

OSTEOARTHRITIS BIOMARKERS NETWORK

RELEASE DATE: February 14, 2003

RFA: AR-03-006

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
(<http://www.nih.gov/niams/>)

Letter of Intent Receipt Date: March 17, 2003

Application Receipt Date: April 17, 2003

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PURPOSE OF THIS RFA

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invites applications for cooperative agreements for the development and characterization of new or refinement of existing osteoarthritis (OA) biomarkers. The Principal Investigators of each project will become members of a national OA Biomarkers Network that the NIAMS will establish immediately following award. Investigators in the Network will work collaboratively and share resources for the development, evaluation, and validation of biochemical markers for osteoarthritis onset, severity, progression, and response to treatment. A Network Steering Committee (NSC) composed of the Principal Investigators in the Network and appropriate NIAMS staff (such as a Science Officer or Program Officer) will coordinate the work of the Network and with other ongoing NIH sponsored OA studies. If appropriate, the NIAMS will issue subsequent RFAs for Biomarker Validation and a Data Management and

Coordinating Center.

RESEARCH OBJECTIVES

Background

Osteoarthritis is the most common joint disorder, producing pain and disability, and ultimately resulting in the destruction of articular cartilage. Abnormal metabolic processes begin in the articular cartilage several years before destruction of the articular surface can be detected radiologically. The development and validation of standardized, sensitive assays for disease markers in blood/urine may facilitate the ability to diagnose the disease during the pre-radiologic stages, to monitor disease progression and the effects of surgical or pharmacological treatment, and to accelerate the pace of drug discovery.

Biomarkers are defined as molecules that reflect a specific biological or pathological process, consequence of a process, or a response to therapeutic intervention. Biochemical studies indicate that in OA there are marked increases in the breakdown and biosynthesis of the major cartilage matrix molecules, the collagens and proteoglycans. Exploration of the mechanisms responsible for breakdown and biosynthesis of articular cartilage in OA has prompted interest in the potential use of cartilage-derived molecules as markers of cartilage metabolism in OA. Also, the enhanced synthesis and degradation of matrix molecules in OA cartilage involves not only accelerated turnover but also the upregulation of molecules synthesized in immature cartilage but not in healthy adult articular cartilage. In addition, early changes in OA have been shown to involve significant changes in markers of bone turnover. Some of these molecules may be of value for further investigation and are included in this RFA. A current assessment of the research needs in OA biomarker research is presented in the NIH Osteoarthritis Initiative White Paper on Biomarkers, which can be located at the following web address:
<http://www.niams.nih.gov/nc/oi/oabiomarwhipap.htm>

Among the technical approaches that can be exploited are the identification of cellular and molecular markers of inflammation, tissue destruction and repair, and their detection using sera, peripheral blood cells or tissue. New assay systems have been developed to measure intracellular cytokines, to identify and isolate cells (such as chondrocytes and synovial cells) and to simultaneously measure the expression of thousands of genes. An additional technology applicable to such questions is that of differential gene expression, detected by the use of microchip array presentation of cDNAs from affected vs. unaffected tissues, active vs. inactive time points, or affected vs. unaffected individuals. Experimental studies correlating outcomes measured by imaging technologies (spectral techniques, bioluminescent approaches, multiphoton imaging) with current or new biomarkers would dramatically improve our understanding about their interactions and their responses to mechanical and inflammatory stimuli, and would potentially identify targets for pharmacologic agents, especially disease modifying agents. All or any of these markers would assist in the clinical management of patients with OA for diagnostic, prognostic, and response-to-treatment assessment purposes.

Scope of This RFA

The purpose of this solicitation is to encourage the submission of applications from qualified investigators interested in research and development projects designed to identify and characterize biochemical markers to assess OA disease risk, onset, progression, and response to treatment. Areas of interest include:

- o Small scale studies to evaluate promising biomarkers or technologies, including evaluation of diagnostic predictive accuracy, sensitivity, specificity, and whenever possible, medical benefits, of known and newly identified potential biomarkers;
 - o Development of biomarkers and biomarker expression patterns, sometimes of multiple markers simultaneously, which will serve as background information for subsequent large definitive validation studies;
 - o Collaborative approaches among academic and industrial leaders in molecular biology, molecular genetics, biochemistry, rheumatology, computer science, public health, etc., for the development of high throughput, sensitive assay methods for biomarkers from an early diagnosis, risk assessment treatment response monitoring viewpoint;
 - o Translational research in the biology and pathogenesis of OA that directly leads to development, characterization, and testing of biomarkers for early disease diagnosis, assessment of disease risk, evaluation of disease course, and treatment responses (the search for new markers should reflect new information about the biology of tissues and organs involved in OA as well as new knowledge on disease etiology and pathogenesis, such as apoptosis, cell cycle control, etc.);
 - o Identification of biomarkers based on advances on the genetic epidemiology of OA;
 - o Identification of biomarkers that can potentially be useful to define disease subsets and risk for severe disease or response to treatments;
- Identification of biomarkers that may inform therapeutic approaches in relation to symptoms, such as pain or structural change;
- o Use of new technologies and approaches to identify new potential targets for the development of biomarkers;
 - o Development of new assays and technologies for the rapid and accurate measurement of biomarkers in OA;
 - o Use of animal models and other experimental systems to identify biomarkers of loading and other physical properties and changes in structures affected by OA that may be indicators of disease onset or evolution;

o Exploratory, small scale ancillary studies to existing cohorts to determine feasibility of an assay or approach for the identification or use of biomarkers in the context of ongoing OA studies in patients.

Research of a fundamental nature, such as studies on basic inflammatory processes, growth regulation, cell cycle control, or other basic studies that are not explicitly focused on identification of target process or mediators for biomarker development are NOT included under the scope of this RFA. This RFA will not support large-scale evaluation studies of new or existing biomarkers.

Network Goals

This research initiative also seeks to promote the interactions of investigators with scientific expertise, facilities, and capabilities to conduct controlled studies through the establishment of the OA Biomarkers Network. Principal Investigators of the individual cooperative agreements must actively participate in the OA Biomarkers Network. The purpose of the Network is to establish a scientific consortium of investigators, academic as well as industrial, with resources for basic, translational, and clinical research. The goals of the Network will be to discover and to coordinate the evaluation of biomarkers for the earlier detection of OA and for the assessment of risk and response to treatments. Because early diagnosis and treatment issues are often related, the Network will need meaningful participation from various medical organizations. In some of its activities, the Network may need to relate programmatically to the research infrastructures supported by NIAMS and other NIH components (for example, Specialized Centers of Research in OA, Multidisciplinary Clinical Research Centers, Osteoarthritis Initiative), with ongoing NIH clinical research programs/trials (for example, Glucosamine in OA Trial), or with other agencies, such as Food and Drug Administration.

MECHANISM OF SUPPORT

This RFA will use a Cooperative Agreement (U01) mechanism. The NIH U01 is a cooperative agreement award mechanism in which the Principal Investigator retains the primary responsibility and dominant role for planning, directing, and executing the proposed project, with NIH staff being substantially involved as a partner with the Principal Investigator, as described under the section "Cooperative Agreement Terms and Conditions of Award. At present, the plans for extending the cooperative agreement projects beyond the initial award period are indefinite. Future plans will be based on evaluation of scientific progress achieved by awardees during the initial funding period. The anticipated award date is September 30, 2003.

This RFA is a one-time solicitation. At this time the NIAMS does not anticipate that there will be a renewed competition after five years. If the NIAMS does not continue the program, awardees may submit grant applications through the usual investigator-initiated grants program. However, before submitting such applications, applicants are advised to contact the Program

Director listed under INQUIRIES.

FUNDS AVAILABLE

The NIAMS intends to commit an estimated \$1,000,000 total costs in FY 2003 to fund approximately 3 to 4 new grants in response to this RFA. An applicant may request a project period of up to 5 years. 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. Although the financial plans of the NIAMS 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.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your 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
- o Faith-based or community-based 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

COOPERATIVE AGREEMENT TERMS AND CONDITIONS OF AWARD

Within 90 days of award the NIAMS will establish the OA Biomarkers Network. As part of the U01 Cooperative Agreement Grant process, the following Terms and Conditions of Award and details of the arbitration procedures pertaining to the scope and nature of the interaction between the NIH staff and the participating awardees will be incorporated into the Notice of Grant Award and provided to the Principal Investigator and the institutional official at the time of award. These procedures will be in addition to the customary programmatic and financial negotiations that occur in the administration of grants.

Cooperative agreements are assistance mechanisms subject to the same administrative requirements as grants. The special Terms and Conditions of Award are in addition to, and not in lieu of, otherwise applicable OMB

administrative guidelines, HHS Grant Administration Regulations at 45 CFR Part 74 and 92, and other HHS, PHS, and NIH grant administration policies and procedures. Facilities and Administrative Cost (indirect cost) award procedures will apply to cooperative agreement awards in the same manner as for grants.

