recombinant DNA molecules into the genome of one or more human subjects, requires Biosafety Levels 3 and 4, or uses animals captured from the wild), further information may be requested from the investigator to determine the environmental impact of the proposed research. This information should be submitted in a timely manner in order to receive an award.

[1] Title 40, Code of Federal Regulations, Sections 1500-1508

Certificate of Environmental Compliance

The offeror currently ☐ IS ☐ IS NOT (check appropriate category) in compliance with applicable national, state, and local environmental laws and regulations. (If not in compliance, attach details and evidence of approved mitigation measures.)

The offeror has examined the activities encompassed within the proposed action entitled

"_____

_____"

(enter title and Principal Investigator's name), for compliance with environmental laws and regulations. The offeror states that the conduct of the proposed action:

1. WILL NOT violate any applicable national, state, or local environmental law or regulation, and

2. WILL NOT have a significant impact on the environment.

The offeror agrees that if the work required under the proposed action at any time results in a significant impact on the environment or a violation of any applicable environmental law or regulation, the offeror will immediately take appropriate action, to include notifying and/or coordinating with the appropriate regulatory agencies as required by law and notifying the Grants Officer.

_____	_____
Name of Official Responsible for Environmental Compliance	Signature
_____	_____
Title	Date
_____	
Name of Organization	

Principal Investigator Safety Program Assurance

- I assure that I have involved the Facility Safety Director/Manager in the planning of this research proposal, discussed with him/her all aspects of the proposal that relate to occupational health and safety, and will help him/her prepare the annual Facility Safety Plan Status Report.

- I assure that I will comply with my institution's safety program and its requirements.

- I understand that I am directly responsible for all aspects of safety and occupational health specific to my research protocol.

- I assure that I will report to the Facility Safety Director/Manager any changes in the safety or occupational health practices due to changes in my originally planned research.

- I assure that hazards associated with my research have been identified, eliminated and/or controlled.

- I assure that all Safety Plan requirements are in compliance with 32 CFR 626 and 627, "Biological Defense Safety Program and Biological Defense Safety Program, Technical Safety Requirements" (*if applicable*).

_____
Name of Principal Investigator (print)

_____ _____
Signature Date

Mailing Address: _____
Street

_____
City State Zip Code

Phone Number: _____

Fax: _____

E-mail Address: _____

Appendix C

Proposal Information

The Proposal Information and instructions for completing it will be available at the Congressionally Directed Medical Research Programs-related web site http://cdmrp.org/proposals. The web site will be available for proposal submission by May 7, 2002. One electronic PDF (Portable Document Format) version of the proposal is required and will count as the official proposal submission. Applicants should refer to sections on individual award mechanisms and Appendix B for appropriate submission requirements.

Several steps are critical for successful electronic submission of your proposal.

1. The applicant is required to submit Proposal Information online at http://cdmrp.org/proposals, to include the e-mail address of an Administrative Representative from the Sponsored Programs Office who is authorized to conduct negotiations on the applicant's behalf. **The Proposal Information must be submitted prior to submission of the proposal. We encourage applicants to begin this part of the submission process at least 2 weeks prior to the submission deadline.**

2. Once the applicant has submitted the Proposal Information, the Administrative Representative from the Sponsored Programs Office will receive an e-mail notification that the Proposal Information is ready for his or her review.

3. Applicants will need to provide the Administrative Representative with an electronic copy of the proposal. Applicants are encouraged to coordinate early with their Sponsored Programs Office.

4. The Administrative Representative is required to provide final approval of the Proposal Information and then to upload/submit the proposal file in PDF. Please note that the web site does not allow applicants to upload/submit their proposals directly. **Proposals may ONLY be uploaded/submitted by the Administrative Representative from the Sponsored Programs Office and this can be done ONLY after he or she has approved the Proposal Information.**

Please note that all proposals must be submitted electronically to this program; printed supplemental materials will not be accepted. Any supporting documentation that the applicant wishes to include with the proposal must be scanned and incorporated into the PDF file prior to upload/submission. Proposal Information must be completed online and the PDF proposal uploaded/submitted through the web site (http://cdmrp.org/proposals) no later than **11:59 p.m. (applicant's local time) on June 4, 2002.** Detailed instructions for electronic submissions will be available at http://cdmrp.org/proposals.

