

This Program Announcement expires on October 5, 2004, unless reissued.

## FUNCTIONAL TISSUE ENGINEERING OF MUSCULOSKELETAL TISSUES

Release Date: October 18, 2001

PA NUMBER: PA-02-014

National Institute of Arthritis and Musculoskeletal and Skin Diseases  
National Institute of Child Health and Human Development  
National Institute of Dental and Craniofacial Research

THIS PA USES "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. MODULAR INSTRUCTIONS MUST BE USED FOR RESEARCH GRANT APPLICATIONS UP TO \$250,000 PER YEAR. MODULAR BUDGET INSTRUCTIONS ARE PROVIDED IN SECTION C OF THE PHS 398 (REVISION 5/2001) AVAILABLE AT <http://grants.nih.gov/grants/funding/phs398/phs398.html>.

### PURPOSE

The purpose of this Program Announcement (PA) is to encourage the submission of applications for research to enhance our understanding of functional tissue engineering of musculoskeletal tissues (articular cartilage, ligaments, tendons, bone, meniscus, intervertebral disc and skeletal muscle). Innovative approaches to these scientific areas will be stressed.

### HEALTHY PEOPLE 2000

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 Program Announcement(PA), Functional Tissue Engineering of Musculoskeletal Tissues, 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>.

### 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

The Research Project (R01) grant mechanism will be used to support projects under this PA. Under this mechanism, the applicant will plan, direct, and carry out the research plan. The proposed project period during which the research will be conducted should adequately reflect the time required to accomplish the stated goals and be consistent with the policy for grant support. For R01s, the total requested project period may not exceed five years and applicants should apply for the length of time appropriate for the work proposed, typically three to five years. NIDCR will allocate funds to support individual R01s, provided the applications are of high scientific merit. It is possible that a collaborative project in a topic area that overlapped the interests of the NIAMS, NICHD and NIDCR could be co-funded by any combination of these three Institutes, if the project is of high scientific merit.

Specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts that have been adopted by the NIH. Complete and detailed instructions and information on Modular Grant applications have been incorporated into the PHS 398 (rev. 5/2001). Additional information on Modular Grants can be found at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

Consistent with recommendations from the NIH Bioengineering Consortium, applications with a bioengineering perspective that are submitted in response to this PA may be either design/technology-driven, hypothesis-driven, or a combination of the two.

## RESEARCH OBJECTIVES

### Background

The goal of tissue engineering is to repair or replace tissues and organs by delivering implanted cells, scaffolds, DNA, proteins or protein fragments to areas where they are needed. Despite early success, tissue engineers have faced challenges in repairing or replacing injured or diseased tissues that serve a predominantly biomechanical function, such as bone and articular

cartilage. An evolving discipline, “functional tissue engineering” seeks to address these challenges [Butler, et al, Functional Tissue Engineering: The Role of Biomechanics, Journal of Biomechanical Engineering, December 2000 122(6), pages 570-575]. Principles of functional tissue engineering include the following: (1) In vivo stress/strain histories need to be measured for a variety of activities. Such data provide mechanical thresholds that tissue repairs/replacements will likely encounter; (2) Mechanical properties of the native tissues must be established for sub-failure and failure conditions. These baseline data provide parameters within the expected thresholds for different in vivo activities and beyond these levels if safety factors are to be incorporated; (3) A subset of these mechanical properties must be selected and prioritized. This subset is important, given that the mechanical properties of the designs are not expected to completely duplicate the properties of native tissues; (4) Standards must be set when evaluating the repairs/replacements after surgery to determine “how good is enough?” New and improved methods must also be developed for assessing the function of engineered tissues; (5) The effects of physical factors on cellular activity must be determined in engineered tissues. Knowing these signals may shorten the iterations required to successfully replace a tissue, and direct cellular activity and phenotype toward a desired end goal; and (6) To effect a better repair outcome, cell-matrix implants may benefit from being mechanically stimulated using in vitro “bioreactors” prior to implantation. How mechanical stress, as well as other physical factors, influences cell activity in bioartificial matrices and bioreactors needs to be assessed.

Incorporating each of these principles of functional tissue engineering should result in safer and more efficacious repairs and replacements for the patient. In addition, these “principles” outline scientific research opportunities that could vastly improve the scientific knowledge base and the result in tissue engineering applications for musculoskeletal injuries and diseases that involve musculoskeletal tissues (articular cartilage, ligaments, tendons, bone, meniscus, intervertebral disc and skeletal muscle).

This PA is an outgrowth of the NIAMS, NICHD and NIDCR continued interest in, and support of, musculoskeletal tissue engineering research, and the National Institutes of Health BECON 2001 Symposium on Reparative Medicine: Growing Tissues and Organs. Further information on this meeting can be found at: <http://www.becon.nih.gov/becon.htm>.

#### Scope

The following are examples of research topics that are appropriate for this PA; however, they are not to be considered as all inclusive or limiting:

Better understand and define the normal mechanical properties of the musculoskeletal tissues (i.e., the micro-environment) that we are trying to repair or replace.

Develop new and/or improved methods for the non-invasive measurement of mechanical function at the cell level and/or micro-environmental level.

Better understand the interactions between mechanical force and inflammatory processes with specific reference to musculoskeletal tissue engineered applications.

