

NEW IMAGING TECHNOLOGIES FOR AUTOIMMUNE DISEASES

Release Date: February 11, 1999

RFA: AI-99-004

P.T.

National Institute of Allergy and Infectious Diseases
National Cancer Institute
National Center for Research Resources
National Eye Institute
National Heart, Lung and Blood Institute
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Mental Health
National Institute of Neurological Disorders and Stroke
Office of Research on Women's Health

Letter of Intent Receipt Date: March 15, 1999

Application Receipt Date: May 6, 1999

THIS RFA USES THE MODULAR GRANT APPLICATION AND AWARD PROCESS. THIS RFA INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS THAT MUST BE FOLLOWED WHEN PREPARING AN APPLICATION IN RESPONSE TO THIS RFA.

PURPOSE

The National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI), the National Center for Research Resources (NCRR), the National Eye Institute (NEI), the National Heart, Lung and Blood Institute (NHLBI), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke (NINDS), and the Office of Research on Women's Health (ORWH) invite

applications for research project grants to develop new methods for in vivo imaging of the immune system in small animal models of human autoimmune diseases. Support will be provided for the development of high-resolution imaging technologies to visualize active processes of immune cells in vivo, including instrumentation and computational improvements, and the design, development, synthesis and testing of new contrast agents. These projects will require the coordinated effort of experts in imaging and immunology to develop innovative approaches for imaging immune cell movement, behavior and functions in vivo using animal models of human autoimmune diseases. Of particular interest are studies designed to specifically label and follow lymphocytes and other immune effector cells at various activation states throughout an ongoing immune response.

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), New Imaging Technologies for Autoimmune Diseases, is related to the priority areas of immunization and infectious diseases and diabetes and chronic disabling conditions. 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 202-512-1800).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic 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 this RFA. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

The mechanism of support will be the individual research project grant (R01). The total requested project period for an application submitted in response to this RFA may not exceed five years. 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.

Specific application instructions have been modified to reflect the "MODULAR GRANT APPLICATION AND AWARD" process which has been adopted by the NIH (see the NIH Guide, December 15, 1998).

For this RFA, funds must be requested in \$25,000 direct cost modules. A feature of the modular grant is that no escalation is provided for future years, and all anticipated expenses for all years of the project must be included within the number of modules being requested. Only limited budget information is required and any budget adjustments made by the Initial Review Group will be in modules of \$25,000.

More detailed information about modular grant applications, including a sample budget narrative justification pages and a sample biographical sketch, is available via the Internet at url:

<http://grants.nih.gov/grants/funding/modular/modular.htm>

FUNDS AVAILABLE

The estimated total funds (direct and indirect) available for the first year of support for all awards made under this RFA will be \$3,500,000. In Fiscal Year 1999, the participating Institutes and Centers (ICs) plan to fund approximately 5 awards. Budget requests for the first and, in some cases, the second year of the project period should include the one-time costs associated with the acquisition of necessary equipment. Applicants requesting in excess of \$750,000 in total (direct and indirect) first-year costs must obtain approval from the Dr. Vicki Seyfert at the address listed under INQUIRIES prior to submission.

The usual PHS policies governing grants administration and management will apply. Although this program is provided for in the financial plans of the cosponsors, awards pursuant to this RFA are contingent upon the availability of funds for this purpose and the receipt of a sufficient number of applications of high scientific merit. 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

Considerable progress has been achieved in the identification of immune cells and factors involved in immune responses and the underlying mechanisms of immune cell function. However, little is known about the behavior and function of immune cells *in vivo*. For example, the kinetics of immune effector function in normal and autoimmune responses and the influence of the three-dimensional environment of the immune system on lymphocyte and other immune cell functions are not well understood. Increased knowledge of these aspects of immune responses are critical for understanding both protective and pathogenic aspects of immunity, as in the case of autoimmune diseases. Currently available techniques are limited in that they rely largely on the use of *in vitro* tissue culture systems, histological analyses of tissues from animals or humans, or analyses of cells or factors from peripheral blood or excised tissues/organs from sacrificed animals.