Help lines will be available by May 7, 2002 to answer specific questions regarding Proposal Information and the preparation of proposals for electronic submission, or the process of

electronic submission. The help line phone numbers will be provided on two web sites: the CDMRP web site (http://cdmrp.army.mil) and the proposal submission web site (http://cdmrp.org/proposals). Alternately, help can be obtained by e-mail, at help-proposals-cdmrp@cdmrp.org.

Appendix D

Sample Abstracts and Statements of Work

Page
Sample Abstracts (Technical and Lay) D-2
Sample Statements of Work D-6

TECHNICAL ABSTRACT

Steroid Hormones in NF1 Tumorigenesis
Margaret R. Wallace, Ph.D., Investigator-Initiated Research Award Recipient

Background: Clinical literature suggests that steroid hormones may play a role in NF1 since neurofibroma growth shows some parallels with hormonal changes. For example, many patients develop neurofibromas at puberty, pregnancy often increases tumor size/number, women with NF1 may have a higher risk of malignancy and a higher neurofibroma burden, and neurofibroma development often slows in older adults. The steroid hormone field is being intensely researched in many types of cancer, but virtually nothing is known about these pathways in normal or NF1-tumor derived Schwann cells. Schwann cells comprise the bulk of these tumors, in which they are somatically mutated.

Objective/Hypothesis: The growth responses of normal and NF1 tumor Schwann cells to steroid hormones will be characterized, focusing on estrogen and progesterone. The hypothesis is that human neurofibroma (and malignant peripheral nerve sheath tumor [MPNST]) Schwann cells have increased hormone responsiveness compared to normal Schwann cells, leading to tumor growth.

Specific Aims: (1) To determine steroid hormone receptor expression in human normal, NF1 neurofibroma, and NF1 MPNST Schwann cells pre- and post-hormone treatment, (2) to test in vitro responses (proliferation and cell survival) of cultured human Schwann cells from normal nerve, NF1 neurofibromas and NF1 MPNSTs to estrogen and progesterone and their antagonists, and (3) to test in vivo responses of NF1-derived tumor Schwann cell lines to estrogen and progesterone, through a xenoplant model in *Nf1*/*scid* mice.

Study Design: We have developed a set of neurofibromin-negative Schwann cell cultures from NF1 patient tumors. The steroid receptor profile of normal and tumor-derived Schwann cells will be characterized before and after steroid treatment to establish a basis for the mechanism of action of these hormones. The cells will be tested for increased proliferation and survival rates in response to these hormones in vitro. These cells will also be analyzed in vivo by reconstitution of tumors through sciatic nerve injection of these cells into *Nf1* heterozygous mutant mice that are also immunodeficient (carry the *scid* genotype). This mouse line is being established in our group. The mice carrying xenoplants will be treated with estrogen and progesterone to determine if there are any hormone-regulated proliferative or survival effects in the in vivo situation.

Relevance: There is a crucial need for information about how NF1 tumors respond to steroid hormones, especially for patients who are candidates for hormone therapies for various reasons. Understanding steroid hormone signaling in tumor cells will help predict responses to such therapies in order to establish guidelines. Also, differences in neurofibroma/MPNST receptor profiles or responses compared to normal ones could be a target for antitumor therapies. The in vivo work will produce an animal model for testing such therapies. Many selective estrogen receptor modulators are being developed for this purpose in other tumor types that could be useful in NF1 if there is a research-based rationale supporting clinical trials. Our work will address this need.

LAY ABSTRACT

Steroid Hormones in NF1 Tumorigenesis
Margaret R. Wallace, Ph.D., Investigator-Initiated Research Award Recipient

Neurofibromatosis type 1 (NF1) is a common genetic disease with a wide variety of features primarily involving the nervous system and related tissues. NF1 is characterized by abnormal cell growth, the most common form being the neurofibroma, a generally slow-growing benign nerve tumor composed mostly of Schwann cells. Dermal neurofibromas can cause disfigurement and affect function, depending on location and size. Plexiform neurofibromas can grow very large and may be disabling or fatal. There are clinical reports suggesting that neurofibromas may be initiated or aggravated in growth at times of hormonal fluctuations, particularly when steroid sex hormones increase (infancy, puberty, pregnancy). This is an area of great interest in research of cancer. However there has been virtually no research in this field in NF1 or Schwann cells. This project will determine scientifically whether the hormones estrogen or progesterone have a growth-promoting effect in neurofibromas. The results of these studies will have relevance for doctors prescribing hormone therapies (for reasons such as birth control, menopause, and breast cancer, for example), and for therapy development aimed specifically at stopping or preventing neurofibroma growth. We will also study the malignancy (malignant peripheral nerve sheath tumor [MPNST]) that can develop in plexiform tumors.

