

## MECHANISMS UNDERLYING SECONDARY CONDITIONS IN MOBILITY DISORDERS

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P.T.

National Institute of Child Health and Human Development  
National Institute on Aging  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
National Institute of Diabetes and Digestive and Kidney Diseases  
National Institute of General Medical Sciences  
National Institute of Nursing Research

THIS PROGRAM ANNOUNCEMENT 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 PA.

### PURPOSE

Physical impairments that limit mobility can dramatically reduce the opportunities for persons to participate in the activities of daily life that contribute to their well being. Such activities may include work, schooling, recreation, or social interaction. Unfortunately, primary disabling conditions are often associated with secondary conditions that further inhibit full participation, cause additional negative health consequences, and dramatically increase the burden of the disorder. Treatment or prevention of such secondary conditions (e.g., spasticity, pain, ulceration, infection, weakness and limited motion) will help to create a more enabling environment for persons with limited mobility, so that functioning of the whole person is enhanced. To accomplish these goals, additional research is required to investigate the underlying mechanisms that exacerbate secondary conditions in mobility disorders.

### 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 program announcement, Mechanisms Underlying Secondary Conditions in Mobility Disorders, is related to the priority areas of nutrition, physical activity and fitness, heart disease and stroke, cancer, and diabetes and chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2000" 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 or 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 PA will use the National Institutes of Health (NIH) research project grant (R01) award mechanism. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. An applicant may request a budget of up to \$250,000 per year in direct costs. The total project period of an application submitted in response to this PA may not exceed five years.

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://www.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. 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 the 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 by 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 for applications being considered for award. Additional budget information will be requested only under special circumstances.

This is not a one-time solicitation, but a continuing call for applications.

## RESEARCH OBJECTIVES

### Background

The NIH provides support for scientists to conduct research on the functional changes that result from illness, injuries, or congenital conditions, and the treatment and rehabilitation strategies that may improve whole body functioning. Research efforts must address health-related improvement in function at many levels: from pathophysiology through physical impairment, functional limitation, disability, and societal impact. Primary mobility disorders include both degenerative disorders, such as arthritis, diabetic neuropathy or multiple sclerosis; and injury, such as trauma,

stroke, or amputation. These disorders are accompanied by significant secondary conditions that can lead to further impairment and disability. Secondary conditions include physical limitations as spasticity, seizures, osteoporosis, weakness, pain, limited joint motion or instability, skin breakdown, gastrointestinal and urinary tract dysfunction, respiratory problems, recurrent infection, and sensory impairments. Additional emotional, behavioral and psychiatric disorders can also result from the primary disability or from the stress brought on by recurring secondary conditions. Prevention and early treatment of secondary conditions are an important part of medical rehabilitation, and additional strategies to intervene in the cascade of disablement would be of great benefit. Understanding the biological and behavioral mechanisms that underlie and compound these secondary conditions will help investigators and clinicians to design new interventions aimed at optimizing function in persons with disabilities.

The National Institute on Aging is particularly interested in studies of how aging may affect the development of secondary impairments and/or the progression of impairments to functional limitations and disabilities. Potential populations for these studies may include persons that develop impairments in old age, as well as individuals who have aged with disabilities.

The National Institute of General Medical Sciences (NIGMS) maintains their long-standing interests in studies towards understanding the normal and pathophysiologic responses to injury (exclusive of central nervous system injury). Such studies include early events like shock; prolonged consequences like hypermetabolism, the restoration of homeostasis, and wound healing and tissue repair; and potential complications such as systemic inflammatory response syndrome, sepsis, and multiple organ dysfunction syndrome.

The National Institute of Nursing Research (NINR) is particularly interested in clinical research to determine the factors associated with improvement in the psychosocial functioning of persons with limited mobility and the clinical management of secondary conditions in persons with limited mobility.

#### Objectives and Scope

This program announcement seeks research projects concerned with mechanisms of long-term injury, whole-body effects, long-term consequences, and potential interventions for secondary conditions that accompany primary disability.

