

## MECHANISMS OF CHONDROPROTECTION

Release Date: April 15, 1999

RFA: AR-99-004

P.T.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Letter of Intent Receipt Date: August 1, 1999

Application Receipt Date: September 8, 1999

THIS RFA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. IT INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS THAT MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS RFA.

### PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invite applications for research on mechanisms of chondroprotection. The applications may be for individual research projects (R01) or for exploratory/developmental grants (R21). The objective of the exploratory/developmental mechanism (R21) is to encourage applications from individuals who are interested in testing innovative or conceptually creative ideas that are scientifically sound and may advance our understanding of chondroprotective mechanisms. The research should be specifically targeted towards identification and evaluation of chondroprotective agents to prevent cartilage destruction and/or facilitate its repair in such conditions as rheumatoid arthritis, juvenile rheumatoid arthritis, and osteoarthritis, where there is a decline in the structural integrity of the articular cartilage. This Request for Applications (RFA) requests basic and applied research projects, but not epidemiological or clinical treatment projects.

### 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 RFA, Mechanisms of Chondroprotection, is related to the priority areas of chronic

disabling conditions and of older adults and preventive services. 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 202-783-3238) or at <http://www.crisny.org/health/us/health7.html>.

## ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

## MECHANISM OF SUPPORT

This RFA will use the National Institutes of Health (NIH) individual research grant (R01) and the exploratory/developmental grant (R21) mechanisms. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The anticipated award date is April 1, 2000. Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the size of an award will also vary. This RFA is a one time solicitation. Future unsolicited competing continuation applications will compete with all investigators initiated applications and be reviewed according to customary peer review procedures.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC Program Director or Principal Investigator should be included within the application.

R01 Applications. R01 awards will vary in size and duration reflecting the nature and scope of the research proposed. Future unsolicited competing continuation applications will compete with all investigator initiated applications and be reviewed according to customary peer review.

R21 Applications. Use of this novel mechanism by investigators experienced in cartilage research who wish to adapt new methods or techniques established in other fields to develop scientific approaches and models to study the chondroprotection are encouraged to apply. Also

encouraged to apply are investigators with expertise in fields other than cartilage research who wish to establish new research programs in this research area.

Exploratory/developmental studies are not intended for large scale undertakings nor to support or supplement ongoing research. Instead, investigators are encouraged to explore the feasibility of an innovative research question or approach which may not be justifiable through existing research to compete as a standard research project grant (e.g., R01), and to develop a research basis for a subsequent application through other mechanisms, i.e., R01, P01.

Exploratory/developmental (R21) grants, may not exceed \$75,000 per year in direct costs, including indirect costs for collaborating institutions, if any. The total project period for an R21 application submitted in response to this RFA may not exceed three years. These grants are non-renewable and continuation of projects developed under the R21 program will be through the traditional unsolicited (R01 or P01) grant programs.

Specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts being examined by the NIH. The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and Institute staff. Complete and detailed instructions and information on Modular Grants can be found at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

Applications will request direct costs in \$25,000 modules, up to a total direct cost request of \$250,000 per year for R01s and up to \$75,000 for R21s. A typical modular grant application will request the same number of modules in each year.

Application budgets will be simplified. Detailed categorical budget information will not be submitted with the application; budget form pages of the application kits will not be used. Instead, total direct costs requested for each year will be presented. Information, in narrative form, will be provided only for Personnel and, when applicable, for Consortium/Contractual costs. See section on application instructions below.

Additional narrative budget justification will be required in the application only if there is a variation in the number of modules requested.

There will be no routine escalation for future years. In determining the total for each budget year, applicants should first consider the direct cost of the entire project period. Well-justified modular increments or decrements in the total direct costs for any year of the project that reflect substantial changes in expected future activities may be requested. For example, purchase of major equipment in the first year may justify a higher overall budget in the first, but not in succeeding years.

Other Support pages of the PHS 398 will not be submitted with the application.

Information on research projects ongoing or completed during the last three years of the principal investigator and key personnel will be provided as part of the "Biographical Sketch." This information will include the specific aims, overall goals and responsibilities and should include Federal and non-Federal support. This information will be used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project.

Following peer review, information about Other Research Support will be requested by NIH from the applicant for applications being considered for award.

Additional budget information will be requested only under special circumstances.

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

#### FUNDS AVAILABLE

It is anticipated that six to eight awards will be made in fiscal year 2000 as a result of applications for "Mechanisms of Chondroprotection." The estimated funds available for the first year of support for the program are \$1,500,000 total costs. Actual funding is contingent upon receipt of a sufficient number of scientifically meritorious applications. Funding beyond the first and subsequent years of the grant will be contingent upon satisfactory progress during the preceding years and the availability of funds. Direct costs will be awarded in modules of \$25,000, less any overlap or other necessary administrative adjustments. Facilities and Administrative costs will be awarded based on the negotiated rates.