Since there is no established neurofibroma animal model to test hormone effects, we will use Schwann cell cultures we obtained from NF1 neurofibromas and MPNSTs. These cultures can grow after transplantation into the mouse nerve, developing a small version of the original human tumor. The goal of this project is to use this unique set of cultures to test the tumor growth-promoting effects of steroid hormones in tissue culture and in the animals carrying the engrafted tumors. Furthermore, we will use a new line of immunodeficient mice that we are developing that carry an *NF1* gene mutation to better replicate the human situation and provide a future model to test new therapies.

The first specific aim will examine the genes responsible for transmitting the hormone signals (steroid receptors) and other genes that are turned on or off by hormones. Thus, we can examine which genes are affected by hormone treatments and relate that to cell growth. The second aim is to test whether these tumor cells show increased growth or cell survival in tissue culture in response to estrogen or progesterone and to see if these effects can be reversed with hormone antagonists such as tamoxifen. The third aim will then test for this growth-promoting property in tumors grown in mice. This project takes an innovative approach to studying steroid hormone effects in NF1 tumorigenesis by using human neurofibroma or MPNST cells and using a unique mouse transplant model. The combination of tissue culture and animal work using human tumor cells (from both sexes) should provide data most closely translatable to the patient situation. The results of these experiments will be the basis for future patient clinical trials. It is possible that the results will be mixed, suggesting that these effects may vary between individuals or tumors. But this, too, would be an important observation to help physicians choose therapies best suited to individual patients or tumors (perhaps through use of screening tests based on our work).

TECHNICAL ABSTRACT

Structure-Function Relationships in Merlin, the Product of the NF2 Causal Gene
Zygmunt S. Derewenda, Ph.D., Investigator-Initiated Research Award Recipient

Background: The NF2 causal gene encodes a protein known as merlin (or schwannonin). This protein is a member of the ERM (ezrin, radixin, moesin) family of regulatory molecules, which play a role in the control of cytoskeletal functions mediated by the small cytosolic GTPases from the Rho family. These proteins contain two interacting domains, connected via a helical linker, which bind other components of signaling pathways, linking surface receptors to cytoskeleton. One of the presumed functions of ERM proteins is transient interaction with RhoGDI (Rho guanine nucleotide exchange inhibitor). This process may lead to the activation of nucleotide exchange factors and promote cell growth, transformation, etc. Malfunction of this pathway due to mutations in the NF2 gene is the likely cause of tumors in neurofibromatosis.

Objective: The objective of this project is to obtain direct information regarding the atomic structure of merlin, its internal dimerization, and of the way in which its N-terminal domain interacts with RhoGDI. An additional objective is to map the functional domains on RhoGDI and merlin and to analyze the contributions of the individual amino acids through systematic site-directed mutagenesis and microcalorimetry.

Specific Aims: The project will result in the crystallization and crystal structure determination of the N-terminal fragment of merlin, its complex with the C-terminal lobe, and the complex of the N-domain with the smallest fragment of RhoGDI, which would show the wild-type affinity. Structure solution and refinement will be conducted at the highest possible resolution, hopefully better than 2Å.

Study Design: Individual proteins will be overexpressed in *Escherichia coli* in fusion with affinity tags, typically GST (glutathione S transferase), and purified by a combination of affinity and gel filtration, and/or ion exchange chromatography. The complexes will be typically isolated by size exclusion chromatography. Crystallization will be carried out by hanging and sitting drop methods following established protocols. The 'minimum entropy' method recently developed in the Principal Investigator's laboratory will be used to increase the efficiency of the crystallization process. Diffraction data will be collected using synchrotron radiation to achieve the highest possible resolution and precision. The structures will be solved by a combination of molecular replacement and MAD (multiwavelength anomalous dispersion methods) and refined by standard methods using software packages CNS, CCP4, and SHELX, depending on the resolution of the data. Thermodynamics of the merlin-RhoGDI interactions will be assessed by isothermal titration calorimetry and analyzed using ORIGIN software.

