

NIH GUIDE

for GRANTS and CONTRACTS

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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REQUEST FOR RESEARCH GRANT APPLICATIONS: RFA

ANNOUNCEMENT

TITLE - *PATHOGENESIS OF INFLAMMATION IN THE LUNG*

The Division of Lung Diseases of the National Heart and Lung Institute is inviting research grant applications to study the process of inflammation in the lung.

This type of solicitation (the RFA) is utilized when the Division wishes to stimulate investigator interest in a particular research area that is important to the National Program. Unlike the RFP (Request for Contract Proposals), the RFA identifies the scope of the Division's interest but does not require that the proposal conform to specified research requirements. Moreover, the RFA is supported through the customary NIH grant-in-aid and is governed by the policies for regular research grants. However, the RFA solicitation represents a single competition, with a specified deadline for receipt of applications. All applications in response to the RFA will be reviewed at the same time by a special ad hoc review panel. Approved applications that receive grant awards will be administered in the same fashion as regular research grants.

Applications should be prepared in accordance with the aims and requirements which are described in the following sections.

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The GUIDE is published at irregular intervals to provide policy and administrative information to individuals and organizations who need to be kept informed of requirements and changes in grants and contracts activities administered by the National Institutes of Health.

Supplements, printed on yellow paper, are published by the respective awarding units concerning new projects, solicitations of sources, and requests for proposals.

If you have questions relating to this announcement, you should contact Dr. Suzanne S. Hurd at (301) 496-7332.

PATHOGENESIS OF INFLAMMATION IN THE LUNG

1. Program Specifications

A. The Pathophysiology Branch

The Pathophysiology Branch of the Division of Lung Diseases sponsors fundamental and clinical research grants and contracts related to normal and abnormal function of the lung. In addition, studies related to diagnostic tests, therapeutic management and the fundamental pathogenetic mechanisms by which causal agents trigger alterations leading to lung disease are supported. This request for applications is intended to encourage submission of individual research grant proposals designed to study the pathogenesis of inflammation in lung tissue.

B. Program Objectives

Over the past several decades much new information has been obtained about the mechanisms of the inflammatory response. Special attention has been given to inflammatory mediators derived from plasma proteins and from cells. In general the mediators seem either to increase vascular permeability, to alter leucocyte migration, or to modify leucocyte metabolism so as to enhance certain biologic functions, of which phagocytosis is a prime example. Much has been learned about the complement, coagulation, plasmin and kinin-forming systems, and more recently considerable knowledge has accumulated on the role of lymphokines (mediators of cellular immunity) in the inflammatory process. There has been relatively little direct application of this information to mechanisms of inflammation in the lung. It is likely that the special structural and functional characteristics of the lung might modify the expression of these mechanisms. These special features would seem to make the lung an especially intriguing organ for the study of the mechanisms, regulation and resolution of the inflammatory reaction. Because of the lack of basic knowledge concerning inflammatory reactions in the lung, and because of the great need to have such information so that the clinical problems of inflammatory lung disease can be more effectively diagnosed and treated, the Division desires to encourage research on mechanisms of inflammation in the lung, and on how these basic processes lead to lung tissue injury.

C. Research Scope

The research topics presented below are intended only to provide a perspective of the scope of research that would meet the goals of this program. Investigators are encouraged to consider other approaches. The direct emphasis of the proposal, however, must be related to mechanisms of lung injury. Several specific areas of study are listed as examples.

1. Agents that Trigger the Inflammatory Process in the Lung

While considerable information is available from in vitro studies in tissues other than the lung about factors that can trigger generation of inflammatory mediators, little is known about how this occurs in the lung and what the unique properties of the lung might be in the generation of these mediators. It is unclear why some agents trigger acute and chronic inflammatory reactions while others induce granulomatous reactions. Some viruses cause neutrophil-rich reactions in the lung while other viruses induce chronic inflammatory cellular responses consisting predominantly of mononuclear cells. The basis for these different responses is poorly understood. Similar considerations apply to other agents such as particulate matter, bacteria, and immune complexes.

2. Production of Inflammatory Mediators by Lung

While a variety of mediators can be generated by lung tissue, especially during anaphylactic injury (but also during other types of injury), the origin of these mediators is not known. In addition, much more needs to be known about the ability of the normal lung or abnormal lung to generate and release inflammatory mediators. Also, there is virtually no information available concerning the production of inflammatory mediators during the course of cell-mediated immune reactions in the lung, or in various experimental or clinical granulomatous states.