The administrative and funding instrument used for this program is a Cooperative Agreement (U01), an "assistance" mechanism (rather than an "acquisition" mechanism) in which substantial NIAMS scientific and/or programmatic involvement with the awardee is anticipated during performance of the activity. Consistent with this concept, the dominant role and prime responsibility for the activity resides with the awardee(s) for the project as a whole, although specific tasks and activities in carrying out the studies will be shared among the awardees and the NIAMS Science Officer.

Failure of the awardees to meet the performance requirements, including these special terms and conditions of award, or significant changes in level of performance, may result in a reduction of budget, withholding of support, suspension and/or termination of the awards.

1. Awardee Rights and Responsibilities

Awardees have primary authorities and responsibilities to define objectives and approaches, and to plan, conduct, analyze, and publish results, interpretations, and conclusions of their studies. The primary responsibilities of the awardees are to:

- o Define the research objectives
- o Design the necessary research protocols
- o Conduct specific studies
- o Analyze and interpret research data
- o Propose protocol modifications as required
- o Participate in Network collaborative activities approved by the Network Steering Committee (NSC)
- o Serve on the NSC
- o Agree to sharing of reagents and technologies in accordance with approved sharing plans
- o Provide information to the NIAMS staff concerning progress
- o Abide by all scientific, practical and policy decisions of the NSC

Awardees will retain custody of and primary rights to their data and intellectual property developed under the award, subject to current government policies regarding rights of access as consistent with current HHS, PHS, and NIH policies and subject to the terms and conditions of this RFA. All research publications shall be submitted to NIH for administrative and policy review prior to submission for publication. This review shall not be for the purpose of scientific oversight, but rather to ensure that NIH policies and/or representations that may imply NIH endorsement of clinical or research standards are not proposed. These reviews may not unreasonably delay submission for publication.

2. NIAMS Responsibilities

NIAMS Science Officer

NIAMS Science Officer will be NIAMS Program staff member who will have substantial scientific involvement during the conduct of this activity, through technical assistance, advice, and coordination above and beyond normal Program stewardship for grants. The NIAMS Science Officer will be selected by the NIAMS. The degree of involvement of the NIAMS Science Officer will include the following:

- o Assist in coordinating collaborative research efforts that involve multiple laboratories and avoiding unwarranted duplication of effort across laboratories;
- o Review and comment on critical stages in the research program before subsequent stages are implemented;
- o Assist in the interaction between the awardee and the FDA, when appropriate;
- o Assist in the interaction between the awardee and investigators of other institutions, as well as between the awardee and potential commercial sponsors;
- o Retain the option of recommending termination of studies if technical performance falls below acceptable standards, or when specific lines of research cannot be effectively pursued in a timely manner;
- o Retain the option to recommend additional research endeavors within the constraints of the approved research and negotiated budget;
- o Serve on the NSC.

NIAMS Program Officer:

NIAMS will appoint a Program Officer who will have program oversight responsibilities for each grant and for the entire Network. The Program Officer will:

- o Exercise the normal stewardship responsibilities of an NIAMS Program Officer

o Carry out continuous review of all activities to ensure objectives are being met

o Have the option to recommend withholding support to a participating institution if technical performance requirements are not met

3. Collaborative Responsibilities/ Network Steering Committee (NSC)

Collaborative activities of the Network, consistent with the stated intent of the RFA, will be done by a NSC consisting of the Principal Investigators of each grant and the NIAMS Science Officer. Each Principal Investigator (or designee) will have one vote, and the NIAMS will have one vote. Membership on the NSC becomes effective upon issuance of the Notice of Grant Award. The NSC may establish additional by-laws, subcommittees, or workgroups for specific tasks. The NIAMS Science Officer may not chair any committee or subcommittee. During the first year there will be one planning committee meeting within 6 months of the award date and one NSC meeting in the Bethesda, MD area. After the first year the NSC meetings will be convened twice yearly in the Bethesda, MD area. The purpose of these meetings is to share scientific information, assess scientific progress, identify new research opportunities, and discuss strategy and potential avenues of collaborations such as with industry, private foundations and/or NIH intramural scientists, establish priorities that will accelerate the translation of preclinical findings into clinical applications, reallocate resources and conduct the business of the cooperative research program. Awardees must set aside 20% of their annual budget after the first year for Network collaborative studies. The NSC will develop the process and review procedures for handling the 20% funds in future years. The use of these set aside funds will be restricted and must be reviewed and approved by the NSC and then recommended to, and approved by the NIAMS for release from the individual U01 awards. Decisions will be made by a majority vote of a quorum, with an attempt for consensus when possible. The NSC can convene through telephone conference or in person. Outside consultants/experts may be asked to participate in these discussions as nonvoting advisors. Collaborative projects among the Network members will require NSC approval.

