

## BASIC AND CLINICAL RESEARCH ON FIBROMYALGIA

Release Date: March 26, 1998

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P.T.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute of Dental Research

National Institute of Neurological Disorders and Stroke

Office of Alternative Medicine

Office of Behavioral and Social Sciences Research

Office of Research on Women's Health

Letter of Intent Receipt Date: May 15, 1998

Application Receipt Date: July 15, 1998

### PURPOSE

The Rheumatic Diseases Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), Chronic Disabling Diseases Program, National Institute of Dental Research (NIDR), Division of Convulsive, Infectious and Immune Disorders, National Institute of Neurological Disorders and Stroke (NINDS), Office of Alternative Medicine (OAM), Office of Behavioral and Social Sciences Research (OBSSR), and the Office of Research on Women's Health (ORWH) invite research grant applications (R01) and exploratory/developmental grants (R21) from interested investigators for tightly focused innovative research studies related to all aspects of pathogenesis and clinical manifestations of fibromyalgia syndrome (FMS) and to relationships between FMS and temporomandibular disorders (TMDs). Improved understanding of the origins and the biological, neurological and psychosocial mechanisms underlying the clinical manifestations of fibromyalgia syndrome will have an impact on the development of more effective diagnostic tests and new therapies for both FMS and related disorders.

This Request for Applications (RFA) involves the use of the traditional research project grant (R01) and the exploratory/developmental grant (R21). The objective of the exploratory/developmental mechanism (R21) is to encourage applications from individuals who are interested in testing innovative or conceptually creative ideas that are scientifically sound and

may advance our understanding of FMS and TMDs. Another objective is to encourage necessary initial development to provide a basis for future research project applications.

## HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This RFA, Basic and Clinical Research on Fibromyalgia, is related to the priority areas of chronic disabling conditions and of older adults and preventive services. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No.017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800).

## ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

## MECHANISM OF SUPPORT

Support of the program will be through the National Institutes of Health (NIH) individual research project grant (R01) and the exploratory/developmental grant (R21) mechanism. This RFA is a one time solicitation. The anticipated award date is March 1, 1999. All PHS and NIH grants policies will apply to applications received and awards made in response to this request for applications. Applicants will be responsible for the planning, direction, and execution of the proposed project.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC Program Director or Principal Investigator should be included within the application.

R01 Applications. R01 awards will vary in size and duration reflecting the nature and scope of the research proposed. Future unsolicited competing continuation applications will compete with all investigator initiated applications and be reviewed according to customary peer review.

R21 Applications. Use of this novel mechanism by investigators experienced in fibromyalgia research who wish to adapt new methods or techniques established in other fields to develop scientific approaches and models to study the pathogenesis, epidemiology and clinical aspects of FMS are encouraged to apply.

Also encouraged to apply are investigators with expertise in fields other than FMS who wish to establish new research programs on FMS or related disorders, such as the TMDs.

Exploratory/developmental studies are not intended for large scale undertakings, nor to support or supplement ongoing research. Instead, investigators are encouraged to explore the feasibility of an innovative research question or approach which may not be justifiable through existing research to compete as a standard research project grant (e.g., R01), and to develop a research basis for a subsequent application through other mechanisms, i.e., R01, P01.

Exploratory/developmental (R21) grants, may not exceed \$75,000 per year in direct costs, not including indirect costs for collaborating institutions, if any. The total project period for an R21 application submitted in response to this RFA may not exceed three years. These grants are non-renewable and continuation of projects developed under the R21 program will be through the traditional unsolicited (R01 or P01) grant programs.

## FUNDS AVAILABLE

The estimated total funds (direct and indirect) available for the first year of support for this RFA will be \$1.825 million (\$750,000 from the NIAMS, \$400,000 from NIDR, \$300,000 from NINDS, \$250,000 from ORWH and \$125,000 from OAM). In fiscal year 1999, approximately 5 to 10 awards related to this RFA are planned. Actual funding is contingent upon receipt of a sufficient number of scientifically meritorious applications. Funding beyond the first and subsequent years of the grant will be contingent upon satisfactory progress during the preceding years and the availability of funds.