Recent advances in *in vivo* imaging technologies have the potential to overcome many of these limitations. Currently, most biomedical imaging devices have been optimized for use in humans and do not possess the spatial resolution necessary to visualize individual cells *in vivo*. However, new scaled-down instrumentation and high power computers have recently allowed for high-resolution and signal sensitivity in small animal model systems.

More importantly, recent advances in the design and synthesis of contrast agents have provided the means to specifically label cells and monitor their functions. One example is the addition of radiolabels to organic compounds that bind selectively to receptors found only on nerve cells in the brain. This approach has allowed researchers to map the distribution of nerve cells that use dopamine and serotonin with positron emission tomography (PET) scans.

Another example of high-resolution imaging is magnetic resonance imaging (MRI) aided by injection of engineered paramagnetic metal ions such as gadolinium (III), *i.e.*, gadolinium surrounded by bulky organic groups that prevent its interaction with water. One of these engineered molecules, that has proven to work well *in vivo*, is gadolinium bound to an organic group via a sugar molecule that is cleaved by beta-galactosidase. Cells or tissues genetically engineered to express beta-galactosidase can then be specifically labeled by encounter with the engineered gadolinium injected into the animal. Use of these reagents in conjunction with high-resolution MRI allows for mapping of specific cells or tissues in living mice.

The application of these new high-resolution imaging strategies in animal models of immune system diseases will provide a powerful non-invasive means to visualize ongoing normal and deleterious immune responses. In the case of autoimmune diseases, specific cells involved in the process of tissue destruction could be identified and followed. Analysis of each cell's

activation state and effector functions in vivo will provide new insights into the mechanisms underlying autoimmune pathogenesis in any organ in vivo. Other aspects of immunity that could be addressed through the application of high-resolution imaging include: localization and trafficking of lymphocytes following antigen encounter; development of immune cells; and activation, proliferation, and effector functions of lymphocytes following antigen encounter or during graft rejection. The eventual adaptation of high-resolution imaging for use in humans holds promise for non-invasive detection, diagnosis and monitoring of immunologic diseases, and a new approach for evaluating the efficacy of vaccines and therapeutic agents, both of which will have significant impact on clinical practice.

Research Objectives and Scope

The purpose of this RFA is to support R01 projects to develop new high-resolution imaging technologies for visualizing cells in the immune system and how they function to generate normal or deleterious immune responses. This objective will require a coordinated effort among experts in imaging, contrast agent design and synthesis, and immunology to design the reagents and instrumentation necessary to identify, follow and evaluate the function of different immune cells in normal and abnormal immune responses. Examples of relevant technology development areas include, but are not limited to, the following:

- o Development of new and/or refinement of existing imaging instrumentation to analyze immune cell movement and function in small animals

- o Development of informatics tools necessary for data storage, analysis, visualization and manipulation

- o Development of new classes of imaging agents with many of the following properties:
 - The ability to specifically bind and label for different cell populations, including specific T cells, B cells, dendritic cells, or other immune effector cells in vivo;

 - The ability to specifically bind different antigen receptors on B or T cells, including adaptation of anti-idotypic antibodies or soluble MHC/peptide as imaging agents;

 - The ability to alter imaging properties in response to physiologic changes to enable in vivo detection of cellular responses such as metabolism, activation or proliferation;

- The ability to remain inert until encounter with a specific reporter protein in distinct cell populations, i.e., beta-galactosidase inducible gadolinium (see above);
- The ability to bind specific cellular receptors, such as cytokine or chemokine receptors and;
- The ability to specifically bind to viral or bacterial proteins for detection and localization of pathogenic organisms in vivo.