NSC members will abide by all scientific, practical, and policy decisions of the NSC.

4. Arbitration Process

Any disagreement that may arise on scientific/programmatic matters (within the scope of the award), between award recipients and the NIAMS may be brought to arbitration. An arbitration panel consist of one person selected by the Principal Investigators, one person selected by the NIH, and a third person selected by both NIH staff and the Principal Investigators. The decision of the arbitration panel, by majority vote, will be binding. This special arbitration procedure in no way affects the awardee's right to appeal an adverse action that is otherwise appealable in accordance with the PHS regulations at 42 CFR Part 50, Subpart D and HHS regulation at 45 CFR Part 16.

5. Public Domain of Data

All data from collaborative studies will first be available to be analyzed and interpreted by the collaborators in the project. However, since the creation of the data set is funded through public monies and because the data set will constitute a national scientific resource for the research community, the awardees will make data of all types available to the larger research community no more than 24 months from the date after which the final wave of data for a particular project have been collected and cleaned. More rapid sharing of data is encouraged.

6. Progress Reviews

Progress of the Network projects will be reviewed annually by the NIAMS staff at the time each continuation application is considered for funding to assure that satisfactory progress is being made in achieving the project objectives and that each site is following the procedures recommended and approved by the NSC. During the first year of funding, and during subsequent years, if deemed necessary by the Program Officer, reviews will be more frequent. Should problems arise in the conduct of a project, the NIAMS staff may require that the awardee submit quarterly reports on progress and fiscal matters. By acceptance of this award, the awardee agrees to abide by decisions and policies of the NSC and the other terms and conditions listed above or referenced in the Notice of Grant Award.

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 your questions about scientific/research issues to:

Bernadette Tyree, Ph.D.
National Institute of Arthritis and Musculoskeletal and Skin Diseases
6701 Democracy Blvd.
Suite 800
Bethesda, MD 20892-6500
Telephone: (301) 594-5032
FAX: (301) 594-4543
Email: <mailto:tyreeb@ep.niams.nih.gov>

o Direct your questions about peer review issues to:

John R. Lyman grover, Ph.D.
National Institute of Arthritis and Musculoskeletal and Skin Diseases
6701 Democracy Blvd, Suite 800
Bethesda, MD 20892-4872

Telephone: (301) 594-4952
FAX: (301) 402-2406
or (301) 480-4543
Email: <mailto:lymangrj@ep.niams.nih.gov>

o Direct your questions about financial or grants management matters to:

Melinda Nelson
National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIAMS, NIH
6701 Democracy Blvd.
Suite 800
Bethesda MD 20892-6500
Telephone: (301) 594-3535
FAX (301) 480-5450
Email: <mailto:nelsonm@ep.niams.nih.gov>

LETTER OF INTENT

Prospective applicants are asked to submit 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 NIAMS staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document. The letter of intent should be sent to:

John R. Lymangrover, Ph.D.
National Institute of Arthritis and Musculoskeletal and Skin Diseases
6701 Democracy Blvd, Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-4952
FAX: (301) 402-2406
or (301) 480-4543
Email: <mailto:lymangrj@ep.niams.nih.gov>

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> in an interactive format. For further assistance contact Grants Info, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov

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 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 and number 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>

SPECIAL INSTRUCTIONS FOR PREPARATION OF THE APPLICATION: "The Research Plan" section must not exceed a total of 35 pages. To promote the development of a collaborative program among the award recipients, a number of issues need to be addressed in their applications as discussed below.

