

AGING MUSCULOSKELETAL AND SKIN EXTRACELLULAR MATRIX

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Department of Health and Human Services (DHHS)

PARTICIPATING ORGANIZATIONS:

National Institutes of Health (NIH)

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

COMPONENTS OF PARTICIPATING ORGANIZATIONS:

National Institute on Aging (NIA)

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

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

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

National Institute of Child Health and Human Development (NICHD)

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

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PURPOSE OF THIS PA

The purpose of this PA is to solicit grant applications for basic research projects to investigate how changes in the extracellular matrix with age affect the function of the tissues of the musculoskeletal system and skin. Projects are encouraged that determine

how cellular aging processes lead to altered matrix production and maintenance, and how aging-related altered matrix composition and organization affect the function of these tissues.

RESEARCH OBJECTIVES

Background

The elderly frequently experience problems associated with the musculoskeletal system and skin that affect their quality of life. Some of these problems, for example, muscle weakness, are due to changes in tissue that are thought to be unavoidably linked to aging. Other problems are due to disease processes accumulation of disabling conditions for which the elderly are particularly susceptible, likely due to changes in the diseased tissue with age and/or changes in tissues upon which the diseased tissue depends.

Cartilage and bone are classified as connective tissues and are composed largely of extracellular matrix. The structural support these tissues give to the body depends on the matrix composition and structure; that composition and structure being a result of activity of the resident cells (chondrocytes, osteoblasts, osteocytes, and osteoclasts). Reciprocally, the matrix and the mechanical and biochemical processes it is subject to, affect the cells. Muscle and skin are not connective tissue, but each depends on connective tissue for function: the dermis and subcutaneous fat in the case of skin, and the endo- peri- and epimesium layers and tendons in the case of muscle. The interaction of the epidermis and the muscle fibers with their associated connective tissue and, in particular, the extracellular matrix, is fundamental to the function of these tissues. In most of these tissues there is evidence of increased turnover of extracellular matrix with age as well as changes in composition of the matrix with age. Paradoxically, however, the matrix can become increasingly insoluble, less digestible and more cross-linked with age. Because these tissues depend on matrix for function and cell viability, these aging-associated changes in matrix are likely key to altered integrity and function of the musculoskeletal tissues and skin in the elderly.

More needs to be done to understand the changes that take place in extracellular matrix composition and structure with age, why those changes occur and the mechanisms by which they result in altered tissue function. Changes include both collagenous and non-collagenous proteins, as well as the post-translational modifications that may be different in aged vs. younger tissues. Important post-translational modifications may include glycosylation, phosphorylation and sulfation, as well as glycation and formation of cross-linkages. Some of these modifications play specific roles in specific tissues and have been shown to change with age. Furthermore, there is evidence that the extracellular matrix acts as a reservoir of humoral factors such as hormones and growth factors, and mediates cell interactions with these factors. Thus, changes in matrix composition with age could lead to altered local balances or effects of these factors.

The extracellular matrix is involved in normal tissue function on a number of levels, including regulation of cell fate, growth and function within the tissue. The matrix is a

mediator of signals for cell proliferation and differentiation, and for apoptosis. Cell adhesion to extracellular matrix, may, in and of itself, help prevent apoptosis. The extracellular matrix may have an influence on vascular function and neurological function, and the converse may also be true. Work in cancer shows that the matrix influences angiogenesis. Thus, matrix influences on blood vessels and nerves in aging tissues of the musculoskeletal system and skin may be important to understand, as vascular and neural function change. Because stem cells may play a role in maintaining cell numbers and function and in healing of aging tissues, it is also important to understand how the matrix microenvironment of these tissues affects recruitment, differentiation, and functional integration of stem cells.

The structural support lent by the matrix is critical to the structure and function of tissues of the musculoskeletal system and skin. The extracellular matrix is the medium through which mechanotransduction takes place, which is vital to the health of cartilage, bone and muscle. Furthermore, the ability to generate force (in the case of muscle) or respond to forces with appropriate structure (in the case of cartilage, skin and bone) is inherent in the arrangement of the extracellular matrix.

Within the musculoskeletal system, and to some degree where there is mechanical action on skin, the health of the tissue is dependent on interaction with associated tissues, notably through the extracellular matrix. These interactions can be endocrine, paracrine, or mechanical. In some cases, changes in one tissue may result in changes in the extracellular matrix and resulting tissue health of another associated tissue. For example, in osteoarthritis changes occur in the quality and quantity of cartilage matrix, and the underlying bone is also affected, but it is unclear whether these are interdependent changes.

