

## PATHOBIOLOGY OF TEMPOROMANDIBULAR JOINT DISORDERS

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National Institute of Dental and Craniofacial Research (NIDCR)

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

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

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

Office of Research on Women's Health (ORWH)

(<http://www4.od.nih.gov/orwh/>)

LETTER OF INTENT RECEIPT DATE: October 20, 2002

APPLICATION RECEIPT DATE: November 20, 2002

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### PURPOSE OF THIS RFA

The purpose of this initiative is to stimulate cross-cutting, integrative research aimed at delineating the mechanisms underlying the etiology and pathogenesis of the orofacial structures associated with Temporomandibular Joint Disorders (TMJDs). The ultimate goal of this initiative is a systems approach, from the gene, molecule, cell to tissue, and organ, that will provide the basis to better understand TMJDs and lead to the development of new insights into treatment and management of these disorders. In the context of this initiative, integrative research is defined as the combined use of approaches from several different scientific disciplines such as cell biology, physiology, neurobiology, neuroendocrinology, genetics, molecular biology and imaging technologies to probe developmental, neurological, endocrine, immune and other relevant systems in order to define the mechanisms underlying the etiology and pathogenesis of TMJDs.

## RESEARCH OBJECTIVES

### Background

TMJDs refer to a collection of medical and dental conditions affecting the Temporomandibular Joint (TMJ) and the muscles of mastication, as well as contiguous tissue structures. Pain in the masticatory muscles, in the TMJ, and in the associated hard and soft tissues and limitation in jaw function and sounds in the TMJ are common symptoms. Epidemiological data suggest that approximately 10.8 million American adults experience symptoms associated with TMJDs. It has been shown that the disorder is 1.5-2 times more prevalent in women than in men and that 80 percent of the patients treated for TMJDs are women. Given the variation among the problems labeled TMJDs, it is not surprising that the etiology and pathogenesis of TMJDs are still unclear. This initiative is structured to address the complexity of the underlying genetic, cellular and molecular mechanisms of the different tissues (mandibular condyles, the mandibular fossa and articular eminence of the temporal bone, articular disc, ligaments, muscles of mastication and vascular tissues) as well as peripheral and central neural processes associated with TMJDs. Moreover, the use of contemporary biomedical techniques such as biocomputing for modeling the different components of the TMJ and advanced imaging techniques are encouraged.

The elucidation of the developmental events leading to the formation of the TMJ can provide an understanding of the contribution(s) of each of the TMJ components in the pathogenesis associated with TMJDs. In humans the TMJ develops from the neural crest derived ectomesenchymal blastemas. Differentiation of the embryonic mesenchyme to form the primitive TMJ cavity occurs at about the twelfth week of embryonic development. Interestingly, the mandibular condyles develop as secondary cartilage from a proliferative layer of progenitor cells that turn into extracellular matrix producing chondrocytes that are eventually replaced by

osteoblasts. This particular developmental origin explains, in part, the lack of articular cartilage and the presence of a fibrous articular tissue cap in its place. Although in recent years there has been significant progress in understanding the putative regions and the signaling networks controlling the outgrowth and development of the mandible, the precise developmental mechanisms by which the TMJ as a unit is formed are unclear. Obviously more research is needed to decipher the molecular mechanisms regulating development and morphogenesis of the TMJ. Such knowledge is fundamental in understanding the contribution(s) of each of the TMJ components in the pathogenesis of TMJDs as well as understanding the pathogenesis of several abnormalities and congenital syndromes. For example, abnormalities in the mandibles of various mouse mutants caused by targeted inactivation of individual and multiple candidate molecules provide powerful tools to examine not only the hierarchy of the signaling mechanisms and molecules involved but also the specific abnormalities that the inactivation of candidate genes may cause in the formation of each TMJ component (i.e., condyle, coronoid, and angular process of the mandible) and in the formation of the TMJ as a unit.

The structures of the TMJ that are mainly shown to be associated with TMJDs are the temporomandibular joint disc, the ligaments and the masticatory muscles. Although there have been tremendous advances concerning the understanding of the cell biology, physiology and molecular genetics of skeletal, and to some extent the orofacial muscles, there is a paucity of information regarding the pathophysiology of orofacial muscles (masticatory and facial muscle). The lack of such information makes it difficult to delineate the molecular basis for repair of the masticatory muscle systems as well as elucidate the normal function of muscle cells when affected by inflammatory processes (e.g., do they express surface molecules or release soluble mediators or structural components that may activate an immune or inflammatory response?).