## RESEARCH OBJECTIVES

The purpose of this RFA is to stimulate basic research on mechanisms of chondroprotection for conditions affecting articular cartilage such as rheumatoid arthritis, juvenile rheumatoid arthritis, and osteoarthritis. A characteristic feature of rheumatoid arthritis and osteoarthritis is the progressive decline in the structural integrity of joint articular cartilage. The synovium in rheumatoid arthritis is characterized by an increase in lining layer thickness and infiltration of inflammatory cells into the synovium. Fibroblast and macrophage-derived cytokines such as interleukin 1 (IL-1) and (tumor necrosis factor  $\alpha$ ) TNF- $\alpha$  are abundant in the rheumatoid synovium and may stimulate these cells to produce destructive enzymes. Other cytokines such as IL-4 and IL-10 may represent physiological attempts to reverse the inflammatory process. Adhesion molecules facilitate both the migration of cells to the joint as well as the attachment of synovium to bone and cartilage. Joint destruction may be mediated by enzymes such matrix metalloproteinases (MMPs), the cathepsins, and other proteases. The mechanisms responsible for cartilage destruction in osteoarthritis are not well understood. It is not clear whether the primary lesion occurs in cartilage (a chondrocyte or cartilage matrix defect), in the subchondral bone or the synovium (with production of inflammatory mediators and proteinases). Current therapeutic modalities primarily involve treatment with nonsteroidal anti-inflammatory drugs, analgesics, and glucocorticoids that provide marginal symptomatic relief and with few exceptions have no effect on the preservation of the articular cartilage or on disease progression.

While the underlying causes of articular cartilage damage in such these conditions has not been identified, increasing evidence suggests a critical role for the connective tissue degrading enzymes, free radicals, growth factors, and inflammatory cytokines in the pathogenesis of arthritic joint destruction. This RFA invites research projects on basic studies on mechanisms of chondroprotection. Additionally, utilization of patients and patient materials from clinical trials evaluating promising chondroprotective agents to correlate *in vivo* effects with effects in model systems, to identify surrogate markers of chondroprotection, and to study the mechanisms underlying chondroprotective effects are encouraged. Such studies are not part of the parent or core clinical trial, and are commonly referred to as substudies or ancillary studies. The parent or core clinical trial must have independent financial support and will not receive support under this RFA. Clinical trials of any phase (i.e. I-IV) and supported by any source, public or private, are eligible. Appropriate research areas may include, but are not limited to, the following:

- o development and evaluation of new chondroprotective agents that protect cartilage directly or indirectly by affects on metabolism of component joint structures

- o development of new in vivo and in vitro models for the evaluation of chondroprotective agents
- o studies on mechanisms of suppression of mediator-induced cartilage destruction
- o studies on mediators of cartilage repair
- o studies of the altered metabolic control mechanisms in degenerative joint diseases of biosynthetic and degradative processes in cartilage
- o design of innovative approaches for delivery of chondroprotective agents, including gene therapy
- o design of systems and approaches to evaluate the efficacy of chondroprotective agents

This list is intended to be illustrative and not exclusive or restrictive. Applications combining interdisciplinary approaches that include collaborations between cartilage researchers and experts in other scientific fields are strongly encouraged.

#### INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study. If women or minorities are excluded or inadequately represented a clear compelling rationale must be provided. All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and reprinted in the NIH Guide for Grants and Contracts, Volume 23, Number 11, March 18, 1994. This information is available on the internet 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 the NIH that children must be included in all human subjects research conducted or supported by the NIH unless there are scientific or ethical reasons not to include them. The

goal of the policy is to increase the participation of children in research to obtain appropriate data. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998. The policy does not apply to ongoing studies (e.g., Type 5, Type 2) or previously reviewed amended applications. 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" which was published in the NIH Guide for Grants and Contracts, March 6, 1998. This information is available on the internet at <http://grants.nih.gov/grants/guide/notice-files/not98-024.html>.

Investigators also may obtain copies of the policies on "Inclusion of Women and Minorities in Research Involving Human Subjects" and "Inclusion of Children as Participants in Research Involving Human Subjects" from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

#### LETTER OF INTENT

Prospective applicants are asked to submit, by August 1, 1999, a letter of intent that includes a title of the proposed research, the name, address, and telephone number of the Principal Investigator, the identities of other key personnel and participating institutions, and the number and title of the RFA in response to which the application may be submitted. Although a letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information that it contains allows NIAMS 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:

Tommy L. Broadwater, Ph.D.  
Scientific Review Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
Natcher Building, Room 5AS-25U  
45 Center Drive, MSC 6500  
Bethesda, MD 20892-6500  
Telephone: (301) 594-4952  
FAX: (301) 480-4543  
[broadwater@nih.gov](mailto:broadwater@nih.gov)

#### APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 4/98) is to be used in applying for these grants, with the modifications noted below. These forms are available at most institutional offices of sponsored research; 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, e mail: [grantsinfo@nih.gov](mailto:grantsinfo@nih.gov); and on the internet at <http://grants.nih.gov/grants/forms.htm>

The RFA label available in the PHS 398 (rev. 4/98) application form must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title (Mechanisms of Chondroprotection) and number (RFA AR-99-004) must be typed on line 2 of the face page of the application form and the YES box must be marked.