New imaging technologies with the above properties should be used to address fundamental mechanisms of immune responses in animal models of human autoimmune diseases. Areas of investigation include, but are not limited to, the following:

- o Identification of immune cell types, i.e., B, T or NK cells, involved in an immune response to self-antigen in any organ or tissue in vivo.
- o Evaluation of immune cell types and their activation states in vivo during the process of tissue destruction.
- o Assessment of antigen specific immune cell migration in vivo in response to antigen. Studies should be designed to evaluate the effect of antigen route of entry on immune cell trafficking.
- o Assessment of the effects on immune cell migration, localization, and function in genetically altered animal models.
- o Identification and migration of immune cells in vivo in response to transplanted organs, cells and tissues, including the determination of cell types involved in the acute rejection process and where they are localized.
- o Location of memory B and T cells when quiescent and following reactivation.

The areas outlined above are not intended to be all-inclusive.

SPECIAL REQUIREMENTS

Grantees will be invited to attend an annual meeting to be held at the NIH. This meeting will serve to bring together all investigators funded by this RFA to discuss the progress of their projects and to identify gaps and opportunities in imaging technologies as it applies to study of

the immune system. This meeting will also serve to promote exchange of information and ideas between scientists and to make recommendations to assist NIH Program Staff in planning future initiatives in this area. Budget requests should include travel expenses to attend these annual meetings.

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 sub-populations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear, compelling rationale, and justification are provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research", published in the Federal Register of March 28, 1994 (FR 59 14508- 14513) and the NIH Guide for Grants and Contracts, Vol. 23, No. 11, March 18, 1994 which is available via the WWW. at:

<http://grants.nih.gov/grants/guide/notice-files/not94-100.html>

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and which is available at the following URL address: <http://grants.nih.gov/grants/guide/notice-files/not98-024.html>

Investigators may obtain copies from these sources or from the program contacts listed under INQUIRIES who may also provide additional relevant information concerning the policy.

LETTER OF INTENT

Prospective applicants are asked to submit, by March 15, 1999, 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 NIAID 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. Madelon Halula at the address listed under INQUIRIES.

APPLICATION PROCEDURES

Applicants are strongly encouraged to contact the program contacts listed under INQUIRIES with any questions regarding the responsiveness of their proposed project to the goals of this RFA.

The research grant application form PHS 398 (rev. 4/98) is to be used in applying for these grants. Application kits are available at most institutional offices of sponsored research and from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone (301) 435-0714, email: GrantsInfo@nih.gov. Applications are also available on the World Wide Web at: <http://grants.nih.gov/grants/forms.htm>.

BUDGET INSTRUCTIONS

- o FACE PAGE: Items 7a and 7b should be completed, indicating Direct Costs (in \$25,000 increments) and Total Costs [Modular Total Direct plus Facilities and Administrative (F&A) costs] for the initial budget period. Items 8a and 8b should be completed indicating the Direct and Total Costs for the entire proposed period of support.
- o DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD - Do not complete Form Page 4 of the PHS 398. It is not required and will not be accepted with the application.
- o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT - Do not complete the categorical budget table on Form Page 5 of the PHS 398. It is not required and will not be accepted with the application.
- o NARRATIVE BUDGET JUSTIFICATION - Use a Modular Grant Budget Narrative page.

(See <http://grants.nih.gov/grants/funding/modular/modular.htm> for sample pages.)

At the top of the page, enter the total direct costs requested for each year.

o Under Personnel, list key project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided.

For Consortium/Contractual costs, provide an estimate of total costs (direct plus facilities and administrative) for each year, each rounded to the nearest \$1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made, the percent effort of key personnel, and the role on the project. The total cost for a consortium/contractual arrangement is included in the overall requested modular direct cost amount.

Provide an additional narrative budget justification for any variation in the number of modules requested.

o BIOGRAPHICAL SKETCH - The Biographical Sketch provides information used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team. A biographical sketch is required for all key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at:

<http://grants.nih.gov/grants/funding/modular/modular.htm>

- Complete the educational block at the top of the form page;
- List current position(s) and then previous positions;
- List selected peer-reviewed publications, with full citations;
- Provide information, including overall goals and responsibilities, on research projects ongoing or completed during the last three years.

o OTHER SUPPORT - Form Page 7. This form must be completed for applications in response to this RFA to allow awards to be negotiated and made on or before September 30, 1999.

o CHECKLIST - This page should be completed and submitted with the application.