To date it remains unclear what additional mediator mechanisms and molecules are associated with orofacial muscle pathophysiology. The only information to date derives from analysis of TMJ synovial fluid. Molecules such as serotonin (5-HT), Prostaglandin E<sub>2</sub>, (PGE<sub>2</sub>) and leukotriene B<sub>4</sub> that are known to be associated with hyperalgesia/allodynia of the masseter muscle in patients with fibromyalgia have been detected in the synovial fluid of arthritic TMJ. Cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor (TNF) have also been found in the synovial fluid of arthritic TMJs as have neuropeptides such as substance P, calcitonin gene-related peptide (CGRP) and neuropeptide Y (NPY).

Degradation markers of the articular disc such as keratan sulfate and proteoglycans are also present in this arthritic joint. The contribution of these molecules to pathogenesis and clinical expression of TMJDs remains uncertain. New imaging methodologies as well as improved animal

models will help to elucidate the inflammatory processes that are involved in response to injury, as well as the contribution of the nervous system to inflammatory diseases of TMJ structures. As with other synovial joints, the TMJ is subject to external loading and to constraints that are imposed on soft tissues such as the ligaments, the articular disc, the fibrous capsule (fibrocartilage) and the temporal bone. During joint motion the ligaments, articular disc and the fibrous capsule are deformed and are incapable of further movement. Both the ligaments and the fibrous capsule of the joints are richly innervated by sensory (afferent) neurons that are stimulated by motion. Other sensory neurons found in the soft tissues of the TMJ are nociceptors, neurons that mediate the sensation of pain. It is important to expand the knowledge of the function of sensory neurons (sensory afferent) that are stimulated by motion as well as those nociceptors associated with TMJDs. To date, pharmacological and physiological studies have shown that disordered sensory processing arises from changes in sensory afferent function and organization of sensory neurons. Agents such as growth factors and cytokines induce pronounced changes in the expression of a variety of functional proteins including receptors and ion channels in the affected afferent axons and sensory neurons. The lack of targeted effective pharmacological agents available for the treatment of pain reflects our incomplete understanding of the mechanisms associated with TMJDs and orofacial pain processing. Therefore, the design of better preventive and therapeutic interventions for TMJD neuropathic pain is dependent on the expansion of our knowledge of the molecular mechanisms of pain. The development of improved animal models can provide new tools to elucidate TMJD associated pain and orofacial pain processing. Sensitivity to pain and inhibition of pain are traits subject to considerable variability, both clinically and experimentally. As mentioned before, women make up the majority of patients treated with TMJDs. Therefore, it is important to examine the role of gender difference in the frequency and severity of TMJD associated pain and the response to analgesics.

## Scope

The objectives and scope of this initiative are the application of a systematic multidisciplinary research approach to the elucidation the pathobiology and pathophysiology of the TMJ diseases and disorders. It is envisioned that the scientific knowledge gained through studies supported by this initiative will lead to the development of therapeutic strategies for these disorders.

The following are some examples of potential research areas:

- o Utilization of laser capture and microarray technologies for profiling/fingerprinting of TMJ structures including muscles, tendons and nerves in experimental conditions of TMJDs.

- o Identification of the cellular and molecular events leading to remodeling of the components of the TMJ to adapt to biomechanical changes.
- o Elucidation of gender influences associated with TMJDs and orofacial pain.
- o Development of computer/mathematical modeling systems for the evaluation of anatomy and physiology of facial and TMJ structures and for the prediction of pathological changes.
- o Generation of knockout and transgenic animals, subtraction cloning and differential screening for the definition of developmental pathways that may indicate differences in TMJ function and pain sensitivity.
- o Development of animal models for the identification of pain modulators, for the examination of pain modulation circuitry attributed to inflammation and for the examination of possible overlap between TMJD associated pain and pain associated with other painful pathologies such as osteoarthritis, rheumatoid arthritis and fibromyalgia.
- o Development of model systems to understand the inflammatory mechanisms leading to extracellular matrix degeneration in TMJDs as well as the role of sex-specific hormones (e.g., estrogens) in cartilage and bone degeneration.
- o Identification of cell (e.g., neutrophils, macrophages, Langerhans cells), inflammatory mediators, (e.g., cytokines TNF $\alpha$ , IL-1, IL-6) and signal transduction mechanisms leading to inflammatory neuropathies associated with TMJDs (e.g., osteoporosis, osteoarthritis).
- o Use of genomic and proteomic analytical approaches to define the characteristics and molecular responses of normal versus diseased TMJ tissues for the discovery of novel regulators required for normal function.
- o Identification of specific biomarkers that can be used to predict risk, aid in early diagnosis, and assess progression and evaluation of TMJDs.
- o Utilization of innovative imaging technologies (e.g., high field/high resolution methods) to define the processing of nociceptive (pain) information from craniofacial musculoskeletal tissue.

o Development of molecular imaging probes and contrast agents based on biological markers for in vivo imaging of biological processes; for discovering, understanding, and diagnosing TMJDs as well as clarifying molecular and cellular aspects of muscle degeneration in inflammation.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invites investigator-initiated research applications for ancillary studies to existing clinical studies of patients with rheumatoid arthritis and juvenile rheumatoid arthritis to investigate temporomandibular involvement in these diseases. Specifically, the applications should focus on the utilization of patients and patient materials from such studies for: i) the evaluation of prevalence and clinical presentation of temporomandibular involvement in these diseases; ii) surrogate markers of disease activity; iii) genetic markers; iv) and therapeutic effects. The parent or core clinical study must have independent financial support and will NOT receive support under this RFA.