Better understand the intrinsic properties of extracellular musculoskeletal matrices (synthesis, characterization, fabrication; cell responsiveness; adaptation to the environment; and ways to improve marginal, inter-fascial attachments).

Better understand how mechanical stress, as well as other physical factors, influence cell activity in musculoskeletal bioartificial matrices and bioreactors.

Better understand the mechanical events that occur during rehabilitation following musculoskeletal tissue-engineered repair.

Identify and validate a minimum set of tests (in vitro and in vivo) to functionally validate engineered musculoskeletal tissues.

Develop and validate constitutive models of scaffold degradation and fatigue for use in musculoskeletal tissue engineering.

Develop and validate better mathematical (non-linear, time dependent) and computational (robust, finite element) models for use in musculoskeletal tissue engineering.

Better understand mechanical factors and their interaction with construct design parameters in musculoskeletal tissue engineering.

Develop and/or validate minimally-invasive imaging modalities to assess the progress/success of musculoskeletal tissue-engineered constructs.

Develop and/or validate other non-imaging-related, minimally-invasive modalities (i.e., biochemical, serologic, ultrasound, etc.) to assess the progress/success of musculoskeletal tissue-engineered constructs.

As science in this area advances, ultimately develop randomized, controlled outcome studies of the use of tissue-engineered constructs for the reparative medical treatment of musculoskeletal injuries and diseases.

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

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are 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 research involving human subjects should read the UPDATED "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," published in the NIH Guide for Grants and Contracts on August 2, 2000

(<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html>);

a complete copy of the updated Guidelines is available at

[http://grants.nih.gov/grants/funding/women\\_min/guidelines\\_update.htm](http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm). The revisions relate to NIH defined Phase III clinical trials and require: a) all applications or proposals and/or protocols to 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) all investigators to report accrual, and to conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

#### INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

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

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects"

that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: <http://grants.nih.gov/grants/guide/notice-files/not98-024.html>.

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

#### 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 found in the NIH Guide for Grants and Contracts Announcement dated June 5, 2000, at the following website: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.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. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

#### 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](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.

## APPLICATION PROCEDURES

The PHS 398 research grant application instructions and forms (rev. 5/2001) at <http://grants.nih.gov/grants/funding/phs398/phs398.html> are to be used in applying for these grants and will be accepted at the standard application deadlines (<http://grants.nih.gov/grants/dates.htm>) as indicated in the application kit. This version of the PHS 398 is available in an interactive, searchable format. Although applicants are strongly encouraged to begin using the 5/2001 revision of the PHS 398 as soon as possible, the NIH will continue to accept applications prepared using the 4/1998 revision until January 9, 2002. Beginning January 10, 2002, however, the NIH will return applications that are not submitted on the 5/2001 version. For further assistance contact GrantsInfo, Telephone 301/435-0714, Email: [GrantsInfo@nih.gov](mailto:GrantsInfo@nih.gov).

Applicants planning to submit an investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting \$500,000 or more in direct costs for any year are advised that he or she must contact the Institute or Center (IC) program staff before submitting the application, i.e, as plans for the study are being developed. Furthermore, the applicant must obtain agreement from the IC staff that the IC will accept the application for consideration for award. Finally, the applicant must identify, in a cover letter sent with the application, the staff member and Institute or Center who agreed to accept assignment of the application.

This policy requires an applicant to obtain agreement for acceptance of both any such application and any such subsequent amendment. Refer to the NIH Guide for Grants and Contracts, March 20, 1998 at <http://grants.nih.gov/grants/guide/notice-files/not98-030.html>.

## SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS

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 NIH staff. The research grant application

form PHS 398 (rev. 5/2001) at <http://grants.nih.gov/grants/funding/phs398/phs398.html> is to be used in applying for these grants, with modular budget instructions provided in Section C of the application instructions. Applicants are permitted, however, to use the 4/1998 revision of the PHS 398 for scheduled application receipt dates until January 9, 2002. If you are preparing an application using the 4/1998 version, please refer to the step-by-step instructions for Modular Grants available at <http://grants.nih.gov/grants/funding/modular/modular.htm>. Additional information about Modular Grants is also available on this site.

The title and number of the program announcement must be typed on line 2 of the face page of the application form and the YES box must be marked.

Submit a signed, typewritten original of the application, including the Checklist, and five 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)

#### REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be evaluated for scientific and technical merit by an appropriate scientific review group convened in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will 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 applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council or board.

#### 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?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

- o The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

- o The reasonableness of the proposed budget and duration in relation to the proposed research.

- o 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 The adequacy of the proposed plan to share data, if appropriate.

#### AWARD CRITERIA

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

- o scientific merit
  
- o availability of funds
- o programmatic priorities.

#### INQUIRIES

Inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

James S. Panagis, MD, MPH  
Director, Orthopaedics Program  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
45 Center Drive, Room 5AS-37K  
Bethesda, MD 20892-6500  
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FAX: (301) 480-4543  
Email: [jp149d@nih.gov](mailto:jp149d@nih.gov)

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National Center for Medical Rehabilitation Research, NICHD  
6100 Executive Blvd. Rm. 2A-03  
Bethesda, MD 20852  
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FAX: (301) 402-0832  
Email: [lq2n@nih.gov](mailto:lq2n@nih.gov)

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FAX: (301) 480-8318  
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Direct inquiries regarding fiscal matters to:

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## AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846, 93.929 and 93.158. 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 and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, and 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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