Relevance: The proposal is directly related to the main objectives of the neurofibromatosis research program. It addresses the very nature of the type II disease, its molecular causes and mechanisms involved in the onset. It also relates directly to key problems of cell regulation and cell transformation in general.

LAY ABSTRACT

Structure-Function Relationships in Merlin, the Product of the NF2 Causal Gene
Zygmunt S. Derewenda, Ph.D., Investigator-Initiated Research Award Recipient

Neurofibromatosis type II is a fairly common syndrome that leads to multiple tumors on nerves and other lesions of the brain and spinal chord, often affecting hearing nerves. It is distinct from neurofibromatosis type I in its symptoms and roots. The disease is known to be caused by mutations, i.e., changes in the DNA sequence, in the gene known as the NF2 causal gene. The NF2 gene contains genetic code that leads, in living cells, to the synthesis of a specific protein molecule—merlin—also called schwannonin. The mutations in the gene, which occur in afflicted individuals, result in the changes in the chemistry of the protein, so that 'incorrect' amino acids are incorporated in place of normal ones. Merlin is a fairly large protein made up of nearly 500 amino acids and folded into a structure that is not fully understood. What is known is that this molecule contains three distinct lobes, two of which—located at either end—are involved in interactions with other protein molecules that in turn regulate many of the functions in a normal cell. It has been shown that inert merlin folds onto itself, with the two terminal lobes (or domains) interacting with each other. The biologically active molecule is open, with each lobe involved in contacts with its partners from the signaling cascade. One of such partner molecules for merlin is known as GDI, a protein involved in the activation of many cells leading to transformation and tumor growth. We propose in our application to study the atomic structure of merlin both in its inactive form and when one of its domains is bound to GDI. This will lead to a better understanding of the mechanisms, the malfunction of which appears to be associated with the onset of NF2.

We propose to accomplish our goal by first producing samples of both terminal lobes of merlin and of GDI in the bacterium *Escherichia coli* using recombinant DNA methods and by crystallizing these protein alone and in complexes. Once single crystals become available, we will use the technique of x-ray crystallography to obtain accurate three-dimensional models of the atomic structure of the protein molecules. The technique of x-ray crystallography is uniquely suited to probe the issues of structure and function in biomolecules and the structural models generated by this approach are very reliable. Using the model structures, we will identify the surfaces in the proteins that are involved in signaling, and we will probe the specific function of each amino acid involved in those surfaces (or epitopes) using site directed mutagenesis and another experimental technique known as microcalorimetry.

The results generated by our research are likely to dissect the functionality of merlin and to explain, at least in part, the impact that NF2-causing mutations have on merlin. This improved understanding in the causes of the disease may then be used by those who are involved in the design of novel therapeutic approaches.

JONES, REBECCA E.

Statement of Work

Development of Peptide Inhibitors of the "Cancer" Receptor (CR)

Task 1. To identify the minimal region of the CR polypeptide able to inhibit intact CR when co-expressed in cultured cells (Months 1-18):

a. Develop a series of plasmids for expressing the CR open reading frame (Months 1-7).
b. Perform assays to ascertain which fragments of CR block DNA-binding (Months 7-18).
c. Confirm that fragments of the CR open reading frame that block DNA-binding activity also inhibit CR function *in vivo* (Months 18-24).

Task 2. To identify short peptides modeled after the receptor that act as inhibitors of DNA binding and subunit association (Months 18-36):

a. Obtain synthetic CR peptides (Months 18-21).
b. Test the effect of synthetic peptides on the DNA-binding activity of CR (Months 20-24).
c. Characterize the inhibitory potency of active peptides and attempt to optimize the effect by testing additional overlapping peptides (Months 21-36).
d. Perform feasibility experiments to assess the ability of selected peptides to inhibit CR function in cultured cells (Months 20-36).

WILSON, JOHN R.

Statement of Work

Ultrasound Imaging

Task 1. Modification of ultrasound imaging gantry, Months 1-12:

a. Modify imaging gantry to permit measurements of the optics.
b. Perform measurements using a multi-modal scanning configuration.
c. Design of final optics.