#### MECHANISM OF SUPPORT

This RFA will use the NIH Research Project Grant (R01). As an applicant you will be solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation. Future unsolicited, competing-continuation applications based on this project will compete with all investigator-initiated applications and will be reviewed according to the customary peer review procedures. The anticipated award date is July 30, 2003.

This RFA uses just-in-time concepts. Applications for the R01 mechanism use the modular budgeting formats (see <http://grants.nih.gov/grants/funding/modular/modular.htm>). An R01 applicant may request a project period of up to 4 years and a budget for direct costs of up to \$250,000 per year.

#### FUNDS AVAILABLE

The NIDCR intends to commit approximately \$3,000,000 in FY 2003 to fund 10-12 new grants in response to this RFA. The NIAMS intends to commit approximately \$300,000 in FY 2003 to fund one new grant in response to this RFA.

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 FY 2003 financial plans of the NIDCR and NIAMS provide support for this program, awards pursuant to the

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 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 National laboratories
- o Units of state and local governments
- o Eligible agencies of the Federal government
- o Domestic or foreign

#### 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 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:

Eleni Kousvelari, DDS, D.Sc.,  
Chief, Cellular & Molecular Biology, Physiology  
& Biotechnology Branch  
National Institute of Dental and Craniofacial Research  
National Institutes of Health  
Building 45 Room 4AN-18A  
Bethesda, MD 20892  
Telephone: (301) 594-2427

FAX: (301) 480-8318

Email: [Kousvelari@de45.nidr.nih.gov](mailto:Kousvelari@de45.nidr.nih.gov)

Bernadette Tyree, Ph.D.

Director, Cartilage and Connective Tissue Program

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institutes of Health

6701 Democracy Blvd., Rm. 884

Bethesda, MD 20892

Telephone: (301) 594-5032

FAX: (301) 480-4543

Email: [bt16w@nih.gov](mailto:bt16w@nih.gov)

o Direct your questions about peer review issues to:

H. George Hausch, Ph.D.

Acting Director, Division of Extramural Activities

National Institute of Dental and Craniofacial Research

National Institutes of Health

45 Center Drive, Room 4AN-44F

Bethesda, MD 20892-6402

Telephone: (301) 594-2904

FAX: (301) 480-8303

Email: [George.Hausch@nih.gov](mailto:George.Hausch@nih.gov)

Direct your questions about financial or grants management matters to:

Robert L. Tarwater,

Grants Management Specialist

Division of Extramural Activities

National Institute of Dental and Craniofacial Research

National Institutes of Health

Building 45, Room 4AN32A

45 Center Drive

Bethesda, Maryland 20892-6402

Telephone: (301) 594-4836

FAX: (301) 480-8301

Email: [tarwater@nih.gov](mailto:tarwater@nih.gov)

Melinda Nelson

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6701 Democracy Blvd., Rm. 884

Bethesda, MD 20892

Telephone: (301) 594-3535

FAX: (301) 480-4543

EMAIL [nelsonm@mail.nih.gov](mailto:nelsonm@mail.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 NIDCR 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. It is preferred that the letter of intent be sent electronically to [Kousvelari@de45.nidr.nih.gov](mailto:Kousvelari@de45.nidr.nih.gov) If necessary, the letter of intent can be sent by regular mail to Dr. Eleni Kousvelari, listed in the WHERE TO SEND INQUIRIES section of this announcement.

## 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 GrantsInfo, Telephone (301) 435-0714, Email: [GrantsInfo@nih.gov](mailto:GrantsInfo@nih.gov).

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

**USING THE RFA LABEL:** The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number 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>.

**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:

Dr. H. George Hausch  
Division of Extramural Activities  
National Institute of Dental and Craniofacial Research

National Institutes of Health  
45 Center Drive, Room 4AN-44F  
Bethesda, MD 20892-6402

**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 NIDCR. Incomplete applications will be returned to the applicant without further consideration. And, if the application is not responsive to the RFA, CSR staff may 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 appropriate NIH review cycle.

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 NIDCR 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 appropriate Institute 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 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 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:	October 20, 2002
Application Receipt Date:	November 20, 2002
Peer Review Date:	February/March 2003
Council Review:	May/June 2003
Earliest Anticipated Start Date:	July 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](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](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](http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm).

Applicants may wish to place data collected under this initiative 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 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 No. 93.121 (NIDCR) 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.

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