3. Inflammatory Cells of the Lung

With its pre-existing store of alveolar macrophages, the lung is particularly suitable for studies of the inflammatory process. Little is known about the influx and efflux of inflammatory cells in the lung and the extent to which interstitial inflammatory cells are derived from alveolar macrophages. Similarly, the processes whereby alveolar macrophages become activated are worthy of further investigation. For example, do opsonins, lymphokines and chemotactic factors affect alveolar cells in the same manner as peritoneal macrophages?

4. Regulation of the Inflammatory Process in the Lung

It is likely that the inflammatory reaction falls under regulatory control. There is already good evidence that the lung has the ability to destroy kinins. It is likely that other inhibitors also exist which might be reactive with vasopermeability and leukotactic factors, with lymphokines and with proteases, to name only a few examples.

5. Resolution of the Inflammatory Process

It is difficult experimentally to quantitate the tissue damage which occurs in the course of an inflammatory reaction in the lung. Is there a loss of basement membrane, elastin or other structural protein? What controls the resolution of the inflammatory process? What are the determinants that dictate restoration prior to the inflammatory state?

The topics cited above are examples presented for illustrative purposes only; other approaches to meet the goals of this program are encouraged. However, the proposal must clearly state how the proposed research is directly related to the topic of inflammation in the lung. Each research application should clearly define the rationale, background, specific scientific goals and detailed methods of procedure for the project.

D. Mechanism of Support

The support mechanism for this program will be the traditional NIH grant-in-aid; successful applicants will plan and execute their own research program. Upon initiation of the program, the Division of Lung Diseases will sponsor periodic workshops to encourage exchange of information between investigators who participate in this program.

Although this program is included and provided for in the financial plans for fiscal year 1976, award of grants pursuant to this request for grant applications is contingent upon ultimate receipt of appropriate funds for this purpose. A variety of approaches would represent valid responses to this announcement; accordingly, it is anticipated that there will be a range of costs among individual grants awarded. Applicants are requested to furnish their own estimates of the time required to achieve the objectives of the proposed research project; however, the total project period of this proposal must not exceed five years. At the end of the project period, renewal proposals may be submitted for competitive review.

Unless stated to the contrary, the regulations (Code of Federal Regulations, Title 42, Part 52 and, as applicable to State and local governments, Title 45, Part 74) and the current policies which govern the research grant programs of the NIH will prevail.

II. Method and Criteria for Review

A. Review

Upon receipt, applications will be reviewed by the Division of Research Grants (DRG) and NHLI staff for responsiveness to this announcement. If an application is judged unresponsive, the applicant will be given an opportunity to withdraw the application or to submit it for consideration in the traditional grant program of NIH. Applications judged responsive will be reviewed initially for scientific merit by the DRG, utilizing the Special Study Section mechanism, and secondly by the National Heart and Lung Advisory Council in June 1976.

B. Review Criteria

The factors considered in evaluating each application will be:

- o The responsiveness to this announcement - that is, the relevance of the proposal to the goals of this program announcement and guidelines.

- o The scientific merit of the research design, approaches and methodology.
- o The research experience and competence of the staff to carry out the proposed investigations.
- o Adequacy of time (effort) to be devoted to the project by investigators and technical staff.
- o The adequacy of existing and proposed facilities and resources.
- o The adequacy of the organizational arrangements for scientific direction.
- o The evidence of institutional commitment to the program.

III. Method of Applying

A. Letter of Intent

Prospective applicants should submit a brief, one-paragraph letter not later than December 1, 1975 to:

Dr. Samuel Schwartz
Associate Director for Review
Division of Extramural Affairs
National Heart and Lung Institute
Room 554, Westwood Building
Bethesda, Maryland 20016

The Institute requests such letters only to provide a perspective of the number and the scope of applications. A letter of intent is not binding, and it will not enter into the review of any proposal subsequently submitted.

B. Format for Applications

Applications should be submitted on Form NIH-398, the application form for the traditional research grant. The conventional presentation for research grant applications should be utilized; the points identified under the Review Criteria must be fulfilled.

C. Application Procedure

The original and twenty-four (24) copies of the application must be received before 5:00 p.m. Eastern time on February 15, 1976. Applications should be sent or delivered to:

Division of Research Grants
National Institutes of Health
Westwood Building
Bethesda, Maryland 20016

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A brief covering letter should accompany the application indicating that it is in response to this Program Announcement - NHLI Program on Pathogenesis of Inflammation in Lung. A copy of the covering letter should be sent to the Associate Director for Review, Division of Extramural Affairs, National Heart and Lung Institute, Westwood Building, Room 554, Bethesda, Maryland 20016, to indicate that the application has been submitted.