Task 2. Extensive evaluation of ultrasound imaging gantry with the final optics, Months 13-36:

a. Repeat measurements using the final optics.
b. Measure the contrast improvement provided by the new detector configuration relative to conventional detector configuration.
c. Conduct specimen experiments to evaluate the increase in resolution provided by the magnification.
d. Investigate the extent of artifacts in fixed and scanning modes.
e. Participate in design of a clinical evaluation study comparing modified ultrasound mammography with conventional mammography.

YOUNG, SUSAN D.

Statement of Work

Follow-up Care for Men and Women with Cancer

Task 1. Develop Plan for Follow-up Patient Interviews, Months 1-3:

a. The tracking system shell from the previous cancer project will be modified to track patient recruitment and contact process.
b. The follow-up patient interview will be pre-screened with cancer patients from our hospital who are not enrolled in our study and modifications will be incorporated.
c. The environmental process interview (EPI) used for the baseline interview will be adapted for the follow-up interview.
d. Institutional Review Board approval will be obtained from all hospital sites.
e. The patient interviewer will be trained in medical terminology, measures of the interview, and use of the modified EPI system.

Task 2. Preparation for Medical Record Abstractions, Months 3-9:

a. The Medical Record Abstract form will be finalized and the investigator trained to perform patient data reviews using the instrument.
b. The Medical Record Abstract form will be revised for direct computer data entry.

Task 3. Subject Recruitment and Data Collection, Months 9-20:

a. Patients enrolled in our previous study will be recruited for the proposed follow-up study.
b. Interviews subsequent to the first follow-up will be modified as necessary to reflect issues relevant to patients beyond the period of adjuvant therapy.
c. Surveys will be sent to and data collected from enrolled patients every 6 months.

Task 4. Abstraction of Medical Records, Months 12-24:

a. Medical record abstractions will be performed for surviving enrolled patients annually.
b. Data entry and quality control measures will be ongoing.
c. Follow-up interviews will be conducted once annually with surviving enrolled patients over the 4-year study period.

Task 5. Interim Analyses, Months 24-44:

a. Interim statistical analyses of data obtained from interviews and medical record abstractions will be performed periodically.
b. Annual reports will be written.

Task 6. Final Analyses and Report Writing, Months 44-48:

a. Final analyses of data from interviews and medical record abstractions will be performed.
b. A final report and initial manuscripts will be prepared.

Appendix E

Biographical Sketches

Provide the following information for the key personnel listed on page 1 of the Detailed Cost Estimate form (see Appendix F) for the initial budget period.

NAME	POSITION TITLE

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and representative earlier publications pertinent to this application. PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY. DO NOT EXCEED 3 PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

Appendix F

Detailed Cost Estimate Form Instructions

The following sections describe the categories of costs that should be recorded on the Detailed Cost Estimate form. All amounts entered should be in U.S. dollars.

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Part		Page
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2.	Consultant Costs	F-2
3.	Major Equipment	F-3
4.	Materials, Supplies, and Consumables	F-3
5.	Travel Costs	F-3
6.	Research-Related Subject Costs	F-3
7.	Research-Related Injury Medical Costs	F-3
8.	Other Expenses	F-4
9.	Consortium Costs	F-4
10.	Indirect Costs	F-4
11.	Total Costs for the Entire Proposed Period of Support	F-4
12.	Justification	F-5
13.	Relocation of Principal Investigator	F-5
	Detailed Cost Estimate Form	F-6

1. Personnel

- **Name:** Starting with the Principal Investigator (PI), list the names of all participants who will be involved in the project during the initial budget period, regardless of whether salaries are requested. Include all collaborating investigators, research associates, individuals in training, and support staff. Only **ONE** person may be identified as the PI of the proposal.

- **Role on Project:** Identify the role of each individual listed on the project. Describe his or her specific functions in the "Justification" section of the Detailed Cost Estimate form.

- **Type of Appointment (Months):** List the number of months per year reflected in an individual's contractual appointment with the offering organization. The Department of Defense (DOD) staff assumes that appointments at the applicant organization are full time for each individual. If an appointment is less than full time, e.g., 50 percent, note this with an asterisk (*) and provide a full explanation in the "Justification" section of the Detailed Cost Estimate form. Individuals may have split appointments (e.g., for an academic period and a summer period). For each type of appointment, identify and enter the number of months on separate lines.

