

Full Text AI-95-011

## MUCOSAL AND SYNOVIAL GENE TRANSFER IN INFECTION/INFLAMMATION

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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: July 15, 1995

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### PURPOSE

The National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH) invite submission of investigator-initiated research applications for basic and preclinical studies targeted at molecular methods for transferring genes into cells of mucosal membranes and synovial tissues to augment host defenses and alter inflammatory responses for the treatment or prevention of infectious and rheumatic and other immunologic 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), Mucosal and Synovial Gene Transfer in

Infection/Inflammation, is related to the priority areas of diabetes and chronic disabling diseases and immunization and infectious diseases. 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) 782-3238).

#### ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private institutions, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Foreign institutions are not eligible to apply 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

The mechanisms of support will be the individual research project grant (R01) and the FIRST (R29) award. The total project period for an application submitted in response to this RFA may not exceed five years; a foreign application may not request more than three years of support. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant.

This RFA is a one-time solicitation. Future competing renewal applications will compete with all investigator-initiated applications and will be reviewed according to customary referral and review procedures.

The National Heart, Lung, and Blood Institute (NHLBI) also has interest in supporting applications concerned with gene transfer to respiratory cells for the purpose of modulating host defense processes and inflammatory responses which may apply to treatment or prevention of infectious or inflammatory diseases. For applications of mutual interest, the NHLBI is likely to be given a secondary assignment in accordance with DRG Referral Guidelines.

#### FUNDS AVAILABLE

The estimated funds available for the total (direct and indirect) first-year costs of all awards made under this RFA will be \$950,000, \$750,000 from the NIAID and \$200,000 from the NIAMS. In

Fiscal Year 1996, the NIAID plans to fund approximately three to four R01s and/or R29s and the NIAMS plans to fund one R01/R29. The NIH is currently limiting annual inflationary increases to no more than four percent for future years of awards. 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

The pathogenesis of many infectious diseases involves a combination of mucosal colonization, production and release of toxins and invasion of tissue. Both host and microbial factors that may contribute to or limit infection are now being understood at molecular and genetic levels. Among these are microbial adhesins and virulence factors important for attachment and penetration of host tissues; opsonic factors and host cell surface molecules involved in microbial adherence and uptake; antimicrobial peptides of phagocytic and mucosal cells; host cellular factors that may alter microbial metabolism as well as microbial toxins that may mediate inflammation through effects on host cell metabolism.

Gene transfer into mucosal cells offers the potential to modify the course of infectious diseases by altering the expression of factors that participate in host/pathogen interactions. Potential advantages might include an ability to change colonization and tissue invasion in clinical situations where effective antibiotics are lacking; providing antimicrobials in high concentrations at critical sites; and altering cell turnover in targeted tissues (increased resistance).

The ability to transfer into mucosal cells genes that encode molecules that are anti-microbial, anti-inflammatory, or vaccine epitopes would confer enormous advantages in treating or preventing infectious and immunologic diseases. Mucosal gene transfer could be a useful adjunct in a variety of clinical situations including: (a) viral, bacterial, fungal or parasitic infections of the respiratory and gastrointestinal tracts; (b) infection of the genitourinary tract and sexually transmitted diseases (STDs); (c) intrabdominal and post surgical wounds as well as decubitus ulcers; (d) mucosal vaccination with recombinant immunogens; (e) noninfectious inflammatory disorders involving mucosal tissues such as asthma; and (f) introduction of self molecules into the

gastrointestinal tract for induction of tolerance in autoimmune diseases. In the case of rheumatic diseases such as rheumatoid arthritis, delivery of genes to the synovial membranes may induce significant local changes to reduce inflammation and limit tissue destruction and disability.

Advantages include: delivery of the active molecule to the optimal site; high concentrations of therapeutic agent; continuous presence of this molecule for days or weeks; and a defined end of exposure to the molecule (due to cellular turnover). In experimental systems of rheumatoid arthritis, the approach has shown promising results.

### Research Objectives and Scope

While exciting advances have occurred in gene therapy, much of the work has focused on hematologic cells or the cells of solid organs and less effort has been focused on mucosal cells. The main work in the area concerns introducing the cystic fibrosis gene into respiratory epithelial cells. The aim of this RFA would be to support basic research leading to gene transfer intended to augment host defense at mucosal sites. Relevant research includes, but is not limited to, the following:

- o development and characterization of vectors that would efficiently transfer genes into various cells of the respiratory, gastrointestinal or genitourinary tracts and which are safe and suitable for use in humans;
- o modification and packaging for transfection of genes that encode molecules that are antimicrobials or anti-inflammatory and intended to modify host/pathogen interactions;
- o modification and packaging for transfection of genes that are useful as immunogenic or toleragenic epitopes for vaccines;
- o preclinical studies in cell lines and animal models that may prove useful in evaluation of safety and efficacy of such approaches;
- o modification and packaging for transfection of genes to alter mucosal levels of mediators specific or useful in the treatment of asthma, inflammatory bowel disease and other immunologically mediated disorders of unknown etiology.