1. Collaborative Activities

- o Applicants must include their specific plans for responding to the "Terms and Conditions" section. Applicants should state their willingness to collaborate and share data freely with the others in the Network, to serve on the NSC and be bound by its decisions, particularly those which relate to setting priorities for quality assurance and validation phase of the biomarker development, and to be able and willing to interact with each other and the NIAMS in an Internet environment. Applicants must describe computer and Internet resources for this type of interaction. Applicants should also discuss the interaction with the NIAMS Program Director as to how they will fulfill the responsibilities of the Network to work together cooperatively.
- o Interaction with Industry (Patent Rights): Applicants are strongly encouraged to forge a partnership with industry/biotechnology firms in developing biomarkers/reagents. It is anticipated that the creation of the Network will serve as an attractive collaborator for industry, since it will provide clinical opportunities for the evaluation of new echnologies of private companies.
- o Since basic research and development of new biomarkers/reagents is an objective of this effort and since active involvement by the industrial laboratories is often facilitated by the existence of adequate patent coverage, it is essential that applicants provide plans to assure such coverage, as appropriate. Since multiple institutions may be involved, the situation can become complex. Each applicant, therefore, must provide a description of the approach to be used for obtaining patent coverage, and for licensing in particular where the inventions may involve investigators from more than one institution. Attention

is drawn to Bayh-Dole Act (Public Law 96-517). Pursuant to Bayh-Dole, inventions made by the extramural investigators belong to their respective institutions. This may be of concern to collaborators, especially those who are the source of proprietary biomarkers/reagents.

2. Budget

o Applicants must budget for travel and per diem expenses for NSC meetings. In the first year, applicants should plan for two investigators, the principal investigator and an additional senior investigator, to attend a planning meeting and one NSC meeting. In the second and subsequent years, applicants should plan for the PI and another investigator to attend two NSC meetings per year.

o Applicants must set aside 20% of their annual budget after the first year for Network collaborative studies. The use of these set aside funds will be restricted and must be reviewed and approved by the NSC and then recommended to, and approved by the NIAMS for release from the individual U01 awards.

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

At the time of submission, two additional copies of the application must be sent to:

John R. Lyman grover, Ph.D.
National Institute of Arthritis and Musculoskeletal and Skin Diseases
6701 Democracy Blvd, Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-4952
FAX: (301) 402-2406
or (301) 480-4543
Email: <mailto:lymangrj@ep.niams.nih.gov>

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. 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.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NIAMS. 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 NIAMS in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

- o Receive a written critique
- o 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 and assigned a priority score
- o Receive a second level review by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council.

REVIEW CRITERIA

Upon receipt, each application will be reviewed for completeness by the Center for Scientific review (CSR) and for responsiveness by the NIAMS. 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 NIAMS in accordance with the review criteria stated below. As part of the initial scientific merit review, a process may 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 Arthritis and Musculoskeletal and Skin Diseases Advisory Council.

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 your 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 your application's overall score, weighting them as appropriate for each application. Your 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, you 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 your study address an important problem? If the aims of your application are achieved, how do they advance scientific knowledge? 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? Do you acknowledge potential problem areas and consider alternative tactics?

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

(4) INVESTIGATOR: Are you appropriately trained and well suited to carry out this work? Is the work proposed appropriate to your experience level as the principal investigator and to that of other researchers (if any)?

(5) ENVIRONMENT: Does the scientific environment in which your 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?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, your application will also be reviewed with respect to the following:

o INTERACTIONS: Are there adequate plans for effective interaction and coordination with the Network, the NSC, and the NIAMS? Do the investigators state their willingness to collaborate and share information? Do the investigators state their willingness to abide by the priorities and policies agreed upon by the NSC for collaborative studies? Have the applicants proposed sound strategies for communication among themselves and with the NIAMS?

o PROTECTIONS: The adequacy of the proposed protection for humans, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

o INCLUSION: 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 included in the section on Federal Citations, below)

- o 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: March 17, 2003
Application Receipt Date: April 17, 2003
Peer Review Date: TBA
Council Review: September 2003
Earliest Anticipated Start Date: September 30, 2003

AWARD CRITERIA

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

- o Scientific merit (as determined by peer review)
- o Availability of funds
- o Programmatic priorities.

REQUIRED FEDERAL CITATIONS

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. You will find this policy announcement 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://grants.nih.gov/grants/stem_cells.htm 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://escr.nih.gov/>).

It is the responsibility of the applicant to provide 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 RFA 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.

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 RFA, Osteoarthritis Biomarkers Network, is related to several objectives, particularly those listed in the chapter "Arthritis, Osteoporosis, and Chronic Back Conditions." 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 Catalog of Federal Domestic Assistance No. 93.846 and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. 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 described at <http://grants.nih.gov/grants/policy/policy.htm> and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92.

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.