- **Annual Base Salary:** Enter the annual institutional base salary for each individual listed for the project.

- **Percentage of Effort on Project:** The qualifications of the PI and the amount of time that he or she and other professional personnel will devote to the research are important factors in selecting research proposals for funding. For each key staff member identified on the budget form, list the percentage of each appointment to be spent on this project.

- **Salaries Requested:** Enter the salaries in whole dollar figures for each position for which funds are requested. The salary requested is calculated by multiplying an individual's institutional base salary by the percentage of effort on the project.

- **Fringe Benefits:** Fringe benefits may be requested in accordance with institutional guidelines for each position, provided the costs are treated consistently by the applicant organization as a direct cost to all sponsors. A copy of the rate agreement or other documentation to support the fringe benefits should be provided.

- **Totals:** Calculate the totals for each position and enter these as subtotals in the columns indicated.

2. Consultant Costs

Regardless of whether funds are requested, provide the names and organizational affiliations of all consultants, other than those involved in consortium arrangements.

3. Major Equipment

It is the policy of the DOD that all commercial and non-profit recipients provide the equipment needed to support proposed research. In those rare cases where specific additional equipment is approved for commercial and non-profit organizations, such approved cost elements shall be separately negotiated.

4. Materials, Supplies, and Consumables

A general description and total estimated cost of expendable equipment and supplies are required. Itemize supplies in separate categories (e.g., glassware, chemicals, and radioisotopes). Categories in amounts less than $1,000 do not need to be itemized. If animals are to be purchased, state the species, strain (if applicable), and the number to be used.

5. Travel Costs

Travel costs are allotted as a flat rate that varies depending on award mechanism. Please consult the appropriate award mechanism section of this program announcement and enter the amount specified for travel in the Detailed Cost Estimate form.

6. Research-Related Subject Costs

Itemize costs of subject participation in the research study. These costs are strictly limited to expenses specifically associated with the proposed study. The U.S. Army Medical Research and Materiel Command will not provide funds for ongoing medical care costs that are not related to a subject's participation in the research study.

7. Research-Related Injury Medical Costs

Indicate costs for medical care for research-related injuries, should an injury to the subject occur as a result of the subject's participation in the proposed research. If the institution or state provides for this medical care as part of their existing liability insurance, annotate a cost of $0.00 and indicate in the "Justification" section of the Detailed Cost Estimate form that medical care for research-related injuries will be covered by existing institution/state insurance. If additional funds are needed to either supplement an existing policy or purchase a separate insurance policy to meet this requirement, annotate the budget requested and indicate in the "Justification" section of the Detailed Cost Estimate form how medical care for research-related injuries will be covered, and whether the cost is charged as direct or indirect costs. The institution business office can assist applicants with budgeting for this requirement. Subject costs are strictly limited to expenses specifically associated with the proposed study. The U.S. Army Medical Research and Materiel Command will not provide funds for ongoing medical care costs that are not related to a subject's participation in the research study.

8. Other Expenses

Itemize other anticipated direct costs such as publication and report costs, rental for computers and other equipment (giving hours and rates), and communication costs. Unusual or expensive items should be fully explained and justified. Estimate the costs of publishing and reporting research results, including direct charges for clerical preparation, illustrations, reprints, and distribution.

9. Consortium Costs

A description of services or materials that are to be awarded by subcontract or subgrant is required. For awards totaling $10,000 or more, provide the following specific information:

a. The identification of the type of award to be used (e.g., cost reimbursement, fixed price);

b. The identification of the proposed subcontractor or subgrantee, if known, and an explanation of why and how the subcontractor or subgrantee was selected or will be selected;

c. Whether the award will be competitive and, if noncompetitive, rationale to justify the absence of competition; and

d. The proposed acquisition price.

10. Indirect Costs (overhead, general and administrative, and other)

The most recent rates, dates of negotiation, base(s), and periods to which the rates apply should be disclosed along with a statement identifying whether the proposed rates are provisional or fixed. A copy of the negotiation memorandum should be provided.

Training awards frequently have a different institutional overhead charge. All training investigators are encouraged to check with their institution concerning overhead costs.