## RESEARCH OBJECTIVES

### Background

Patients with FMS have chronic widespread pain, fatigue, sleep disturbances and tender points. Paresthesias, anxiety, headache, and irritable bowel syndrome are also frequently seen in patients with FMS. Current estimates of the prevalence of FMS as diagnosed according to American College of Rheumatology classification criteria, suggest that it may occur in up to 2

percent of the population, but the prevalence is higher among women with estimates indicating that it may affect up to 7 percent of women age 70 and older. FMS may co-exist with other conditions, for example TMDs, myofascial pain syndrome, rheumatoid arthritis, lupus and hypothyroidism. Many investigators believe that FMS encompasses a spectrum of diseases with common pathogenic pathways.

There is a need to better understand the etiology and natural history of this condition and to define the patho-physiologic and psycho-social mechanisms leading to its clinical manifestations and responses to therapy.

### Scope

The purpose of this RFA is to promote investigator-initiated research projects and exploratory/developmental projects that will advance our understanding of FMS and related disorders and provide critical knowledge needed for the treatment and prevention of the syndrome. Investigations in all areas related to FMS are included with the exception of Phase II and III clinical trials. Small pilot clinical trials are acceptable under this RFA. (Investigators who wish to develop applications for Phase II-III clinical trials in FMS should contact the program official listed under INQUIRIES.)

This initiative is intended to encourage applications in all areas relevant to FMS, including basic, clinical, epidemiologic and behavioral research projects. Molecular, cellular and physiologic studies of neuroendocrine dysregulation, sleep disturbances and pain control mechanisms are of interest. The development of new in vivo and in vitro experimental systems to dissect and study the components of the syndrome are emphasized. Epidemiological studies on the natural history of the syndrome as well as observational studies on disease progression and responses to interventions are included as are studies of behavioral components and interventions. In addition epidemiological, basic, or clinical research characterizing relationships between FMS and temporomandibular disorders are specifically encouraged. TMDs typically involve pain and/or tenderness in cervical or craniofacial tissues, principally in the muscles of mastication or the region surrounding the temporomandibular joint.

Areas of interest include, but are not limited to, the following:

Studies of pain, including: pain thresholds, exogenous and endogenous modulation of pain perception; neurobiological and/or genetic identification of chemical and structural bases of chronic pain; studies of interaction between peripheral sites and the CNS structures involved in

pain perception; and development of experimental models of pain perception that recapitulate the features of FMS.

Development and validation of new methodologies to measure pain and pain perception in patients with FMS or TMDs.

Research on the role of trauma in the onset of FMS or TMDs.

Molecular and physiologic studies of endocrine and neuroendocrine changes in FMS, neuroendocrine mechanisms triggered as part of stress responses and how they might relate to the onset and chronic course of FMS or TMDs.

Studies of mechanisms underlying FMS-related sleep disturbance and their relationships to cognitive skill performance and memory; dissection of the cellular and molecular factors that mediate the relation of sleep disturbance to fatigue and chronic pain.

Studies aimed at identifying the hormonal and genetic factors that can explain the higher frequency of FMS and TMDs among female patients.

Natural history of FMS; studies to establish the cause and nature of the co-existence and/or overlap of FMS and TMDs with myofascial pain syndrome, rheumatoid arthritis or other diseases, syndromes and conditions; development of clinical, epidemiological or laboratory parameters useful to identify patient subsets; studies of outcomes and responses to treatment.

Identification and analysis of biopsychosocial factors that contribute to predisposition and onset of FMS symptoms; behavioral research on all aspects of FMS, including the relation between disturbed sleep, inactivity, pain and depression that are often observed in some patients with FMS; studies on stress factors, and development of innovative behavioral approaches for treatment of FMS or TMDs.

Pilot research on the effectiveness of alternative medicine approaches or techniques for treatment and/or physical rehabilitation in FMS or TMDs

This list is intended to be illustrative and not exclusive or restrictive. Applications combining interdisciplinary approaches that include collaborations between FMS researchers and experts in other scientific fields are strongly encouraged.

## INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study. If women or minorities are excluded or inadequately represented, a clear compelling rationale must be provided. All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and in the NIH Guide for Grants and Contracts, Volume 23, Number 11, March 18, 1994. This information is available on the Internet at <http://grants.nih.gov/grants/guide/notice-files/not94-100.html>.

