

HYPERACCELERATED AWARD/MECHANISMS IN IMMUNOMODULATION TRIALS

RELEASE DATE: November 10, 2003

RFA Number: RFA-AI-04-001

Department of Health and Human Services (DHHS)

PARTICIPATING ORGANIZATION:

National Institutes of Health (NIH)

(<http://www.nih.gov>)

COMPONENTS OF PARTICIPATING ORGANIZATION:

National Institute of Allergy and Infectious Diseases (NIAID)

(<http://www.niaid.nih.gov>)

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

(<http://www.niams.nih.gov/>)

National Institute of Dental and Craniofacial Research (NIDCR)

(<http://www.nidcr.nih.gov/>)

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

(<http://www.niddk.nih.gov/>)

National Institute of Neurological Disorders and Stroke (NINDS)

(<http://www.ninds.nih.gov/>)

CATALOGUE OF FEDERAL DOMESTIC ASSISTANCE NUMBERS:

No. 93.855, Immunology, Allergy, and Transplantation Research, NIAID

No. 93.856, Microbiology and Infectious Diseases Research, NIAID

No. 93.866, Arthritis, Musculoskeletal and Skin Diseases Research, NIAMS

No. 93.121, National Institute of Dental and Craniofacial Research, NIDCR

No. 93.847, Diabetes, Endocrinology and Metabolism Research, NIDDK

No. 93.848, Digestive Diseases and Nutrition Research, NIDDK

No. 93.849, Kidney Diseases, Urology and Hematology Research, NIDDK

No. 93.853, Extramural Research Programs in the Neurosciences and Neurological Diseases, NINDS

LETTER OF INTENT RECEIPT DATE: One month prior to application receipt date.

APPLICATION RECEIPT DATE: Applications will be accepted MONTHLY on the 9th of each month. The last receipt date will be June 9, 2004.

THIS RFA CONTAINS THE FOLLOWING INFORMATION

- o Purpose of this RFA
- o Research Objectives
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PURPOSE OF THIS RFA

The National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Dental and Craniofacial Research (NIDCR) of the National Institutes of Health (NIH) invite investigator-initiated research applications for mechanistic studies in clinical trials of: (1) immunomodulatory interventions for immune system mediated diseases, including, but not limited to: asthma and allergic diseases; graft failure in solid organ, cell, tissue and stem cell transplantation; and chronic inflammatory, autoimmune, and immunodeficiency diseases; and (2) preventative and therapeutic, vaccines for non-HIV/AIDS infectious diseases, including NIAID Category A, B, and C agents of bioterrorism and emerging/re-emerging infectious diseases. This Request for Applications (RFA) is a continuation and modification of RFA AI-02-003 (<http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-02-003.html>).

In order to review and confer awards to grant applications received in response to this RFA in a timely fashion, without delay of the parent clinical trial, NIAID has developed a pilot project in collaboration with the NIH Center for Scientific Review (CSR): NIAID/CSR PILOT OF HYPERACCELERATED REVIEW/AWARD. All applications responding to this RFA will be subject to this hyperaccelerated review/award process. Highly meritorious applications selected for funding under this RFA will receive their awards thirteen weeks after the application receipt date. Holidays and other circumstances may alter this schedule slightly.

RESEARCH OBJECTIVES

In December 1996, NIAID convened a workshop at which leading basic and clinical immunologists discussed the role the NIH should play in current and projected clinical trials for various immune mediated diseases. It was considered likely that clinical trials of many new immunologic interventions would be supported by the

pharmaceutical/biotechnology industry. However, gaps in both knowledge and in research effort were identified which represent opportunities for the NIH to contribute to progress in this area.

There was agreement that the mechanisms underlying immunologic interventions are poorly understood even in cases where efficacy has been shown (e.g., allergen immunotherapy, treatment of multiple sclerosis with interferons, Copolymer-I, and in other immunomodulatory regimens under development). In addition, clinical trials supported by industry and other sources including NIH often do not include studies of underlying mechanisms. There was consensus that high priority should be given to the utilization of patient samples from clinical trials in immunologic diseases for studies of the basic underlying mechanisms of therapeutic effect, immunologic function, and disease pathogenesis.

There was also agreement that the usual time required for grant review and funding is often incompatible with the time-line of a clinical trial. Specifically, when a clinical protocol is finalized (which is required for applications submitted under this RFA), investigators are often ready to begin as soon as Institutional Review Board approval is obtained. NIAID was encouraged to develop a means of responding rapidly to opportunities to study underlying mechanisms in order to facilitate collaborations with industry-supported clinical trials.