11. Total Costs for the Entire Proposed Period of Support (second page of the Detailed Cost Estimate form)

Enter the totals under each budget category for all additional years of support requested and itemize these totals in the "Justification" section of the Detailed Cost Estimate form. **Note with an asterisk (*) and explain any significant increases or decreases from the initial year budget. Also, explain any escalations of the budget from the initial to the future year(s) of support.** All amounts should be in U.S. dollars. Total costs for the entire proposed period of support should agree with the amount entered in item 4 of the Proposal Information (see Appendix C).

12. Justification (third page of the Detailed Cost Estimate form)

Each item in the budget should be clearly justified under the "Justification" section of the Detailed Cost Estimate form.

13. Relocation of Principal Investigator

Awards are made to institutions. If the PI leaves the recipient institution, both the PI and an official of the recipient institution should notify the U.S. Army Medical Research Acquisition Activity before the PI leaves to discuss options for continued support of the research project.

Detailed Cost Estimate Form

Name of Principal Investigator *(last, first, middle)*

DETAILED BUDGET						FROM	THROUGH
PERSONNEL		TYPE APPT. (MONTHS)	ANNUAL BASE SALARY	% EFFORT ON PROJECT	DOLLAR AMOUNT REQUESTED (OMIT CENTS)		
NAME	ROLE ON PROJECT				SALARY REQUESTED	FRINGE BENEFITS	TOTALS
	Principal Investigator						
SUBTOTALS →→→→→							$
CONSULTANT COSTS							
MAJOR EQUIPMENT (ITEMIZE)							
MATERIALS, SUPPLIES, AND CONSUMABLES (ITEMIZE BY CATEGORY)							
TRAVEL COSTS							
SUBJECT-RELATED COSTS							
RESEARCH-RELATED INJURY MEDICAL COSTS							
OTHER EXPENSES (ITEMIZE BY CATEGORY)							
SUBTOTAL OTHER DIRECT COSTS FOR INITIAL BUDGET PERIOD →→→→→							$
CONSORTIUM COSTS	DIRECT COST						
	INDIRECT COST						
TOTAL PERSONNEL AND OTHER DIRECT COSTS FOR INITIAL BUDGET PERIOD							$
TOTAL INDIRECT COSTS FOR INITIAL BUDGET PERIOD							$
TOTAL COSTS FOR INITIAL BUDGET PERIOD							$

Name of Principal Investigator ***(last, first, middle)***

BUDGET FOR ENTIRE PROPOSED PERIOD OF SUPPORT						
BUDGET CATEGORY TOTALS[1]	INITIAL BUDGET PERIOD (FROM FORM PAGE 1)	ADDITIONAL YEARS OF SUPPORT REQUESTED				TOTAL
		2nd	3rd	4th	5th	
PERSONNEL						
FRINGE BENEFITS						
CONSULTANT COSTS						
MAJOR EQUIPMENT						
MATERIALS, SUPPLIES, AND CONSUMABLES						
TRAVEL COSTS						
SUBJECT-RELATED COSTS						
RESEARCH-RELATED INJURY MEDICAL COSTS						
OTHER EXPENSES						
SUBTOTAL DIRECT COSTS						
CONSORTIUM COSTS — **DIRECT**						
CONSORTIUM COSTS — **INDIRECT**						
TOTAL DIRECT COSTS						
TOTAL INDIRECT COSTS						

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PERIOD OF SUPPORT	**$**
TOTAL INDIRECT COSTS FOR ENTIRE PROPOSED PERIOD OF SUPPORT	**$**
TOTAL COSTS FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT **THIS AMOUNT SHOULD AGREE WITH THAT ENTERED ON THE PROPOSAL COVER BOOKLET, ITEM 4**	**$**

[1] Itemize all budget categories for additional years on the Justification page that follows.

JUSTIFICATION: FOLLOW THE BUDGET JUSTIFICATION INSTRUCTIONS EXACTLY. USE CONTINUATION PAGES AS NEEDED.

Appendix G

General Information

Appendix G of this program announcement contains general information relating to U.S. Army Medical Research and Materiel Command (USAMRMC) policies and procedures.