Expertise on several tissues may need to be integrated to investigate tissue interactions as they affect, and are affected by, altered extracellular matrix with age. Research is needed on interdependent aging changes in bone, skin, muscle, and cartilage, and the role of extracellular matrix in these changes. The biomechanical and biochemical signals from these tissues and how the extracellular matrix mediates these effects may be critical to our understanding of interdependent changes in tissues with age.

Objectives and Scope

This PA is intended to encourage basic research into aging effects on extracellular matrix and how those changes in extracellular matrix composition and organization contribute to the altered function seen with aging in the musculoskeletal system and skin. While some descriptive work may be justified to document changes that take place in extracellular matrix with age, studies are especially encouraged to investigate the mechanisms whereby aging leads to these changes and by which altered matrix affects cell and tissue function. The following examples illustrate areas of research that are of interest, but serve as examples only, and are not exclusive. Basic biology studies on aging that use animal models or human tissues are of interest. However, clinical studies in humans, beyond collection of tissues or cells for in vitro use, are outside the scope of this PA.

- o The mechanisms by which altered composition of the matrix seen with age affects mechanotransduction and the response of cells to loading
- o Effect of age-related changes in matrix structure/function on the susceptibility of cells to altered apoptosis
- o Effect of age-related changes in matrix structure/function on cell proliferation
- o Interactions between cells and matrix that lead to characteristic alterations in cell or tissue morphology and function with age. For example, thinning of epidermis or change in fiber type in muscle.
- o How cell senescence affects matrix synthesis, secretion, assembly, or turnover
- o How altered matrix composition or structure may predispose tissues to diseases commonly associated with aging, such as Paget's disease or osteoarthritis.
- o How alterations in matrix composition or structure with age affect normal tissue repair or cell turnover, including involvement of stem cells in these processes
- o How the changing extracellular matrix environment with age affects the local bioavailability of growth factors or hormones that influence tissue health and function
- o Mechanisms by which changes in one tissue, lead to altered structure and function in another tissue. For example, how muscle weakness of sarcopenia affects the structure and integrity of the associated bone. Such interaction could be effected through mechanotransduction, through soluble factors such as IL-6, or through other mechanisms.
- o How alterations in activity levels or function affect matrix structure and function, particular in the context of disabling conditions; this may include studies of muscle atrophy and contractures or osteoporosis.

MECHANISM(S) OF SUPPORT

This PA will use the NIH R01 Research Project and R21 Exploratory/Developmental Research Grant award mechanisms. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

R21 applications for Exploratory/Developmental Research Grants may request up to two years of support with a combined budget for direct costs of up to \$275 for the two year period. For example, the applicant may request \$100,000 in the first year and \$175,000 in the second year. The request should be tailored to the needs of the project. Normally, no more than \$200,000 may be requested in any single year. Exploratory/development grant support is for new projects only; competing continuation applications will not be accepted for this mechanism. Two revisions of a previously reviewed

exploratory/developmental grant application may be submitted as defined in NIH Policy at <http://grants.nih.gov/grants/policy/amendedapps.htm>. A general announcement for R21 applications can be found at <http://grants.nih.gov/grants/guide/pa-files/PA-03-107.html>.

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

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 institutions/organizations

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

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

WHERE TO SEND INQUIRIES

We encourage your inquiries concerning this PA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into two areas: scientific/research, and financial or grants management issues:

- o Direct your questions about scientific/research issues to:

Jill L. Carrington, Ph.D.
Director, Musculoskeletal Biology
Biology of Aging Program
National Institute on Aging
7201 Wisconsin Avenue, Suite 2C231
Bethesda, MD 20892
Telephone: (301) 496-6402

FAX: (301) 402-2210
Email: Carringtonj@nia.nih.gov

William J. Sharrock, Ph.D.
Musculoskeletal Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH, DHHS
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-5055
FAX: (301) 480-4543
Email: ws19h@nih.gov

Ralph Nitkin, Ph.D.
National Center for Medical Rehabilitation Research
National Institute of Child Health and Human Development
6100 Executive Boulevard, Room 2A03, MSC 7510
Bethesda, MD 20892-7510
Telephone: (301) 402-4206
FAX: (301) 402-0832
Email: m21e@nih.gov

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

Linda Whipp
Grants and Contracts Management Office
National Institute on Aging
7201 Wisconsin Avenue, Suite 2N212, MSC 9205
Bethesda, MD 20892
Telephone: (301) 496-1472
FAX: (301) 402-1758
Email: whipl@nia.nih.gov

Michael G. Morse
Deputy Chief, Grants Management Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH/DHHS
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Phone: (301)594-3506
E-mail: morsem@mail.nih.gov

