

NEW INSIGHTS INTO CHRONIC FATIGUE SYNDROME  
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National Institute of Mental Health

#### PURPOSE

The National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and National Institute of Mental Health (NIMH) invite investigator-initiated research grant applications to support research on the etiology, natural history, and pathogenesis of chronic fatigue syndrome (CFS).

#### 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 program announcement, New Insights into Chronic Fatigue Syndrome, is related to the priority area of chronic disabling diseases. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-0325 (telephone 202-783-3238).

#### 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. Applications from minority individuals and women are encouraged. Foreign institutions are not eligible for First Independent Research Support and Transition (FIRST) (R29) awards.

#### MECHANISM OF SUPPORT

Traditional research project grant (R01) and FIRST award (R29) applications may be submitted in response to this program announcement. The R01 mechanism can be used

to support small studies. Funds and time requested should be appropriate for the research proposed.

## RESEARCH OBJECTIVES

### Background

Chronic fatigue syndrome (CFS) is a multisystem syndrome thought to be triggered by acute infectious illness and characterized by months of debilitating fatigue frequently associated with myalgia, headache, sore throat, low grade fever, cognitive complaints, gastrointestinal symptoms, and tender lymph nodes. There have been reports of immunologic and, more recently, neuroendocrine parameters that differ in CFS patients as a group compared to healthy controls. However, no single marker has been identified that can be used to diagnose the syndrome. CFS is diagnosed three to four times more frequently in women than in men and about 10 times more often in white Americans than in other American population groups. The cause and pathogenic mechanisms of the illness are unknown.

### Research Objectives and Experimental Approaches

Well-designed studies are needed to provide a better understanding of CFS and to develop diagnostic and intervention strategies. Studies should include appropriate sample sizes and test biologically rational hypotheses concerning etiology, natural history or pathogenesis of the syndrome. Applications for small studies that explore new ideas are also encouraged and could provide the basis for submission of a subsequent larger grant application.

Clinical epidemiologic studies may identify factors that affect prognosis or that are associated with susceptibility, including immunogenetic, behavioral, environmental, and psychosocial factors. Several observations reported in the literature merit further study to determine their biologic and/or epidemiologic basis, generalizability and/or role in CFS. These include, but are not limited to:

- o lymphocyte patterns suggestive of immune activation (e.g., alterations in T-cell subsets number and function, altered cytokine levels and function)
- o low levels of cortisol and corticotropin-releasing hormone in CFS patients in the absence of documented adrenal-hypothalamic axis dysfunction attributable to other causes
- o increased frequency of sleep disturbances (hypersomnia or insomnia)
- o overlapping symptomatology with fibromyalgia
- o low tolerance to physical exertion manifested by prolonged generalized fatigue after very moderate exercise

- o demographic risk factors (gender, age, race, socioeconomic class)
- o reactivation of latent viruses (e.g., use of sensitive and specific assays to measure viral reactivation in carefully defined and controlled specimens)
- o increased frequency of psychiatric diagnoses in CFS patients (except those that would exclude an individual from the CFS case definition)
- o increased frequency of atopy in CFS patients compared with the U.S. population as a whole
- o highly active lifestyle prior to onset of CFS

Multidisciplinary studies and collaboration among investigators with expertise in appropriate disciplines are encouraged. When investigators are at different institutions, individual R01 applications may include consortium arrangements.

Collaborative arrangements with on-going studies that provide patient populations, specimens and data are encouraged. Such arrangements should be clearly delineated in the application.

The methodologies and personnel involved in statistical/epidemiological analyses should be described in the application and evident in the study design. The hypothesis(es) to be tested should be clearly stated. The constructs and measurements to be used operationally to obtain statistically and biologically meaningful results should be clearly defined and enumerated.

The value of studies of patients or their specimens will be directly related to the care exercised in selection and initial characterization of cases and controls. A detailed description of case recruitment procedures, the criteria to be used for case definition and the manner in which the criteria are to be applied must be included. Similar care should be given to descriptions of enrollment of comparison groups.