Research interests include, but are not limited to:

- o Development of animal models that address secondary conditions that result from such mobility disorders as neurodegenerative disease, injury to the nervous system, arthritis, diabetic neuropathy, amputation, or birth defects
  
- o Endocrine and neuroendocrine changes associated with long-term immobility and their effects on the functioning of organ systems, such as gut mobility, bladder emptying, bone density, respiratory capacity, and glucose tolerance
  
- o Changes in immune function following paralysis
  
- o Effects of chronic infection or immune stimulation on endocrine function
  
- o Neuromuscular and skeletal changes that result from chronic use or disuse, and interventions to better diagnose or ameliorate these changes
  
- o The role of sensory input in reducing or exacerbating spasticity or seizures
  
- o Changes in receptor pharmacology in response to long-term treatment with agents to control spasticity, pain, or seizures, or to treat infection
  
- o The interaction of the nervous system, including neuropeptides and growth factors, in wound healing
  
- o Use of functional imaging (including 2-deoxyglucose imaging, blood flow measurement and other imaging modalities) to assess changes that may predict the onset or progression of secondary conditions
  
- o Long-term gene expression in tissues affected by secondary conditions after paralysis, such as striated and smooth muscle, endothelium, peripheral nerve, sensory and sympathetic ganglia, connective tissue, and epithelium
  
- o The role of aging, or aging accompanied by long-term disability, in influencing secondary changes in any of the above areas
  
- o Behavioral and psychosocial factors in prevention and worsening of functional changes, and behavioral and psychosocial factors affecting treatment leading to rehabilitation and functional improvement

o Research leading to possible interventions to minimize the emotional, behavioral and psychiatric response that may develop as a result of a primary disability of limited mobility or as a response to the secondary conditions.

#### 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 unless a clear and compelling rationale and justification are provided 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 "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 in the NIH Guide for Grants and Contracts, Volume 23, Number 11, March 18, 1994., available on the web 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 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: <http://www.nih.gov/grants/guide/notice-files/not98-024.html>.

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES.

#### APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 4/98) is to be used for applications submitted in response to this PA, with the modifications noted below. Application kits are available at most institutional offices of sponsored research or 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, Email [grantsinfo@nih.gov](mailto:grantsinfo@nih.gov) and on the internet at <http://www.nih.gov/grants/guide/notice-files/not98-178.html>

Applications will be accepted at the standard applications deadlines as indicated in the application kit.

The title ("Mechanisms Underlying Secondary Conditions in Mobility Disorders") and number of this PA must be typed on line 2 of the face page of the application, 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:

- o FACE PAGE: Items 7a and 7b should be completed, indicating Direct Costs (in \$25,000 increments up to a maximum of \$250,000) 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 p 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 p 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 p Use a Modular Grant Budget Narrative page (See <http://www.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.

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 their roles 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 of a biographical sketch may be viewed at <http://www.nih.gov/grants/funding/modular/modular.htm>

- Complete the educational block at the top of the form page;
- List current positions(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 p 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.

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.

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 NIH referral guidelines. An appropriate scientific review group convened by the Center for Scientific Review (CSR) in accordance with the standard NIH peer review procedures will evaluate applications for scientific and technical merit. 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 methods? 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.

## AWARD CRITERIA

Applications will compete for available funds with all other scored applications. The following will be considered in making funding decisions: 1) scientific and technical merit of the proposed project as determined by peer review, 2) availability of funds, and 3) program balance among research areas.

## INQUIRIES

Inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome. Researchers considering an application in response to this program announcement are encouraged to discuss the project with NIH staff in advance of formal submission.

Direct inquiries regarding programmatic issues to:

Mary Ellen Cheung, 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) 402-2242  
FAX: (301) 402-0832  
Email: [mm108w@nih.gov](mailto:mm108w@nih.gov)

Chhanda Dutta, Ph.D.  
Geriatrics Program  
National Institute on Aging  
7201 Wisconsin Avenue, Suite 3E-327  
Bethesda, MD 20892-9205  
Telephone: (301) 435-3048  
FAX: (301) 402-1784  
Email: [duttac@exmur.nia.nih.gov](mailto:duttac@exmur.nia.nih.gov)

James S. Panagis, M.D., M.P.H.  
Director, Orthopaedics Program  
National Institute of Arthritis and Musculoskeletal and Skin Diseases  
45 Center Drive, Room 5AS-37K, MSC 6500  
Bethesda, MD 20892-6500  
Telephone: (301) 594-5055  
FAX: (301) 480-4543  
Email: [jp149d@nih.gov](mailto:jp149d@nih.gov)

Sanford A. Garfield, Ph.D.  
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National Institute of Diabetes, and Digestive and Kidney Diseases  
45 Center Drive, Room 5AN-24B, MSC 6600  
Bethesda, MD 20892-6600  
Telephone: (301) 594-8803  
Email: [garfields@exec.niddk.nih.gov](mailto:garfields@exec.niddk.nih.gov)

Scott D. Somers, Ph.D.