Kathy Hancock
Grants Management Branch

National Institute of Child Health and Human Development
6100 Executive Boulevard, 8A17, MSC 7510
Bethesda, MD 20892-7510
Telephone: (301) 496-5482
FAX: (301) 402-0915
Email: kh246t@nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at www.dunandbradstreet.com. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 is available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

SUPPLEMENTARY INSTRUCTIONS: All instructions for the PHS 398 (rev. 5/2001) must be followed, with these exceptions:

For R21 Exploratory/Developmental Grants only, Items a – d of the Research Plan (Specific Aims, Background and Significance, Preliminary Studies, and Research Design and Methods) may not exceed a total of 15 pages. No preliminary data are required but may be included if available. Please note that a Progress Report is not needed; competing continuation applications for an exploratory/developmental grant will not be accepted. In addition, for appendix materials, use the instructions for the appendix detailed in the PHS 398 except that no more than 5 manuscripts, previously accepted for publication, may be included.

APPLICATION RECEIPT DATES: Applications submitted in response to this program announcement will be accepted at the standard application deadlines, which are available at <http://grants.nih.gov/grants/dates.htm>. Application deadlines are also indicated in the PHS 398 application kit.

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

SPECIFIC INSTRUCTIONS FOR APPLICATIONS REQUESTING \$500,000 OR MORE PER YEAR:

Applications requesting \$500,000 or more in direct costs for any year must include a cover letter identifying the NIH staff member within one of NIH institutes or centers who has agreed to accept assignment of the application.

Applicants requesting more than \$500,000 must carry out the following steps:

- 1) Contact the IC program staff at least 6 weeks before submitting the application, i.e., as you are developing plans for the study;
- 2) Obtain agreement from the IC staff that the IC will accept your application for consideration for award; and,
- 3) Identify, in a cover letter sent with the application, the staff member and IC who agreed to accept assignment of the application.

This policy applies to all investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended or revised version of these grant application types. Additional information on this policy is available in the NIH Guide for Grants and Contracts, October 19, 2001 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html>.

SENDING AN APPLICATION TO THE NIH: 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)

APPLICATION PROCESSING: Applications must be mailed on or before the receipt dates described at <http://grants.nih.gov/grants/funding/submissionschedule.htm>. The CSR will not accept any application in response to this PA 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 a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

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

PEER REVIEW PROCESS

Applications submitted for this PA will be assigned on the basis of established PHS referral guidelines. Appropriate scientific review groups convened in accordance with the standard NIH peer review procedures (<http://www.csr.nih.gov/refrev.htm>) will evaluate applications for scientific and technical merit.

The NIH R21 Exploratory/Developmental grant is a mechanism for supporting novel scientific ideas or new model systems, tools, or technologies that have the potential to significantly advance our knowledge or the status of health-related research. Because the research plan is limited to 15 pages, an Exploratory/Developmental grant application need not have extensive background material or preliminary information as one might normally expect in an R01 application. Accordingly, reviewers will focus their evaluation on the conceptual framework, the level of innovation, and the potential to significantly advance our knowledge or understanding. Reviewers will place less emphasis on methodological details and certain indicators traditionally used in evaluating the scientific merit of R01 applications including supportive preliminary data. Appropriate justification for the proposed work can be provided through literature citations, data from other sources, or, when available, from investigator-generated data. Preliminary data are not required for R21 applications.

As part of the initial merit review, all applications will:

- o Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
- o Receive a written critique
- o Receive a second level review by the 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 evaluate the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. The scientific review group will address and consider each of the following criteria in assigning the application's overall score, weighting them as appropriate for each application.

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

The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an

investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

SIGNIFICANCE: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

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

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

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

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below). <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

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

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

ADDITIONAL CONSIDERATIONS

Sharing Research Data

Applicants requesting more than \$500,000 in direct costs in any year of the proposed research are expected to include a data sharing plan in their application. The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or priority score. The NIH policy on data-sharing is described at: http://grants.nih.gov/grants/policy/data_sharing/.

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

AWARD CRITERIA

Applications submitted in response to a PA will compete for available funds with all other recommended applications. The following will be considered in making funding decisions:

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

REQUIRED FEDERAL CITATIONS

HUMAN SUBJECTS PROTECTION: Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

DATA AND SAFETY MONITORING PLAN: Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II), efficacy, effectiveness and comparative trials (phase III). The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>).

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

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the "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.

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

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a

project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

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

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

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

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

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

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at <http://www.cfda.gov/> and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284 and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm>

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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