These recommendations were strongly supported by a large number of investigators who participated in NIAID focus groups in the winter/spring of 1997. The [RFA AI-98-006](#) and the NIAID/CSR PILOT OF HYPERACCELERATED REVIEW/AWARD were developed in order to implement these recommendations and exploit the research opportunities identified. Based on the successful implementation of [RFA AI-98-006](#), the follow-up RFAs [RFA-AI-00-005](#), [AI-01-001](#), [AI-02-003](#) and the Pilot, the current RFA is being issued to continue this effort.

The objective of this RFA is to support mechanistic research studies in clinical trials of immunomodulatory interventions for: (1) immune system mediated diseases, including: asthma and allergic diseases; graft failure in solid organ, cell, tissue and stem cell transplantation; and chronic inflammatory, autoimmune diseases, and immunodeficiency diseases; and (2) vaccines for the prevention and treatment of non-HIV/AIDS infectious diseases, including NIAID Category A, B and C agents of bioterrorism and emerging/re-emerging infectious diseases (see list of agents at http://www.niaid.nih.gov/biodefense/bandc_priority.htm.)

Specifically, the goal of this RFA is the inclusion of patients and utilization of patient samples from such clinical trials for the evaluation of immunologic and other relevant parameters in order to study and define the underlying immunological mechanisms of the intervention or vaccine, the mechanisms of disease pathogenesis, surrogate/biomarkers of disease activity and therapeutic effect, and mechanisms of human immunologic function. Such studies are not part of the parent clinical trial, and are commonly referred to as substudies or ancillary studies. The parent clinical trial must have independent financial

support and will NOT receive support under this RFA. Proposed mechanistic studies associated with clinical trials supported by industry are particularly encouraged but clinical trials supported by any source, public or private, are eligible. Clinical trials of any phase (i.e., Phases I-IV) are eligible. Examples of relevant research include, but are not limited to, the following:

- o Quantitation of disease-related, autoreactive or alloreactive lymphocytes using methods such as MHC/peptide tetramers, chimeric antibodies, or very early activation antigens.
- o Analysis of autoreactive or alloreactive cells by PCR for expression of genes implicated in immunity or inflammation, or by flow cytometry for cell surface markers that identify functions (e.g., cytokine receptors that distinguish TH1 from TH2 or chemokine receptors or integrins that indicate preferential patterns of homing).
- o Assessment of reagents that can identify newly recognized populations of regulatory T cells (e.g., V α 24J α Q bearing invariant T cells) which appear to be altered in autoimmune disease.
- o Identification and evaluation of cytokine and cytokine receptor polymorphisms and analysis for genetic linkage to disease.
- o Immune mechanisms of vaccines. Studies to define the underlying mechanisms of protection induced by vaccines against infectious diseases, including investigation of the specificity and kinetics of cellular and antibody responses, Th1/Th2 and cytotoxic T cell characterization, and immune memory.
- o Use of high throughput technologies (e.g., chip technology using expressed sequence tags) to identify and evaluate genes activated in disease sites.
- o Identification of useful surrogate markers by correlation of the above parameters with disease activity and/or response to intervention or vaccine.
- o Comparison of immune parameters from samples from peripheral blood with those from sites of disease, i.e., do peripheral blood samples provide useful information?
- o Assessment for the presence of molecular evidence (e.g., using PCR probes) of potential causative environmental agents.
- o The molecular and cellular mechanisms by which lymphocytes, macrophages, neutrophils, antibodies, cytokines and complement contribute to successful immunotherapy for chronic inflammatory diseases.

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

NOTE: Clinical trials of drug treatments (e.g., antibiotics or antiviral drugs) for infectious diseases (e.g., Lyme Disease), and vaccines and drug/immunomodulatory treatment for HIV/AIDS are NOT eligible for support under this RFA. Applicants are strongly encouraged to contact program staff listed under WHERE TO SEND INQUIRIES well in advance of the anticipated application submission date to allow staff to assess responsiveness to this RFA and provide appropriate guidance as needed.

MECHANISM OF SUPPORT

This RFA will use the NIH individual research project grant (R01) award. The total requested project period for an application submitted in response to this RFA may not exceed four years. Some sponsoring Institutes may administratively limit the duration of award. The applicant will be solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation. Future unsolicited, competing-continuation applications based on this project will compete with all investigator-initiated applications and will be reviewed according to the customary peer review procedures. Applications that are not funded in the competition described in this RFA may be resubmitted as NEW investigator-initiated applications using the standard receipt dates for NEW applications described in the instructions to the PHS 398 application.

Amended applications will be accepted for Hyperaccelerated Review/Award ONLY if invited by NIH. Applicants with minor or easily corrected problems will be invited to submit an abbreviated amendment (5 page limit and one time only), which directly addresses the questions and concerns raised in the initial review.

