

Full Text AR-95-001

## PATHOGENESIS OF PEDIATRIC RHEUMATIC DISEASES

NIH GUIDE, Volume 23, Number 41, November 25, 1994

RFA: AR-95-001

P.T.

Keywords:

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Letter of Intent Receipt Date: February 6, 1995

Application Receipt Date: April 21, 1995

### PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invites applications for basic research on the pathogenesis of pediatric rheumatic diseases. The goal of this Request for Applications (RFA) is to promote research on the genetics basis for disease predisposition and on the immunologic and biochemical mechanisms leading to pediatric rheumatic diseases and their clinical manifestations. The research will improve knowledge of the diseases and will identify critical processes and mediators that could be used to establish a rational basis for new and effective treatments. Multidisciplinary approaches that apply current basic science approaches to the study of rheumatic diseases of childhood through formal collaborations are strongly encouraged.

### 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, Pathogenesis of Pediatric Rheumatic Diseases, is related to the priority area of chronic disabling conditions. 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 20402-9325 (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. Foreign institutions are not eligible for First Independent Research Support and Transition (FIRST) (R29) awards. Racial/ethnic minority individuals, women and persons with disabilities are encouraged to apply as Principal Investigators.

#### MECHANISM OF SUPPORT

This RFA will use the National Institutes of Health (NIH) individual research project grant (R01) and FIRST (R29) awards and the interactive research project grant (IRPG) mechanisms. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for applications submitted in response to the present RFA may not exceed five years. The anticipated award date is September 30, 1995. Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the size of an award will also vary. This RFA is a one-time solicitation. Future unsolicited competing continuation applications will compete with all investigator-initiated applications and be reviewed according to the customary peer review procedures.

#### FUNDS AVAILABLE

The estimated funds (total costs) available for the first year of support for the entire program is \$1.5 million. Funding is contingent upon receipt of scientifically meritorious applications. The NIAMS expects to fund five to eight new awards.

The National Institute of Allergy and Infectious Diseases (NIAID) is interested in basic research on rheumatic diseases of children, including the interaction between the endocrine and the immune systems. Applications that are of mutual interest are likely to be given secondary assignment to the NIAID in accordance with Division of Research Grants (DRG) referral guidelines.

## RESEARCH OBJECTIVES

### Background

The rheumatic diseases of childhood, including juvenile rheumatoid arthritis (JRA), rheumatic fever, systemic lupus erythematosus, juvenile dermatomyositis, scleroderma, and vasculitis, present unique clinical and research challenges. Combined, the rheumatic diseases are the most common form of chronic diseases of childhood, and they are major causes of disability. The pediatric forms of rheumatic disease differ clinically from their counterparts in adults and current evidence suggests that the underlying mechanisms leading to disease may be different as well. For example, pauciarticular juvenile rheumatoid arthritis has complex associations with genes encoding components of the major histocompatibility complex that do not correspond to the associations found in the adult forms. Other mechanisms that appear to play a role in adult rheumatoid arthritis, such as restrictions in the use of certain V beta gene families for the T cell receptors, have not been proven in JRA. Other disease manifestations possibly related to the onset of diseases before completion of skeletal development, such as decreased bone mass and delayed growth, also point to different pathogenic mechanisms.

The current status and future directions of pediatric rheumatology were the subject of a workshop sponsored by the NIAMS held in September 1994. The workshop brought together a group of clinicians and scientists working in the field of pediatric rheumatic diseases to review the biomedical problems facing the pediatric rheumatology community and to identify the areas that can be addressed with current methodologies. In addition to recommending the creation of disease registries, the group emphasized the need for the development of a basic research base as a fundamental step to advance understanding of the diseases. The experts identified the research areas that offered the most promising opportunities for research. Those critical areas are the focus of this solicitation.

The areas of research interest include:

- o Studies on the genetic factors influencing predisposition, onset, and disease severity, including studies on the localization of genes and characterization of the biological activity of gene products in the pathogenesis of the disease;
  
- o Analysis of immunopathogenic mechanisms, including the biochemical and biological characterization of self-antigens, the mechanisms of self-antigen presentation, and the role of antigen-presenting cells in the initiation and perpetuation of disease;

- o The development of technologies to explore the pathogenicity of cells that react with antigens that directly or by cross reactivity may induce autoimmune responses;
  
- o The role of hormones and neuroendocrine factors in the loss of self-tolerance and in the evolution of disease as identified by in vitro tests of disease activity, such as cell-mediated responses or antibody production;
  
- o The mechanisms involved in progression and remission of disease, with emphasis on the identification of molecular mediators that may enhance responses leading to remission;
  
- o Studies of bone metabolism, bone mass, and growth in the context of juvenile rheumatic arthritis or in patients with other rheumatic diseases in which there is delayed growth because of the disease or a complication/adverse effect of treatment.

