

MECHANISMS OF ORAL TOLERIZATION AND IMMUNIZATION

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National Institute of Allergy and Infectious Diseases

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Letter of Intent Receipt Date: April 5, 1993

Application Receipt Date: July 21, 1993

PURPOSE

The Division of Allergy, Immunology and Transplantation (DAIT) of the National Institute of Allergy and Infectious Diseases (NIAID) and the Rheumatic Diseases Branch of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invite applications for studies focused on cellular and molecular mechanisms of oral immunization and oral tolerance. The goal of this initiative is to promote research that will increase our understanding of the mechanisms involved in the induction of protective immunity systemically and in the mucosal surfaces after oral immunization and improve our knowledge about the effects of oral administration of self-molecules as a means of inducing tolerance to prevent or reverse autoimmune and allergic diseases.

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 Request for Applications (RFA), Mechanisms of Oral Tolerization and Immunization, is related to the priority areas of diabetes and chronic disabling conditions, and immunization and infectious 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 20402-9325 (telephone 202-782-3238).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by public and private, foreign and domestic, for-profit and non-profit organizations, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Only domestic institutions are eligible to apply for Program Project (P01) grants. Women and minority investigators are encouraged to apply.

MECHANISM OF SUPPORT

The mechanisms of support for this program will be the research project grant (R01) and the Program Project (P01) grant. The regulations and policies that govern the research grant programs of the National Institutes of Health will prevail. 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 this RFA may not exceed five years. At this time, the NIAID is administratively limiting the duration of P01 grants to four years; this administrative limitation may change in the future. P01 applications may not request budgets in excess of \$500,000, and R01 applications, \$180,000, total direct costs in the first year; neither type of application should request more than 4 percent annual inflationary increases for future years. An application with a first year requested amount in excess of the above will require written approval by senior NIAID or NIAMS officials via the program officers for acceptance of the application for processing.

FUNDS AVAILABLE

The estimated total funds (direct and indirect) available for the first year of support for this RFA will be \$1,500,000. In fiscal year 1994, the NIAID plans to fund approximately seven research projects, either as R01s or as components of P01s. In fiscal year 1994, the NIAMS plans to fund approximately three R01s. The usual PHS policies governing grants administration and management will

apply. This level of support is dependent on the receipt of a sufficient number of applications of high scientific merit. Although this program is provided for in the financial plans of the NIAID and the NIAMS, awards pursuant to this RFA are contingent upon the availability of funds for this purpose. Funding beyond the first and subsequent years of the grant will be contingent upon satisfactory progress during the preceding years, and availability of funds.

RESEARCH OBJECTIVES

Background

Mucosal surfaces are the most common portals of entry of microorganisms and other environmental factors, and effective immune mechanisms exist that afford protection against some of the diseases caused by these organisms. In addition, protective immune responses can be induced in external secretions by oral administration of some attenuated or killed organisms. Although progress has been made in understanding the composition and some of the functions of the mucosal immune system in the induction of protective immunity, the basic mechanisms and molecular mediators involved in the development of immune responses remain largely unknown. Knowledge of the basic cellular and molecular immune mechanisms of the gastrointestinal tract will be the foundation for the development of successful multicomponent oral vaccines and oral tolerization protocols, and an understanding of inflammatory bowel disease.

Experimental autoimmune diseases such as collagen-induced arthritis, experimental allergic encephalomyelitis and experimental uveitis have been successfully treated by the oral administration of the relevant antigen. Evidence suggests that a subpopulation of T cells and cytokines, such as TGF beta, are implicated in the induction of tolerance and prevention and/or delay of disease onset. However, the molecular basis for oral tolerance induction to autoantigens and the mechanisms that govern these processes are not understood. Although results obtained in experimental systems are encouraging, it is not clear whether oral tolerance regimens in established disease suppress or exacerbate autoimmune conditions. Carefully controlled studies using well defined self peptides and antigens in combination with advanced molecular and cellular immunology approaches are necessary before oral tolerance is considered as an effective form of therapy for human disease.

Research Objectives and Scope

Areas of interest include, but are not limited to:

- o Studies of the mechanisms involved in the induction and regulation of oral tolerance to self antigens, with emphasis on the identification of the cell types and cytokine cascades involved.
- o Analysis of the effect of oral administration of self peptides on ongoing autoimmune disease and the cellular and molecular mechanisms that mediate these effects.
- o Characterization of the molecular basis for the observed decrease in tissue damage in organ-specific autoimmune disease following the oral administration of appropriate antigens.
- o Studies to establish the immune parameters of induction of protective immune responses to orally administered antigens including attenuated or killed enteric pathogens, with emphasis on the characterization of cellular and molecular mediators involved in these processes.
- o Studies to analyze and determine peripheral and/or systemic correlates of protective immunity to orally administered antigens, including enteric pathogens and antigens delivered in carrier systems.
- o Studies of antigen processing and presentation by gut epithelial and lymphoid cells and design of methodologies to manipulate them to obtain stronger and/or long lasting protective immunity.