This RFA uses just-in-time concepts. It also uses the modular budgeting format. (see <http://grants.nih.gov/grants/funding/modular/modular.htm>). Specifically, if the investigator is submitting an application with direct costs in each year of \$250,000 or less, use the modular budget format. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

This RFA uses just-in-time concepts. Applicants must not exceed a limit of \$250,000 direct costs per year and modular grant procedures should be used. (See <http://grants.nih.gov/grants/funding/modular/modular.htm>). Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

FUNDS AVAILABLE

The participating Institutes intend to commit approximately \$2,225,000 in FY 2004 to fund 5 to 7 new grants for ancillary studies of immunomodulatory interventions for immune system mediated diseases clinical trials and of vaccine clinical trials for non-HIV/AIDS infectious diseases. NIAID intends to commit an additional \$2,000,000 in FY

2004 to fund 5 to 8 new grants for ancillary studies of vaccine clinical trials for the prevention and treatment NIAID Category A, B and C agents of bioterrorism and non-HIV/AIDS emerging/re-emerging infectious diseases.

Although the financial plans of the IC(s) provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. At this time, it is not known if this RFA will be reissued.

ELIGIBLE INSTITUTIONS

The applicant may submit (an) application(s) if the institution has any of the following characteristics:

- o For-profit or non-profit organizations
- o Public or private institutions, such as universities, colleges, hospitals, and laboratories
- o Units of State and local governments
- o Eligible agencies of the Federal government
- o Domestic or foreign institutions/organizations

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

SPECIAL REQUIREMENTS

1. Application:

The research plan should be limited to 15 pages. In addition to the specific aims, background and significance, preliminary studies, and research design and methods (Sections A to D), the research plan must include a justification for why the proposed studies require the use of patients in the parent clinical trial as opposed to using patients with the same disease state but not in a trial. The manner in which immunological parameters will be related to the clinical outcomes in the main study should also be discussed.

Methods of data analysis and power calculations must be included, as well as a justification for the required sample size. A restatement of the sample size calculations from the parent clinical trial is insufficient. If appropriate to your application, discuss whether it is necessary to perform the mechanistic studies on all patients enrolled in the parent trial or whether a sub-sample would be sufficient. The plan must also include a discussion of the statistical procedures that will be used to analyze the data. It is strongly

recommended that a statistician be part of the research team and active in preparation of the proposal.

2. Appendix:

Appendix A should contain the following clearly labeled materials:

- o parent clinical trial protocol
- o investigator's brochure, if applicable, for the parent clinical trial
- o consent forms for both the parent clinical trial and the mechanistic studies, if different
- o Institutional Review Board (IRB) approval or the parent clinical trial and ancillary studies, if completed (Note: IRB approval is not required at the time of submission of the application)
- o written agreement for conduct of the mechanistic studies from parent clinical trial sponsors, IND holders, and PI of the parent clinical trial.

The protocol and the investigators' brochure for the parent clinical trial should be included with the application as part of the human subjects' section. Inclusion of the complete clinical protocol within the PHS 398 grant application is intended to simplify the application process by eliminating the need to duplicate protocol details in the Research Plan section. NIH will treat as confidential any scientific, preclinical, clinical, or formulation data and information that the sponsor of the parent clinical trial deems to be proprietary and confidential.

IRB approval of the informed consent form(s) is not required at the time of submission of the application. However, drafts of informed consent form(s) for the parent clinical trial and the mechanistic studies, if different, must be included as part of Appendix A. While drafts of the parent clinical trial consent forms at all participating sites are not required, it would be useful to include them if they are available. It is recommended that applications submitted under this program have clear language in the informed consent form(s) that distinguishes mechanistic studies from the clinical trials with which they are linked. It is also recommended that the following items be clarified: (1) additional blood or tissue that will be collected as part of the mechanistic study; (2) the right of the subjects to refuse to participate in the mechanistic study and still participate in the clinical trial; and (3) no charges to the subject for participation in the mechanistic studies. Any incentives provided to subjects to participate in the mechanistic studies (if in addition to those under the parent trial) should be clearly described and justified.

In order to ensure coordination between the mechanistic studies and the parent clinical trial, the clinical trial principal investigator and his or her academic institution, the sponsor of the parent clinical trial (including drug companies, if applicable), and the holder of the IND, if not one of the above, must provide written agreement for the conduct of the mechanistic studies as presented in the application.