NOTE: This RFA is not intended to support studies of gene transfer in genetic deficiencies.

## 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 has 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 person listed below. Program staff may also provide additional relevant information concerning the policy.

## LETTER OF INTENT

Prospective applicants are asked to submit, by July 15, 1995, a letter of intent that includes a descriptive title of the overall proposed research, the name, address and telephone number of the Principal Investigator, 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 NIH 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. Christopher Beisel at the address listed under INQUIRIES.

## APPLICATION PROCEDURES

Applications are to be submitted on the standard research grant application form PHS 398 (rev. 9/91). These application forms may be obtained from the institution's office of sponsored research or its equivalent 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.

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. 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 "MUCOSAL AND SYNOVIAL GENE TRANSFER IN INFECTION/INFLAMMATION" must be typed in.

FIRST award (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.

It is highly recommended that the appropriate NIAID or NIAMS program contact be consulted before submitting the letter of intent and during the early stages of preparation of the application. (See program contacts under INQUIRIES).

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

Division of Research Grants  
National Institutes of Health  
6701 Rockledge Drive, Room 1040 - MSC 7710  
Bethesda, MD 20892-7710  
Bethesda, MD 20817 (for express mail or courier service)

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

Applications must be received by November 15, 1995. Applications received after the receipt date will be returned without review. Applications that do not conform to the instructions contained in PHS 398 (rev. 9/91) application kit will be judged non-responsive and will be returned to the applicant. 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. This does not exclude the submission of

substantial revisions of an application already reviewed. These applications must, however, include an introduction addressing the previous critique.

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 could be included with the application.

## REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the NIH Division of Research Grants (DRG) and for responsiveness by NIAID staff. Incomplete and 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 NIAID in accordance with the review criteria stated 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 to be non-competitive will be withdrawn from further consideration and the principal investigator and the official signing for the applicant organization will be promptly notified. The second level of review will be provided by the National Advisory Allergy and Infectious Diseases Council and the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council. Review, Council and award dates can be found in "SCHEDULE", below.

### Review Criteria

- o scientific, technical, or medical 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, particularly, but not exclusively, in the area of the proposed research;

- 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 and the safety of the research environment.

#### AWARD CRITERIA

Funding decisions will be made on the basis of scientific and technical merit as determined by peer review, program priorities, 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 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  
6003 Executive Boulevard  
Bethesda, MD 20892-7640  
Telephone: (301) 496-7104  
FAX: (301) 402-2571  
Email: [hd7e@nih.gov](mailto:hd7e@nih.gov)

Susana A. Serrate-Sztejn, M.D.  
Rheumatic Diseases Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
Natcher Building, Room 5AS37G

Bethesda, MD 20892-6500  
Telephone: (301) 594-5032  
FAX: (301) 480-4353  
Email: arthrit@ep.niams.nih.gov

Direct inquiries regarding review issues, mail two copies of the application and all five sets of appendices, and mail the letter of intent to:

Christopher E. Beisel, Ph.D.  
Division of Extramural Activities  
National Institute of Allergy and Infectious Diseases  
Solar Building, Room 4C03  
6003 Executive Boulevard  
Bethesda, MD 20892-7610  
Telephone: (301) 402-4596  
FAX: (301) 402-2638  
Email: cb45d@nih.gov

Direct inquiries regarding fiscal matters to:

Ms. Maryellen Connell  
Division of Extramural Activities  
National Institute of Allergy and Infectious Diseases  
Solar Building, Room 4B28  
Bethesda, MD 20892-7610  
Telephone: (301) 496-7075  
FAX: (301) 480-3780  
Email: mc40u@nih.gov

#### Schedule

Letter of Intent Receipt Date: July 15, 1995  
Application Receipt Date: November 15, 1995  
Scientific Review Date: March 1996  
Advisory Council Date: May 1996  
Earliest Award Date: August 1996

## AUTHORITY AND REGULATIONS

The program is described in the Catalog of Federal Domestic Assistance, No. 93.855 and No. 93.846. Awards will be made under the authority 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 and contract 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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