This list is illustrative and not exclusive or restrictive. Applications combining multidisciplinary approaches focused on research hypotheses derived from previous research on pediatric diseases or in diseases of the adult that may be extended to the pediatric forms are encouraged. Collaborations between basic research teams investigating aspects of pathogenesis that may not have been previously applied but that may be relevant to pediatric rheumatic diseases are also 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, 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 were 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 person listed under INQUIRES. Program staff may also provide additional relevant information concerning the policy.

#### LETTER OF INTENT

Prospective applicants are asked to submit, by February 6, 1995, a letter of intent that includes a 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 NIAMS 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. S. Sztejn, M.D.  
Rheumatic Diseases Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
Natcher Building, Room 5AS-37G  
45 Center Drive MSC 6500  
Bethesda, MD 20892-6500  
Telephone: (301) 594-5032  
FAX: (301) 480-4543

The research grant application form PHS 398 (rev. 9/91) is to be used in applying for these grants. These forms are available at most institutional offices of sponsored research and from the Office of Grants Information, Division of Research Grants, National Institutes of Health, 5333 Westbard Avenue, Room 449, Bethesda, MD 20892, telephone 301/435-0714 and from the program administrator listed under INQUIRES.

The RFA label available in the PHS 398 (rev. 9/91) 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 2a of the face page of the application form and the YES box must be marked.

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

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

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

Tommy L. Broadwater, Ph.D.  
Grants Review Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
Natcher Building, Room 5AS-25E  
45 Center Drive MSC 6500  
Bethesda, MD 20892-6500  
Telephone: (301) 594-4952  
FAX: (301) 480-4543

Applications must be received by April 21, 1995. If an application is received after that date, it will be returned to the applicant without review. The Division of Research Grants (DRG) 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 DRG 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 DRG and responsiveness by NIAMS staff. Incomplete applications will be returned to the applicant without further consideration. If the application is not responsive to the RFA, DRG staff will contact the applicant to determine whether to return the application to the applicant or submit it for review in

competition with unsolicited applications at the next review cycle. 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 NIAMS in accordance to the review criteria listed below.

As part of the initial merit review, a process (triage) may be used by the initial review group in which applications will be determined to be competitive or non-competitive based on their scientific merit relative to other applications received in response to the RFA.

Applications judged to be competitive will be discussed and be assigned a priority score.

Applications determined non-competitive will be withdrawn from further consideration and the Principal Investigator and the official signing for the applicant organization will be notified.

The second level of review will be provided by the National Advisory ICD Council/Board.

Review criteria for this RFA are generally the same as those for unsolicited research grant applications:

- o scientific, technical, or clinical significance and originality of proposed research;
- o appropriateness and adequacy of the experimental approach and methodology proposed to carry out the research;
- o qualifications and research experience of the Principal Investigator and staff and collaborations;
- o availability of the resources necessary to perform the research;
- o appropriateness of the proposed budget and duration in relation to the proposed research.
- o adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research. 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.

AWARD CRITERIA

The anticipated date of award is September 30, 1995. Awards will be based upon the following criteria:

- o scientific merit
- o availability of funds
- o programmatic priorities of NIAMS

## 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:

Susana A. S. Sztejn, M.D.

Rheumatic Diseases Branch

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Natcher Building, Room 5AS-37G

45 Center Drive MSC 6500

Bethesda, MD 20892-6500

Telephone: (301) 594-5032

FAX: (310) 480-4543

Email: [arthrit@ep.niams.nih.gov](mailto:arthrit@ep.niams.nih.gov)

Direct inquiries regarding fiscal matters to:

Diane Watson

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Natcher Building, Room 5AS-53

45 Center Drive MSC 6500

Bethesda, MD 20892-6500

Telephone: (310) 594-3505

FAX: (310) 480-5450

Email: [watsond.ep.niams.nih.gov](mailto:watsond.ep.niams.nih.gov)

Schedule

Letter of Intent Receipt Date: February 6, 1995

Application Receipt Date: April 21, 1995

Initial Review: June 1995

Second Level Review: September 1995

Anticipated Award Date: September 1995

#### AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.361. 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 Public Health Service strongly encourages all grant recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

.

---

[Return to RFAs Index](#)

[Return to NIH Guide Main Index](#)