Investigators are encouraged to use the CFS case definition as initially presented in Holmes, et al. (*Annals of Internal Medicine*: 108, 387-389, 1988) and subsequently modified in Schluederberg, et al. (*Annals of Internal Medicine*: 117, 325-331, 1992) and in Fukuda, et al (in press). If other case definitions are proposed, they should be clearly defined and the rationale for their choice clearly delineated.

#### Parameter Measurements

Applications to estimate the frequency of physiological or behavioral variables or responses or to address other quantitative aspects in relevant populations should pay particular attention to sample sizes required to attain the degree of precision sought or needed for statistically and biologically meaningful results. The reliability and validity of markers chosen for measurement should be demonstrated.

Applications attempting to examine interrelationships among two or more separate factors are encouraged to the extent that the types and numbers of subjects are sufficient for such comparisons.

The measurement of cellular phenotypes, cytokine activities and other immunological and viral markers are highly dependent on the assay system chosen and its execution. Thus, it is very important that applicants clearly define the methodologies to be used, the rationale for choosing that methodology and for validating results as well as methods of collection, processing, and storage of samples. When conflicting results have been reported in the literature, applicants should provide possible explanations for such variability and indicate how their approach might resolve the issue.

## STUDY POPULATIONS

### 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, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This new policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43) and supersedes and strengthens the previous policies (Concerning the Inclusion of Women in Study Populations, and Concerning the Inclusion of Minorities in Study Populations) which have been in effect since 1990. The new policy contains some new provisions that are substantially different from the 1990 policies.

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 reprinted in the NIH GUIDE FOR GRANTS AND CONTRACTS of March 18, 1994, Volume 23, Number 11.

Investigators may obtain copies from these sources or from the program staff or contact persons listed below. Program staff may also provide additional relevant information concerning the policy.

## APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev. 9/91) and will be accepted on the standard application deadlines as indicated in the application kit. Application kits are available at most institutional offices of sponsored research and may be obtained from the Office of Grants Information, Division of Research Grants, National

Institutes of Health, Westwood Building, Room 449, Bethesda, MD 20892, telephone (301) 435-0714.

Each application must be identified by checking "YES" on line 2a of the PHS face page, and the number and title of this announcement must be typed in section 2a.

FIRST (R29) applications must include at least three sealed letters of reference attached to the face page of the original application. FIRST applications submitted without the required number of reference letters will be considered incomplete and will be returned without review.

The completed original and five legible, single-sided copies of the application must be sent or delivered to:

Division of Research Grants  
National Institutes of Health  
Westwood Building, Room 240  
Bethesda, MD 20892\*\*

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 Center as a resource for conducting the proposed research. If so, a letter of agreement from the GCRC Program Director must be included in the application material.

#### REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be reviewed for scientific and technical merit by study sections of the Division of Research Grants, NIH, in accordance with the standard NIH peer review procedures. Following scientific/technical review, the applications will receive secondary review by the appropriate national advisory council.

#### AWARD CRITERIA

Applications will compete for available funds with all other favorably recommended applications assigned to that ICD. The following will be considered when making funding decisions: quality of the proposed project as determined by peer review, program balance among research areas of the announcement, availability of funds.

#### INQUIRIES

Written and telephone inquiries are encouraged. The opportunity to clarify any issues from potential applicants is welcome. Direct inquiries regarding programmatic issues to:

Susan Spring, Ph.D.  
Division of Microbiology and Infectious Diseases

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Solar Building, Room 3A14  
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National Institute of Mental Health  
Parklawn Building, Room 11C06  
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Direct inquiries regarding fiscal matters to:

Ms. Victoria Putprush  
Division of Extramural Activities  
National Institute of Allergy and Infectious Diseases  
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Mr. Joseph L. Brown  
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National Institute of Arthritis and Musculoskeletal and Skin Diseases  
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FAX: (301) 594-9950

Mr. Bruce Ringler  
Grants Management Branch  
National Institute of Mental Health  
Parklawn Building, Room 7C08

5600 Fishers Lane  
Rockville, MD 20857  
Telephone: (301) 443-3065

#### AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.856, Microbiology and Infectious Disease Research, No. 93.846, Arthritis, Musculoskeletal, and Skin Diseases Research and No. 93.242, Mental Health Research. 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 grant policies and Federal Regulations at 42 CFR Part 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.

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