Prior to award, the applicant must provide to the funding institute a memorandum of understanding signed by the applicant, an appropriate representative of the applicant institution, the principal investigator of the parent clinical trial and his or her academic

institution, an appropriate representative of the sponsor of the parent clinical trial and holder of the IND, if applicable and not one of the above. This memorandum will confirm agreement among the various parties and will outline the terms and conditions of the agreement in the following areas: 1) ownership, analysis, access, and release of data from the mechanistic studies; 2) access to the data from the parent clinical trial (how/when) that is needed to analyze the mechanistic studies, including procedures for prevention of unblinding of the parent trial; 3) documentation of quality assurance procedures for both the parent clinical trial and the mechanistic studies, and documentation of Data and Safety Monitoring procedures for the parent clinical trial, especially for efficacy trials; 4) ownership of intellectual property developed by the mechanistic studies; and 5) publication of the mechanistic study results.

When clinical studies or trials are a component of the research proposed, NIAID policy requires that studies be monitored commensurate with the degree of potential risk to study subjects and the complexity of the study. AN UPDATED NIAID policy was published in the NIH Guide on July 8, 2002 and is available at:

<http://grants.nih.gov/grants/guide/notice-files/NOT-AI-02-032.html>.

The full policy, including terms and conditions of award, is available at:

<http://www.niaid.nih.gov/ncn/pdf/clinterm.pdf>.

3. Summary Report:

To assist in the overall evaluation of the research program, the Principal Investigators of grants funded under this RFA will be asked to provide a brief (1-2 pages) summary report one year following the end of the project period. The reports will summarize the major scientific knowledge gained and identify other substantive outcomes such as publications, patents, and new grants, contracts, or research studies based on the work supported under this RFA.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific research, peer review, and financial or grants management issues:

o Direct questions about scientific/research issues to:

Kristy Kraemer, Ph.D.
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
Room 3043, MSC-6601
6610 Rockledge Drive
Bethesda, MD 20892-6601
(Express Mail: 20817)
Phone: 301-496-5598
Fax: 301-480-0693

e-mail: kk187y@nih.gov

Susana A. Serrate-Sztein, M.D.
Rheumatic Diseases Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Room 5AS-25E, MSC-6500
45 Center Drive
Bethesda, MD 20892-6500
Phone: 301-594-5032
FAX: 301-480-4543
e-mail: ss86e@nih.gov

Beena Akolkar, Ph.D.
Division of Diabetes, Endocrinology, and Metabolic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
Room 681
6707 Democracy Boulevard
Bethesda, MD 20892
Phone: 301-594-8812
FAX: 301-480-3503
e-mail: ba92i@nih.gov

Ursula Utz, Ph.D.
National Institute of Neurological Disorders and Stroke
Room 234, MSC-2134
6001 Executive Boulevard
Bethesda, MD 20892-2134
Phone: 301-496-1431
FAX: 301-480-2424
e-mail: uu1p@nih.gov

Dennis F. Mangan, Ph.D.
Immunology and Immunotherapy Program
National Institute of Dental and Craniofacial Research
Room 4AN-Suite 18, MSC-6402
45 Center Drive
Bethesda, MD 20892-6402
Phone: (301) 594-2421
FAX: (301) 480-8318
e-mail: dm38q@nih.gov

o Direct questions about peer review issues to:

Samuel C. Edwards, Ph.D.
Immunological Sciences Initial Review Group
Center for Scientific Review

Room 4200, MSC-7812
6701 Rockledge Drive
Bethesda, MD 20892-7812
(overnight carrier - FEDEX, UPS, Airborne, etc.) 20817
Phone: 301-435-1152
FAX: 301-480-4042
email: se83s@nih.gov

o Direct questions about financial or grants management matters to:

Ann White-Devine
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
Room 2118, MSC-7614
6700-B Rockledge Drive
Bethesda, MD 20892-7614
Phone: 301-402-5601
FAX: 301-480-3780
e-mail: ad22x@nih.gov

LETTER OF INTENT

Prospective applicants are asked to submit, at least one month prior to the anticipated application submission date, a letter of intent that includes the following information:

- o Descriptive title of the proposed research
- o Name, address, and telephone number of the Principal Investigator
- o Names of other key personnel
- o Participating institutions
- o Number and title of this RFA

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows NIH staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent one month prior to the application receipt date to Dr. Edwards at the address listed under INQUIRIES.