Division of Pharmacology, Physiology, and Biological Chemistry  
National Institute of General Medical Sciences  
45 Center Drive, Room 2AS-49J, MSC 6200  
Bethesda, MD 20892-6200  
Telephone: (301) 594-5560  
Email: [somerss@nigms.nih.gov](mailto:somerss@nigms.nih.gov)

Karin F. Helmers, Ph.D.  
Program Director  
National Institute of Nursing Research  
Building 45, 3AN12, MSC 6300  
Bethesda, MD 20892-6300  
Telephone: 301-594-2177  
Fax: 301-480-8260  
Email: [Karin\\_Helmerts@nih.gov](mailto:Karin_Helmerts@nih.gov)

Direct inquiries regarding fiscal issues to:

Ms. Mary Ellen Colvin  
Grants Management Branch  
National Institute of Child Health and Human Development  
Building 61E, Room 8A17G, MSC 7510  
6100 Executive Boulevard  
Bethesda, MD 20892-7510  
Telephone: 301-496-1304  
Email [mc113b@nih.gov](mailto:mc113b@nih.gov)

Mr. Joseph Ellis  
Grants and Contracts Management Office  
National Institute on Aging  
7201 Wisconsin Avenue, Suite 2N212, MSC 9205  
Bethesda, MD 20892  
Telephone: 301-496-1472  
Email [ellisj@exmur.nia.nih.gov](mailto:ellisj@exmur.nia.nih.gov)

Ms. Sally A. Nichols  
Grants Management Office

National Institute of Arthritis and Musculoskeletal and Skin Diseases  
Building 45, Room 5AS-49F  
45 Center Drive, MSC 6500  
Bethesda, MD 20892-6500  
Telephone: 301-594-3535  
Fax: 301-480-5450  
Email: [nicholss@ep.niams.nih.gov](mailto:nicholss@ep.niams.nih.gov)

Ms. Charlette Kenley  
Grants Management Specialist  
National Institute of Diabetes and Digestive and Kidney Diseases  
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45 Center Drive, MSC 6600  
Bethesda, MD 20892-6600  
Telephone: 301-594-8847  
Email: [kenley@extra.niddk.nih.gov](mailto:kenley@extra.niddk.nih.gov)

Ms. Toni Holland  
Grants Management Officer  
National Institute of General Medical Sciences  
Building 45, Room 2AN.50B  
45 Center Drive, MSC 6200  
Bethesda, MD 20892-6200  
Telephone: 301-594-5132  
Email: [hollanda@nigms.nih.gov](mailto:hollanda@nigms.nih.gov)

Mr. Jeff Carow  
Grants Management Officer  
National Institute of Nursing Research  
Building 45, Room, 3AN12, MSC 6301  
Bethesda, MD 20892-6301  
Telephone: 301-594-6869  
Email: [Jeff\\_Carow@nih.gov](mailto:Jeff_Carow@nih.gov)

Although not a formal sponsor of this program announcement, the National Institute of Mental Health is interested in receiving applications if the secondary condition of interest is a mental

disorder or related disability, or if the research concerns the prevention or treatment of these disorders or related disabilities. Please contact Peter Muehrer, Ph.D., Chief, Co-Morbidity Research Program, NIMH at (301) 443-4708, Email: [pmuehrer@nih.gov](mailto:pmuehrer@nih.gov).

#### AUTHORITY AND REGULATION

This program is described in the Catalog of Federal Domestic Assistance No. 93.929, Medical Rehabilitation Research; No. 93.866, Aging Research; No. 93.846, Arthritis, Musculoskeletal and Skin Diseases Research; No.93.847, Diabetes, Endocrinology and Metabolism Research; No. 93.859, Pharmacology, Physiology and Biological Chemistry Research; and No. 93.361 Nursing Research. 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, 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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