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Part **Page**

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3. Award Eligibility G-2
4. Government Obligation G-2
5. Information Service G-2
6. Funding Instrument.....G-3
7. Inquiry Review Panel G-3
8. Equipment/Property G-3

General Information

1. U.S. Army Medical Research and Materiel Command Award

The USAMRMC implements its extramural research program predominantly through the award of grants and cooperative agreements. Proposals selected for funding are processed by the U.S. Army Medical Research Acquisition Activity (USAMRAA).

All awards are made to organizations, not individuals. A Principal Investigator (PI) should submit a proposal through, and be employed by or affiliated with, a university, college, non-profit research institute, commercial firm, or government agency (including military laboratories) in order to receive support.

2. Disclosure of Information outside the Government

By submission of an application, the applicant understands that disclosure of information outside the Government shall be for the sole purpose of technical evaluation. The USAMRMC will obtain a written agreement from the evaluator that information in the proposal will only be used for evaluation purposes and will not be further disclosed or utilized. Funded projects may be subject to public release under the Freedom of Information Act; proposals that are not selected for funding will not be subject to public release.

3. Award Eligibility

To be eligible for award, a prospective recipient should meet certain minimum standards pertaining to institutional support, financial resources, prior record of performance, integrity, organization, experience, operational controls, facilities, and conformance with safety and environmental statutes and regulations (Office of Management and Budget Circular A-110).

4. Government Obligation

PIs are cautioned that only an appointed Contracting/Grants Officer may obligate the Government to the expenditure of funds. No commitment on the part of the Government to fund preparation of a proposal or to support research should be inferred from discussions with a technical project officer. PIs or organizations that make financial or other commitments for a research effort in the absence of an actual legal obligation signed by the USAMRAA Contracting/Grants Officer do so at their own risk.

5. Information Service

Offerors may use the technical reference facilities of the National Technical Information Service, 5285 Port Royal Road, Springfield, Virginia, 22161, for the purpose of surveying existing knowledge and avoiding needless duplication of scientific and engineering effort and the expenditure thereby represented. To the extent practical, all other sources should also be consulted for the same purpose.

6. Funding Instrument

All awards under this program announcement are anticipated to be grants or cooperative agreements.

More information on these funding instruments may be obtained by request from:

Fax: 301-619-2937
E-mail: q&a.baa@det.amedd.army.mil
Mail: Director
U.S. Army Medical Research Acquisition Activity
ATTN: MCMR-AAA
820 Chandler Street
Fort Detrick, MD 21702-5014

7. Inquiry Review Panel

Applicants can submit a letter of inquiry to the USAMRMC in response to funding decisions made for a given proposal. Members of the Congressionally Directed Medical Research Programs staff, USAMRMC Judge Advocate General staff, and USAMRAA Grants Officers constitute an Inquiry Review Panel and review each inquiry to determine whether factual or procedural errors in either peer or programmatic review have occurred, and if so, what action should be taken.

8. Equipment/Property

It is the policy of the Department of Defense that all commercial and non-profit recipients possess the equipment and facilities needed to support proposed research. In those rare cases when additional specific equipment is approved for commercial and non-profit organizations, such approved cost elements shall be separately negotiated.

Title to equipment or other tangible property purchased with grant or cooperative agreement funds may be vested in non-profit institutions of higher education or with non-profit organizations whose primary purpose is the conduct of scientific research. Normally, title will vest with the recipient organization if vesting will facilitate scientific research performed by the institution or organization for the Government.

Appendix H

Acronym List

BCRP	Breast Cancer Research Program
CDMRP	Congressionally Directed Medical Research Programs
CEQ	Council on Environmental Quality
CFR	Code of Federal Regulations
DOD	Department of Defense
DOEd	Department of Education
FY	Fiscal Year
HBCU/MI	Historically Black Colleges and Universities/Minority Institutions
HSRRB	Human Subjects Research Review Board
IP	Integration Panel
IRB	Institutional Review Board
K	Thousand
M	Million
PDF	Portable Document Format
PI	Principal Investigator
RCQ	Regulatory Compliance and Quality
SBIR	Small Business Innovative Research
SOW	Statement of Work
TSCRP	Tuberous Sclerosis Complex Research Program
USAMRAA	U.S. Army Medical Research Acquisition Activity
USAMRMC	U.S. Army Medical Research and Materiel Command