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at <http://www.dunandbradstreet.com/>. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The

PHS 398 document is available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS:

Applications requesting up to \$250,000 per year in direct costs must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in \$25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at <http://grants.nih.gov/grants/funding/phs398/phs398.html> includes step-by-step guidance for preparing modular grants. Additional information on modular grants is available at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number (RFA-AI-04-001) on the label. 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: "HYPERACCELERATED AWARD/MECHANISMS IN IMMUNOMODULATORY TRIALS" and number (RFA-AI-04-001) must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: <http://grants.nih.gov/grants/funding/phs398/label-bk.pdf>.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, and five (5) signed, 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)

Applications must be received by the 9th of each month. If the ninth of the month falls on a weekend day or Federal Holiday, then the receipt date is advanced to the next business day. The application must not arrive more than two days prior to the receipt date. Applications, which are received after the 9th, will automatically be processed the following month. Applications not received as a single package on the receipt date or not conforming to the instructions contained in PHS 398 (rev. 5/2001) Application Kit (as modified in, and superseded by, the special instructions below, for the purposes of this RFA), will be judged non-responsive and will be returned to the applicant.

APPLICATION PROCESSING: Applications must be received by the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

The Center for Scientific Review (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. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to an RFA, it is to be prepared as a NEW application. That is the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NIAID.

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 NIH in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

- o Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
- o Receive a written critique
- o Receive a second level review by the National Advisory Council(s) of the assigned Institutes.

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

- o Significance
- o Approach
- o Innovation
- o Investigator
- o Environment

The scientific review group will address and consider each of these criteria in assigning the application's overall score, weighting them as appropriate for each application. The application does not need to be strong in all categories to be judged likely to have 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.

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?

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?

INNOVATION: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

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)?

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?

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below)

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below).

CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH: If vertebrate animals are to be used in the project, the five items described under Section f of the PHS 398 research grant application instructions (rev. 5/2001) will be assessed.

ADDITIONAL REVIEW CONSIDERATIONS

SHARING RESEARCH DATA: Applicants requesting more than \$500,000 in direct costs in any year of the proposed research are expected to include a data sharing plan in their application. The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data-sharing plan into the determination of scientific merit or priority score. (See instructions and URL to policy in the Federal Citations, below.)

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: One month before application receipt date.

Application Receipt Date: 9th of each month.

Peer Review Date: 4-6 weeks after receipt date

Council Review Date: Special Electronic Council

Earliest Anticipated Start Date: 13 weeks after receipt of application.

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

- o Scientific merit of the proposed project as determined by peer review
- o Availability of funds
- o Programmatic priorities

REQUIRED FEDERAL CITATIONS

HUMAN SUBJECTS PROTECTION: Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

DATA AND SAFETY MONITORING PLAN: Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II), efficacy, effectiveness and comparative trials (phase III). The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. (NIH Policy for Data Safety and Monitoring, NIH Guide for Grants and Contracts, June 12, 1998:

<http://grants.nih.gov/grants/guide/notice-files/not98-084.html>).

SHARING RESEARCH DATA: Starting with the October 1, 2003 receipt date, investigators submitting an NIH application seeking more than \$500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible. http://grants.nih.gov/grants/policy/data_sharing Investigators should seek guidance from their institutions, on issues related to institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: 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 clinical research projects unless a clear and compelling justification is provided indicating 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 clinical research should read the AMENDMENT "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS:

The NIH maintains a policy 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 is available at <http://grants.nih.gov/grants/funding/children/children.htm>.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT

PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. This policy announcement is in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at <http://stemcells.nih.gov/index.asp> and at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html>. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see <http://stemcells.nih.gov/registry/>). It is the responsibility of the applicant to provide, in the project description and elsewhere in the application as appropriate the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF

INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH

INFORMATION: The Department of Health and Human Services (DHHS) issued final modification to the “Standards for Privacy of Individually Identifiable Health Information”, the “Privacy Rule,” on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as “covered entities”) must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (<http://www.hhs.gov/ocr/>) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html>.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople>.

AUTHORITY AND REGULATIONS

This program is described in the Catalogue of Federal Domestic Assistance at <http://www.cfda.gov/> in the following citations: No. 93.855, Immunology, Allergy, and Transplantation Research and No. 93.856, Microbiology and Infectious Diseases Research, NIAID; No. 93.847, Diabetes, Endocrinology and Metabolism Research, No. 93.848, Digestive Diseases and Nutrition Research, and No. 93.849, Kidney Diseases, Urology and Hematology Research, NIDDK; No. 93.866, Arthritis, Musculoskeletal and Skin Diseases Research, NIAMS; No. 93.853, Extramural Research Programs in the Neurosciences and Neurological Diseases, NINDS. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The NIH Grants Policy Statement is available at <http://grants.nih.gov/grants/policy/policy.htm>. This document includes general information about the grant application and review process; information on the terms and conditions that apply to NIH Grants and cooperative agreements; and a listing of pertinent offices and officials at the NIH. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the 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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