Investigators also may obtain copies of the policy from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

## LETTER OF INTENT

Prospective applicants are asked to submit, by May 15, 1998, a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the Principal Investigator, the identities of other key personnel and participating institutions, and the number and title of the RFA in response to which the application may be submitted. Although a letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information that it contains allows Institute staff to estimate the potential review workload and to avoid conflict of interest in the review.

The letter of intent is to be sent to:

Susana A. Serrate-Sztein, MD  
Rheumatic Diseases Program  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
45 Center Drive, Room 5AS-25E, MSC 6500  
Bethesda, MD 20892-6500  
Telephone: (301) 594-5032  
FAX: (301) 480-4543  
Email: [szteins@exchange.nih.gov](mailto:szteins@exchange.nih.gov)

## APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 5/95) is to be used in applying for these grants. These forms are available at most institutional offices of sponsored research and from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: [asknih@od.nih.gov](mailto:asknih@od.nih.gov).

The RFA label available in the PHS 398 (rev. 5/95) application form must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked.

### Specific Instructions for Exploratory/Developmental Grant Applications (R21)

Items a-d of the Research Plan may not exceed a total of ten pages. Tables and figures are included in the ten page limitation. Applications that exceed this page limitation or NIH requirements for type size and margins (refer to PHS 398 application for details) will be returned to the applicant without further consideration. The ten page limitation does not include items (e)-(i) (Human Subjects, Vertebrate Animals, Literature Cited, Consortia, Consultants/Collaborators).

Submit a signed original of the application, including the Checklist, and three signed copies in one package to:

CENTER FOR SCIENTIFIC REVIEW  
NATIONAL INSTITUTES OF HEALTH  
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC-7710  
BETHESDA, MD 20892-7710  
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application must also be sent to:

Tommy L. Broadwater, Ph.D.  
Scientific Review Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
45 Center Drive, Room 5AS-25U, MSC 6500

Bethesda, MD 20892-6500

Telephone: (301) 594-4952

FAX: (301) 480-4543

Email: [broadwater@exchange.nih.gov](mailto:broadwater@exchange.nih.gov)

Applications must be received by July 15, 1998. If an application is received after that date, it will be returned to the applicant without review. The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

#### REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by CSR and responsiveness by the NIAMS staff. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration. Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NIAMS in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council, The National Dental Research Advisory Council and the National Neurological Disorders and Stroke Advisory Council.

#### Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written review, comments on the following aspects of the application will be made in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in the assignment of the overall score.

(1) Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(3) Innovation: Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(5) Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements?

In addition, the adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research will be reviewed. Plans for the recruitment and retention of subjects will also be evaluated.

The initial review group will also examine the provisions for the protection of human and animal subjects, the safety of the research environment, and conformance with the NIH Guidelines for the Inclusion of Women and Minorities as Subjects in Clinical Research.

Because the exploratory grant mechanism (R21) is designed to support innovative ideas, preliminary data as evidence of feasibility of the project are not required. However, the applicant does have the responsibility for developing a sound research plan approach. Innovation of the project and potential significance of the proposed research will be major considerations in the evaluation of this mechanism.

#### AWARD CRITERIA

The anticipated date of award is March 1, 1999. Awards will be based upon the following criteria:

- o scientific merit
- o availability of funds
- o programmatic priorities of the funding ICD
- o responsiveness to the RFA

#### Schedule

Letter of Intent Receipt Date: May 15, 1998

Application Receipt Date: July 15, 1998

Initial Review: November 1998

Second Level Review: January 1999

Anticipated Award Date: March 1, 1999

#### INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Dr. Susana A. Serrate-Sztein

Rheumatic Diseases Program

National Institute of Arthritis and Musculoskeletal and Skin Diseases

45 Center Drive, Room 5AS-25E, MSC 6500

Bethesda, MD 20892-6500

Telephone: (301) 594-5032

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National Institute of Neurological Disorders and Stroke  
Federal Building, Room 504  
Bethesda, MD 20892  
Telephone: (301) 496-1431  
FAX: (301) 402-2060  
Email: [ck82j@nih.gov](mailto:ck82j@nih.gov)

Direct inquiries regarding fiscal matters to:

Ms. Carol Fitzpatrick  
Grants Management Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
45 Center Drive, Room 5AS-43B, MSC 6500  
Bethesda, MD 20892-6500  
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## AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846 and 93.121. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410), as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, public law 103-227, the pro-children act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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