New approaches to the study of mucosal immunity and approaches that combine cellular and molecular immunology and bacterial genetics are strongly encouraged as are studies that would yield information directly applicable to the human mucosal system/autoimmune disease interface.

STUDY POPULATIONS

SPECIAL INSTRUCTIONS TO APPLICANTS REGARDING IMPLEMENTATION OF NIH POLICIES CONCERNING INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH STUDY POPULATIONS

NIH policy requires that applicants for NIH clinical research grants and cooperative agreements include minorities and women in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study; special emphasis must be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions which disproportionately affect them. This policy is intended to apply to males and females of all ages. If women or minorities are excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale **MUST** be provided.

The composition of the proposed study population must be described in terms of gender and racial/ethnic group, together with a rationale for its choice. In addition, gender and racial/ethnic issues should be addressed in developing a research design and sample size appropriate for the scientific objectives of the study. This information must be included in the form PHS 398 in items 1-4 of the Research Plan **AND** summarized in item 5, Human Subjects.

Applicants are urged to assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH recognizes that it may not be feasible or appropriate in all research projects to include representation of the full array of U.S. racial/ethnic minority populations [i.e., Native Americans (including American Indians or Alaskan Natives), Asian/Pacific Islanders, Blacks, and Hispanics]. The rationale for studies on single minority population groups should be provided.

For the purpose of this policy, clinical research is defined as human biomedical and behavioral studies of etiology, epidemiology, prevention (and preventive strategies), diagnosis, or treatment of diseases, disorders or conditions including, but not limited to, clinical trials.

The usual NIH policies concerning research on human subjects also apply. Basic research or clinical studies in which human tissues cannot be identified or linked to individuals are excluded. However, clinical samples which may be

coded for use by the applicant but could be identified by another source are not excluded. Every effort should be made and documented to include human tissues from women and racial/ethnic minorities when it is important to apply the results of the study broadly, and this should be addressed by applicants.

For foreign awards, the policy on inclusion of women applies fully; since the definition of minority differs in other countries, the applicant must discuss the relevance of research involving foreign population groups to the U.S. populations, including minorities.

If the required information is not contained within the application, the application will be returned.

Peer reviewers will address specifically whether the research plan in the application conforms to these policies. If the representation of women or minorities in a study design is inadequate to answer the scientific question(s) addressed AND the justification for the selected study population is inadequate, it will be considered a scientific weakness or deficiency in the study design and will be reflected in assigning the priority score to the application.

All applications for clinical research submitted to NIH are required to address these policies. NIH funding components will not award grants or cooperative agreements that do not comply with these policies.

Previous recruitment data for similar studies from the proposed sites should be provided.

LETTER OF INTENT

Prospective applicants are asked to submit, by April 5, 1993, a letter of intent that includes a descriptive title of the overall proposed research, the name, address and telephone number of the Principal Investigator or Program Director (for P01s), and the number and title of this RFA. Although the letter of intent is not required, is not binding, does not commit the sender to submit an application, and does not enter into the review of subsequent applications, the information that it contains allows NIAID and 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 Dr. Mark Rohrbaugh at the address listed under INQUIRIES.

APPLICATION PROCEDURES

In preparing the application in response to this RFA, the applicant should bear in mind the research objectives of this RFA. An R01 application should be prepared according to the instructions in form PHS 398 (rev. 9/91). A P01 application should be prepared using the guidance and instructions provided in the NIAID document titled: "SPECIAL INSTRUCTIONS FOR PREPARING THE GROUP APPLICATION FOR PROGRAM PROJECTS." This document cannot be transmitted electronically, particularly Tables I-IV which may be used by the applicant for appropriate and consistent presentation of summary information on budgets and personnel. The P01 applicant should request and obtain a copy of such document and a copy of the NIAID Information Brochure for Program Projects and Grants, both of which may be sent along with this RFA. Failure to follow the instructions in the document may result in delays in the review or in an incomplete application.

Applications are to be submitted on the standard research grant application form PHS 398 (rev. 09/91). These application forms may be obtained from the institution's office of sponsored research and from the Office of Grants Inquiries, Division of Research Grants, National Institutes of Health, 5333 Westbard Avenue, Room 449, Bethesda, MD 20892, telephone (301) 496-7441.