#### BUDGET INSTRUCTIONS

The total direct costs must be requested in accordance with the program guidelines and the modifications made to the standard PHS 398 application instructions described below:

##### PHS 398

- o FACE PAGE: Items 7a and 7b should be completed, indicating Direct Costs (in \$25,000 increments up to a maximum of \$250,000 for R01 applications and up to a maximum of \$75,000 for R21 applications) 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. Indicate whether the collaborating institution is foreign or domestic. 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 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.

o 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.**

Submit a signed, typewritten original of the application 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, send an additional two copies of the application to Dr. Tommy L. Broadwater at the address listed under INQUIRIES. It is important to send these two copies at the same time as the original and three copies are sent to the Center for Scientific Review (CSR). These copies are used to identify conflicts and help ensure the appropriate and timely review of the application.

Applications must be received by September 8, 1999. 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 announcement 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 by CSR and responsiveness by the NIAMS staff. Incomplete applications will be returned to the applicant without further consideration. If the application is not responsive to the RFA, NIAMS staff will contact the applicant to determine whether to return the application to the applicant or submit it for review in competition with unsolicited applications at the next review cycle.

Remaining applications may be subjected to a streamlined review process by a Special Emphasis Panel convened by NIAMS Scientific Review Office to determine their scientific merit relative to other applications received in response to the RFA. The roster of reviewers for the RFA will be available on the NIH home page approximately four weeks prior to the scheduled review date. Applications determined to be meritorious will be evaluated for scientific and technical merit by the review committee, be discussed and receive a priority score. All other applications will not be

discussed or scored. Secondary review of the applications will be conducted by the National Arthritis and Musculoskeletal and Skin Diseases Advisory 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. 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. Each of these criteria will be addressed and considered 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 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?

Because the exploratory grant mechanism (R21) is designed to support innovative ideas, preliminary data as evidence of feasibility of the project are not required. However, the applicant does have the responsibility for developing a sound research plan approach. Innovation of the project and potential significance of the proposed research will be major considerations in the evaluation of this mechanism.

As part of the scientific and technical merit evaluation of the research plan, reviewers will be instructed to address the adequacy of plans for including both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research, or justification for exclusion.

The personnel category will be reviewed for appropriate staffing based on the requested percent effort. The direct costs budget request will be reviewed for consistency with the proposed methods and specific aims. Any budgetary adjustments recommended by the reviewers will be in \$25,000 modules. The duration of support will be reviewed to determine if it is appropriate to ensure successful completion of the requested scope of the project.

#### AWARD CRITERIA

Applicants should be aware that, in addition to scientific merit, program priorities and program balance, the total costs of the proposed project and the availability of funds will be considered by NIH staff as well as Advisory Council in making funding recommendations. In circumstances in which applications have similar scientific merit, but vary in cost, NIH is likely to select the more cost competitive application for funding.

#### Schedule

Letter of Intent Receipt Date: August 1, 1999  
Application Receipt Date: September 8, 1999  
Date of Initial Review: October 1999  
Review by Advisory Council: February 2000  
Anticipated Award Date: April 1, 2000

#### INQUIRIES

Inquiries concerning this RFA are encouraged. Additional information, including sample budget narratives and biographical sketch, may be found at this site:

<http://grants.nih.gov/grants/funding/modular/modular.htm>. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct letters of intent to:

Tommy L. Broadwater, Ph.D.  
Scientific Review Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
Natcher Building, Room 5AS-25U  
45 Center Drive, MSC 6500  
Bethesda, MD 20892-6500  
Telephone: (301) 594-4952  
FAX: (301) 480-4543  
[broadwater@nih.gov](mailto:broadwater@nih.gov)

Direct inquiries regarding programmatic issues to:

Bernadette Tyree, Ph.D.  
Cartilage and Connective Tissue Program  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
Natcher Building, Room 5AS-37J  
45 Center Drive, MSC 6500  
Bethesda, MD 20892-6500  
Telephone: (301) 594-5032  
FAX: (301) 480-4543  
[tyreeb@ep.niams.nih.gov](mailto:tyreeb@ep.niams.nih.gov)

Susana Serrate-Sztein, M.D.  
Arthritis Branch  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
Natcher Building, Room 5AS-25E  
45 Center Drive, MSC 6500  
Bethesda, MD 20892-6500  
Telephone: (301) 594-5032  
FAX: (301) 480-4543  
[szteins@ep.niams.nih.gov](mailto:szteins@ep.niams.nih.gov)

Direct inquiries regarding fiscal matters to:

Ms. Nancy Curling

Grants Management Branch

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Natcher Building, Room 5AS-43B

45 Center Drive, MSC 6500

Bethesda, MD 20892-6500

Telephone: (301) 594-3503

FAX: (301) 480-4543

[nc23a@nih.gov](mailto:nc23a@nih.gov)

#### AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410), as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant 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 America people.

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