If the F&A rate agreement has been established, indicate the type of agreement and the date. It is important to identify all exclusions that were used in the calculation of the F&A costs for the initial budget period and all future budget years.

The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

Applications not conforming to these guidelines will be considered unresponsive to this RFA and will be returned without further review.

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. In addition, the RFA title and number must be typed on line 2 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, exact, single-sided photocopies, in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, two additional exact copies of the application and all five sets of any appendix material must be sent to Dr. Madelon Halula at the address listed under INQUIRIES. These copies must be sent at the same time as the original and three copies are sent to the Center for Scientific Review (CSR), failure to do so will prevent the application from being peer reviewed in time for award in fiscal year 1999.

Applications must be received by May 6, 1999. If an application is received after that date, it will be returned to the applicant without review. The CSR 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 CSR 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 and adherence to the Special Instructions above by CSR and for responsiveness by NIAID staff. Incomplete and/or 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 will be used by the initial review group in which applications receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed, assigned a priority score, and receive a second level review by the National Advisory Allergy and Infectious Diseases Council.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. The reviewers will comment on the following aspects of the application in their written critiques in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered by the reviewers in assigning the overall score weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have a major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?
2. Approach. Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?
3. Innovation. Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

4. Investigator. Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

5. Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

The initial review group will also examine: the appropriateness of proposed project budget and duration; the adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research and plans for the recruitment and retention of subjects; the provisions for the protection of human and animal subjects; and the safety of the research environment.

Schedule

Letter of Intent Receipt Date: March 15, 1999

Application Receipt Date: May 6, 1999

Scientific Review Date: July 1999

Advisory Council Date: September 1999

Earliest Award Date: September 30, 1999

AWARD CRITERIA

Funding decisions will be made on the basis of scientific and technical merit as determined by peer review, program balance, and the availability of funds. The earliest anticipated date of award is September 30, 1999.

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:

Dr. Vicki Seyfert

Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
6003 Executive Boulevard, Room 4A21
Bethesda, MD 20892
Telephone: (301) 496-7551
FAX: (301) 402-2571
Email: vs62y@nih.gov

Barbara Y. Croft, Ph.D.
Diagnostic Imaging Program
National Cancer Institute
6130 Executive Boulevard, Room 800
Rockville, MD 20892-7440
Bethesda, MD 20852 (for express/courier service)
Telephone: (301) 496-9531
FAX: (301) 480-5785
Email: bc129b@nih.gov

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Bethesda, MD 20892
Telephone: (301) 435-0879
Email: louiseR@ep.ncrr.nih.gov

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FAX: (301) 402-0528
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FAX: (301) 480-3503
Email: Joan_Harmon@NIH.GOV

Dianne Rausch, Ph.D.
Office of AIDS Research
National Institute of Mental Health

6001 Executive Boulevard, Room 6209, MSC 9619
Bethesda, MD 20892-9619
Telephone: (301) 443-6100
Email: drausch@mail.nih.gov

Direct inquiries regarding review issues and special instructions for application preparation; address the letter of intent to; and mail two copies of the application and all five sets of appendices to:

Madelon Halula, Ph.D.
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Solar Building, Room 4C16
6003 Executive Boulevard
Bethesda, MD 20892
Telephone: (301) 402-2636
FAX: (301) 402-2638
Email: mh30x@nih.gov

Direct inquiries regarding fiscal matters to:

Pamela G. Fleming
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
6003 Executive Boulevard, Room 4C25
Bethesda, MD 20892-7610
Rockville, MD 20852 (for express/courier service)
Telephone: (301) 402-6580
FAX: (301) 480-3780
Email: pf49e@nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.856, 93.394, and 93.855. Awards are made under authorization of the Public Health Service Act, Sec. 301 (c), Public Law 78-410, as amended. Awards will be administered under PHS grants policies and

Federal Regulations 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 review.

The Public Health Service 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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