For purposes of identification and processing, item 2a on the face page of the application must be marked "Yes" and the RFA number and the words "MECHANISMS OF ORAL TOLERIZATION AND IMMUNIZATION" must be entered.

Applications must be received by July 21, 1993. Applications that are not received from the applicant organization by the receipt date or that do not conform to the instructions contained in PHS 398 (rev. 09/91) application kit, will be judged to be non-responsive and will be returned to the applicant.

The RFA label available in the application form PHS 398 must be affixed to the bottom of the face page. 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.

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

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

At the time of submission, two additional exact copies of the grant application and all five sets of appendix material must also be sent to Dr. Mark Rohrbaugh at the address listed under INQUIRIES.

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. In such a case, a letter of agreement from either the GCRC Program Director or Principal Investigator should be included with the application.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the Division of Research Grants (DRG) and by NIAID and NIAMS staff for responsiveness. Those judged to be incomplete will be returned to the applicant without review. Those considered to be non-responsive will be either returned without review or, if R01s, be referred to the DRG as unsolicited applications, to be scheduled for initial review at the next DRG review cycle.

Those applications that are complete and responsive may be subjected to a triage by an NIAID peer review group to determine their scientific merit relative to the other applications received in response to this RFA. The NIAID and the NIAMS will withdraw from competition those applications judged to be non-competitive for award.

Those applications judged by the reviewers to be competitive for award will be further reviewed for scientific and technical merit by a review committee convened by the Scientific Review Branch, Division of Extramural Activities, NIAID. The second level of review will be provided by the National Advisory Allergy and Infectious Diseases Council or by the National Arthritis and Musculoskeletal and Skin Diseases Council.

The factors to be considered in the evaluation of scientific merit of each application will be those used in the review of traditional research project grant applications, including: the novelty, originality, and feasibility of the approach; the training, experience, and research competence of the investigator(s); the adequacy of the experimental design; and the adequacy and suitability of the facilities. For program project applications, additional review criteria are used, which are outlined in the NIAID Information Brochure on Program Project and Center Grants. Applicants planning a program project application must request and obtain the NIAID Information Brochure.

While the following review factors do not usually influence the priority score, they are nonetheless carefully considered by the initial review group: the appropriateness of the requested budget to the work proposed; the adequacy of protection of human subjects and/or animals in research; and the adherence, whenever appropriate, to NIH guidelines concerning adequate representation of women and minorities in clinical research. Any documented concerns expressed by the initial review group about any of these factors on a given application may influence the recommendation of the Advisory Council concerning funding of that application.

AWARD CRITERIA

Funding decisions will be made on the basis of scientific and technical merit, as determined by peer review, program needs and balance, and the availability of funds.

INQUIRIES

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

Direct requests for the Information Brochure and the documents referred to under APPLICATION PROCEDURES, as well as inquiries regarding programmatic issues, to:

Howard B. Dickler, M.D.
Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases
Solar Building, Room 4A19
Bethesda, MD 20892
Telephone: (301) 496-7104
FAX: (301) 402-2571

Susan Serrate-Sztein, M.D.
Rheumatic Diseases Branch
National Institute of Arthritis and Musculoskeletal Diseases
Westwood Building, Room 405
Bethesda, MD 20892
Telephone: (301) 402-3340
FAX: (301) 480-7881

Direct inquiries regarding review issues (including the preparation of a program project application if applicable); address the letter of intent to; and mail two copies of the application and all five sets of appendices to:

Mark Rohrbaugh, Ph.D.
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Solar Building, Room 4C22
Bethesda, MD 20892
Telephone: (301) 496-8424
FAX: (301) 402-2638

Direct inquiries regarding fiscal and administrative matters to:

Mr. Jeffrey Carow
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases

Solar Building, Room 4B29
Bethesda, MD 20892
Telephone: (301) 496-7075

The mailing address given for NIAID staff in the Solar Building is the central mailing address for NIH. Applicants who use express mail or a courier service are advised to follow the carrier's requirements for showing a street address. The address for the Solar Building is:

6003 Executive Boulevard
Rockville, MD 20852

Schedule

Letter of Intent Receipt Date: April 5, 1993
Application Receipt Date: July 21, 1993
Scientific Review Date: October 1993
Advisory Council Date: February 1994
Earliest Award Date: April 1994

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance, No. 93.855 - Immunology, Allergy and Transplantation Research and No. 93.846 - Arthritis and Musculoskeletal and Skin Diseases Research. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 78-410, as amended; 42 USC 241) and administered under PHS grants policies and Federal Regulations 42 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.